(14) This compound was previously postulated as an intermediate but found too reactive for isolation: K. Schenker and V. Prelog, *Helv. Chim. Acta,* **36,** 896 (1953).

(15) E. Müller and M. Bauer, *Justus Liebigs Ann. Chem.,* **654,** 92 (1962); K. Schank and B. Eistert, *Chem. Ber.,* **98,** 650 (1965).

(16) **Note Added in Proof.** The preparation of both *cis*-2,5-dibromocyclopentanone and *cis*-2,7-dibromocycloheptanone has recently been implied, although no experimental details have been given; see R. H. Prager and J. M. Tippett, *Tetrahedron Lett.,* 5199 (1973). We believe that the assignment of at least the seven-membered derivative must be reversed.

Synthesis of Phthalimidines from Aromatic Dicarbonyl Compounds

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The reaction between *o*-benzoylbenzaldehyde (**1a**) and aromatic isocyanates (**2a–d**) afforded 2,3-disubstituted phthalimidines **3a–d** in good yield, which would be formed *via o*-benzoylbenzylideneaniline intermediate followed by migration of phenyl group. The same product **3a** was obtained by the reaction using **1a** and aniline. On the other hand, no reaction was observed between *o*-carbetoxybenzaldehyde (**23**) and **2a,** but the reaction of **23** with aniline gave *o*-carbetoxybenzylideneaniline (**24**) and 3-anilino-2-phenylphthalimidine (**21a**), in 83 and 7% yield, respectively.

Previously we reported a synthetic method for *N*-arylphthalimidines by the reaction of an aromatic isocyanate and phthalaldehyde.[1] In the present paper, we report the reactions of isocyanates with aromatic dicarbonyl compounds and a new synthetic method for 2,3-disubstituted phthalimidines.

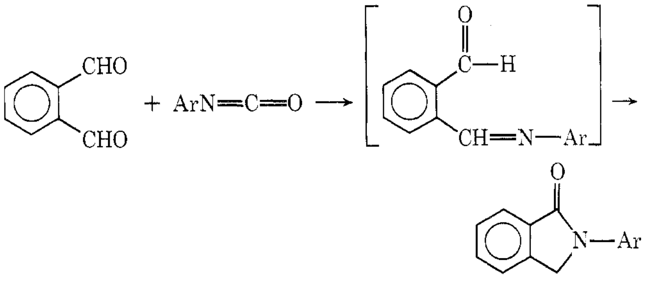
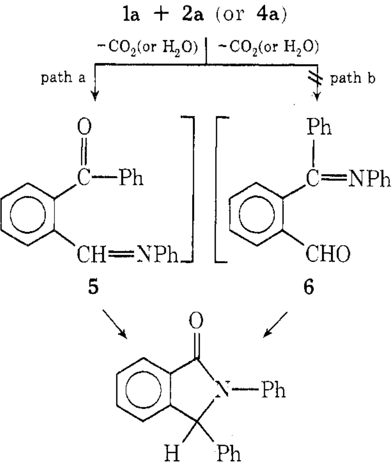
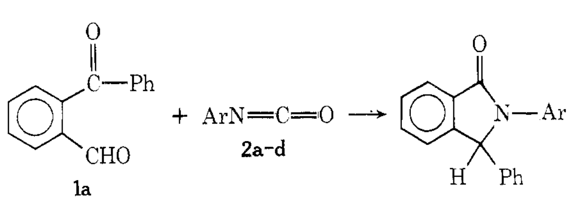


Chart I





2a and 3a, Ar = C_6H_5
2b and 3b, Ar = m-$CH_3C_6H_4$
2c and 3c, Ar = α-naphthyl
2d and 3d, Ar = β-naphthyl

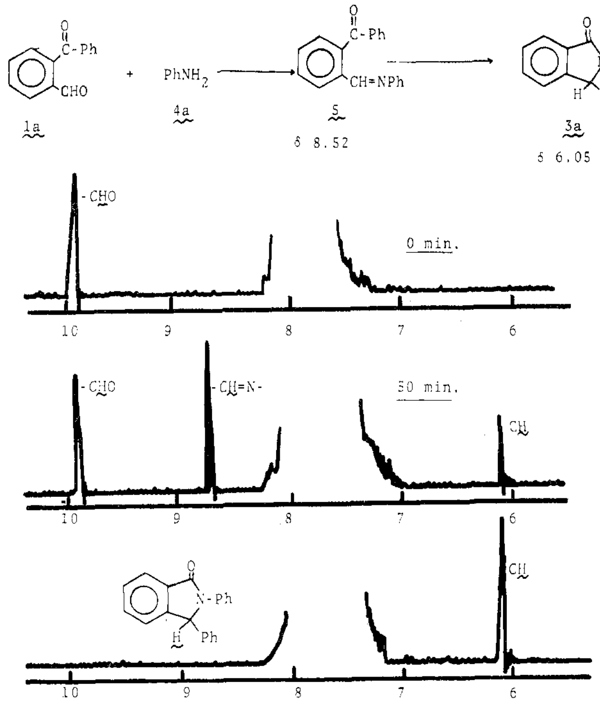
o-Benzoylbenzaldehyde. Treatment of *o*-benzoylbenzaldehyde (**1a**) with an equimolar amount of phenylisocyanate (**2a**) at 200° for 15 hr afforded 2,3-diphenylphthalimidine (**3a**) in 67% yield. The reaction of **1a** with other isocyanates gave phthalimidines **3b–d.** Both the ir (C=O at 1680 cm^{-1}) and nmr (singlet for CH at δ 6.05) spectra of **3a** are fully consistent with the structure; **3b–d** also showed nmr singlets at δ 5.98–6.02. The mass spectrum of **3a** exhibited a molecular ion peak at *m/e* 285, in accordance with a general formula $C_{20}H_{15}ON$, and the fragmentation pattern was in agreement with phthalimidine structure.

As expected, treatment of **1a** with aniline (**4a**) gave **3a** in 65% yield. These observations suggest that the reaction be-

Table I
The Reaction of Aromatic Isocyanate with *o*-Benzoylbenzaldehyde[a]

Products	Reaction time, hr[b]	Yield, %[c]	Mp, °C	Ir(C=O),[d] cm^{-1}	λ_{max}, nm	Nmr, δ CH	CH$_3$	Aromatic
3a	15	67	192–194	1680	275	6.05		7.0–8.1
3b	16	54	175–176	1680	275	6.02	2.25	6.7–8.0
3c	19	84	190–191	1705	275, 283, 293	5.98		6.8–8.2
3d	19	81	200–201	1680	260, 268, 283, 300	5.99		6.7–8.2
3e	9	52	190–190.5	1680		6.03	2.24	7.0–8.1

[a] Satisfactory analytical data (±0.3% for C, H, N) were reported for all compounds. [b] The reaction was monitored by ir. [c] Based on isocyanate. [d] Nujol mull.



Time	Relative Intensity CHO	-CH=N-	CH
0 min.	1	0	0
17 min.	1	2	0.2
50 min.	1	3.5	0.6

Figure 1. Nmr spectra of the reaction of **1a** with aniline at room temperature in $CDCl_3$.

tween **1a** and **4a** proceeds *via* a similar intermediate as that of isocyanates, as shown in Chart I.

The formally different pathways, A and B, can be envisaged for the reaction of isocyanate (or aniline) with *o*-benzoylbenzaldehyde (**1a**) studied in this work: *i.e.*, the reaction of isocyanate (or aniline) with (A) aldehyde function of **1a**, followed by the cyclization accompanied with migration of phenyl group, (B) ketone function of **1a**, followed by the cyclization accompanied with migration of hydrogen. Since ketones are generally much less reactive than aldehydes in the formation of imines,[2] path A should be followed. To verify that the reactions of **1a** with isocyanate (and/or aniline) go through path A, the reactions were monitored by nmr. The nmr spectra showed the proton resonances at δ 8.47 (reaction with isocyanate) and δ 8.52 (reaction with aniline), both being assigned to the CH=N proton (Figures 1 and 2), but did not show any aldehyde proton signal for the intermediate **6.** Based on these observations, the formation of phthalimidines **3a–d** from aldehyde **1a** and isocyanates **2a–d** (and/or aniline) may be accounted for by a pathway in which the initial loss of $CO_2(H_2O)$, resulting in the formation of *o*-benzoylbenzylidene aniline (**5**) (not *o*-formylbenzophenone anil (**6**)), is followed by the cyclization with concerted migration of phenyl group (path A, not path B).

To clarify the migration mechanism of phenyl group, we studied the reaction between *o*-(p-toluoyl)benzaldehyde (**1b**) and **2a.** When a mixture of **1b** and **2a** was heated at 200° for 9 hr, 2-phenyl-3-(*p*-tolyl)phthalimidine (**3e**) was obtained in 52% yield (neither *m*-tolyl- **3f** nor *o*-tolylphthalimidine **3g** were obtained). The structure of **3e** was confirmed by ir, nmr, and carbon-13 FT nmr (Table II[3] and Figure 3) spectra. The carbon-13 nmr spectrum of **3e** showed two singlets at δ 126.802 and 128.804, which were assigned to C-16,20 and C-17,19 by comparison with the carbon-13 nmr spectra of 2-phenylphthalimidine and 2,3-diphenylphthalimidine, as shown in Figure 3. These observations suggest each pair of carbons, C-16 and -20, C-17 and -19, being equivalent, respectively. Therefore the site of the methyl group was determined as being in the para position. Based on this result, we supposed that the reaction may occur *via* bridged intermediate or a concerted process as shown in Chart II, but no other evidence of concerted mechanism has been obtained.

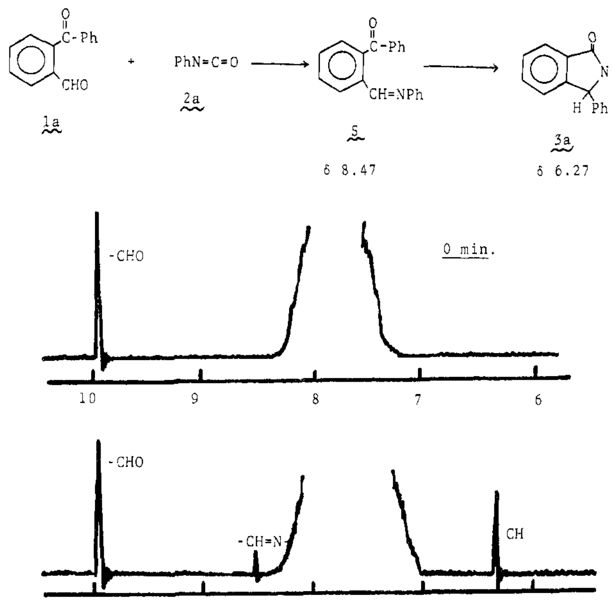
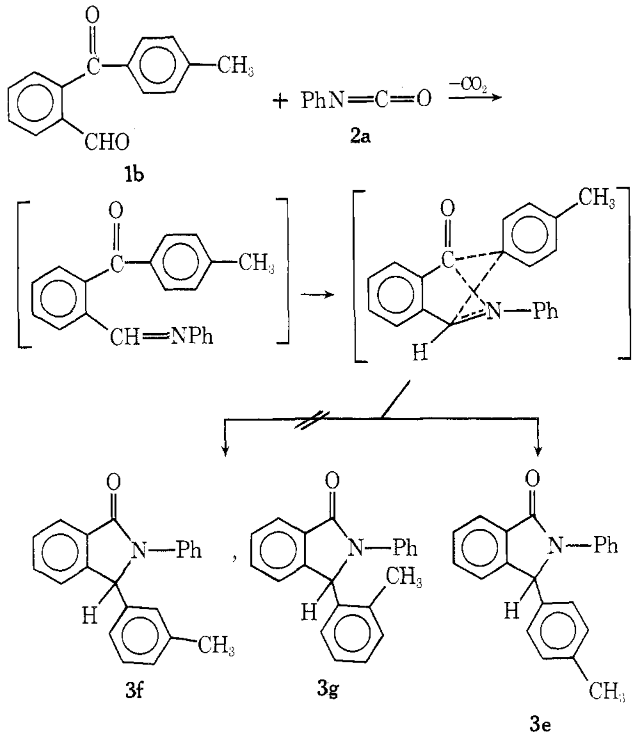


Figure 2. Nmr spectra of the reaction of **1a** with **2a** at 160° in PhN=C=O without solvent.

Chart II



Phthalaldihydic Acid. The reaction of phthalaldehydic acid (**8**) with **2a** afforded 3-hydroxy-2-phenylphthalimidine (**9,** 30%), 3-*N,N'*-(diphenylureido)-2-phenylphthalimidine (**10a,** 12%), phthalic anhydride (**11,** trace), *N*-phenylphthalimide (**12,** 15%), *N,N'*-diphenylurea (**13,**

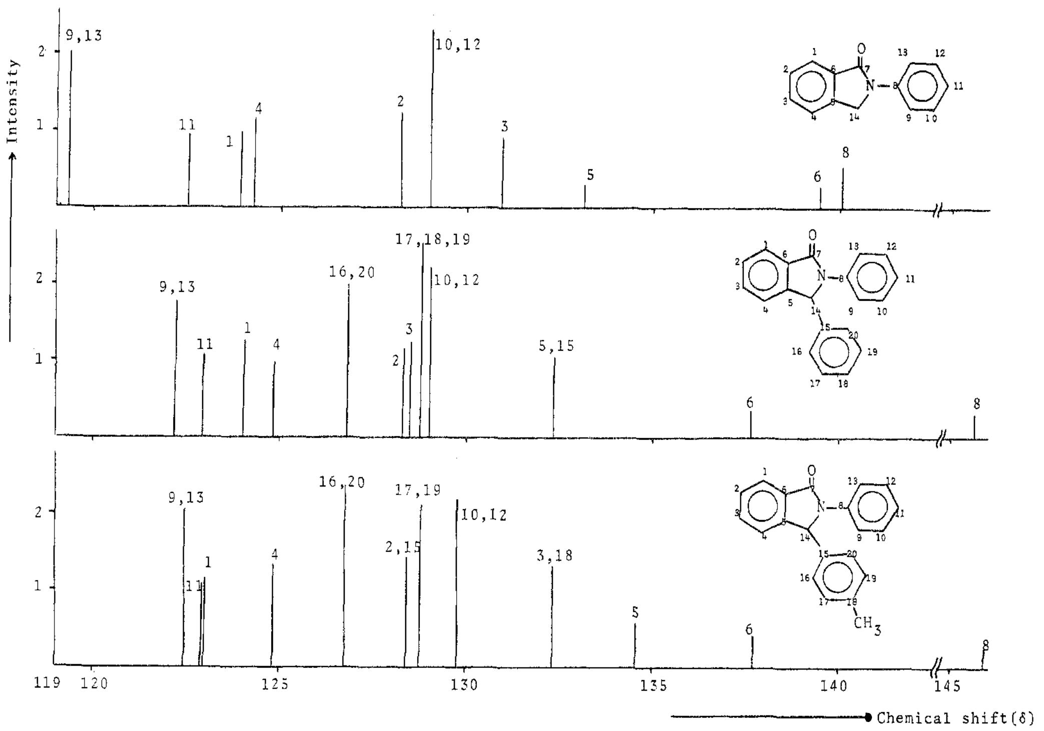
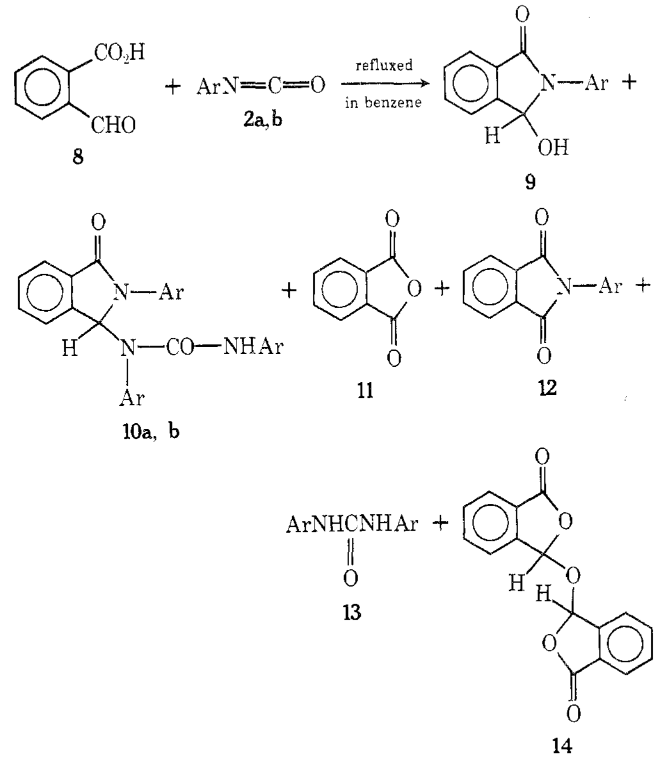


Figure 3. The carbon-13 FT nmr spectra of phthalimidines.

Chart III



a, Ar = C_6H_5; b, Ar = m-$CH_3C_6H_4$

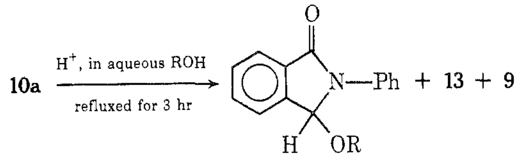
trace), and 3,3′-oxydiphthalide (**14**, trace), as shown in Chart III.

The structure of **10a** was established by the following spectral data and chemical reactions. Product **10a** displayed a NH absorption band at 3300 cm^{-1} and two carbonyl absorptions at 1700 and 1670 cm^{-1}. Its nmr spectrum contained two singlets and a multiplet at δ 6.37, 8.8, and 6.4–7.8 ppm in the ratio of 1:1:19 which were assigned to CH, NH, and aromatic protons, respectively. Furthermore, the mass spectrum of **10a** showed a molecular ion peak at m/e 419 and fragmets at m/e 300, 299, and 208.

Upon the treatment of **10a** with aqueous acetone in the presence of hydrochloric acid, phthalimidine **9** and diphenylurea **13** were obtained in 47 and 38% yield, respectively.

$$\mathbf{10a} \xrightarrow[\text{refluxed for 3 hr}]{\text{H}^+\text{, in aqueous acetone}} \underset{(47\%)}{\mathbf{9}} + \underset{(38\%)}{\mathbf{13}}$$

When **10a** was refluxed in aqueous methanol in the presence of HCl, 3-methoxy-2-phenylphthalimidine (**15a**) and **13** were major products (81 and 98% yield, respectively).

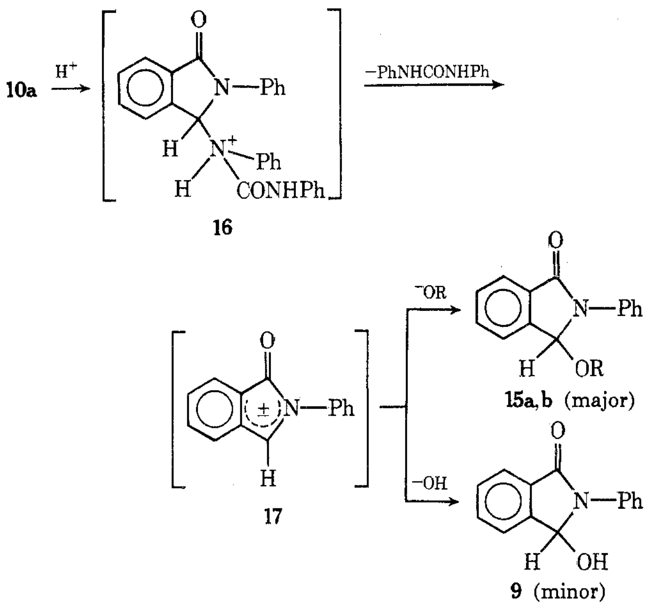


15a, R = CH_3
b, R = C_2H_5

The formation of **9**, **13**, and **15a,b** would be initiated by the protonation at the ureido nitrogen (giving the intermediate **16**), as shown in Chart IV, followed by the elimination of diphenylurea. The intermediate **17** derived from **16** might behave as a soft acid[4] due to the delocalization of positive charge. It would then be attacked by $^-$OR, a rather soft base compared with $^-$OH, to afford **15a,b**, predominantly.

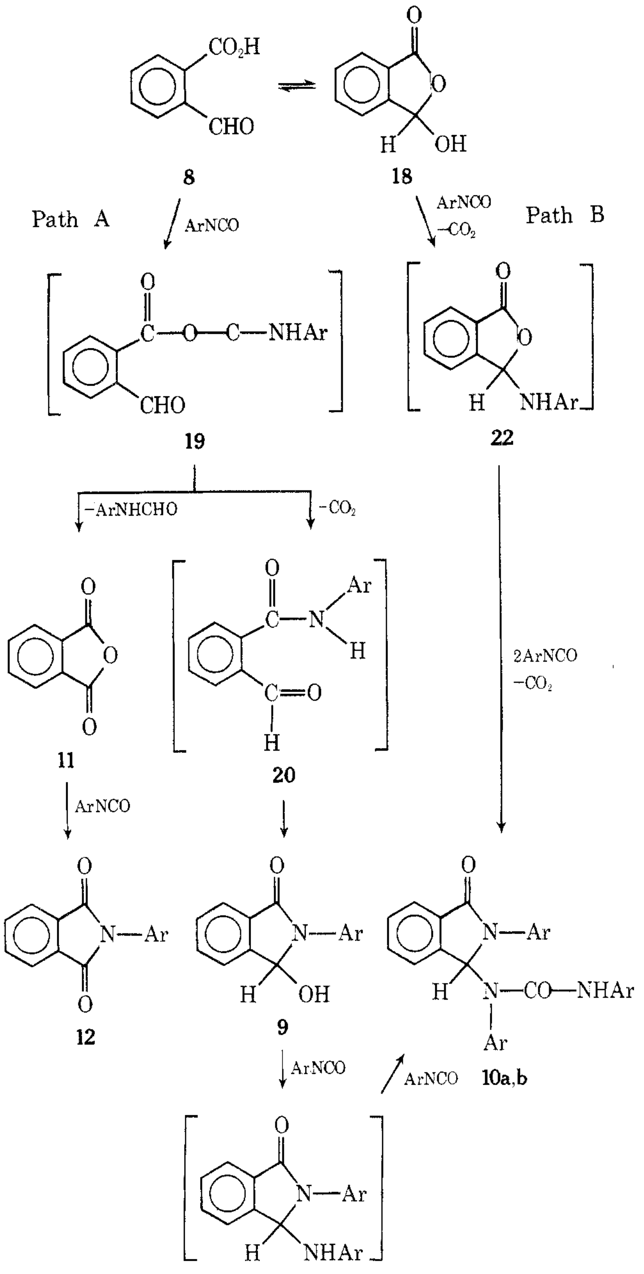
Phthalaldehydic acid is often represented as **8** with an aldehyde and an acid group. But the tautomeric 3-hydroxyphthalide (**18**) has also been suggested. The tautomeric material has been reported to exist in both the open and ring-closed forms depending upon solvent and temperature.[5] Therefore, two possible routes (paths A and B) leading to **10a,b** may be proposed as shown in Chart V. The formation of amide **20** from its precurser **19** is readily explained by the addition reaction of acid into isocyanate (**8** → **19** → **20**, path A). 3-Hydroxyphthalimidine **9** derived by the cyclization of **20** could give intermediate **21**, which would undergo further reaction with isocyanate to produce **10a,b**. Since with path B it is difficult to explain the formation of **9** and **12**, path A may be more preferable. Path A is also supported by the reaction of **2a** with **9**. Refluxing of **2a** with **9** in

Chart IV

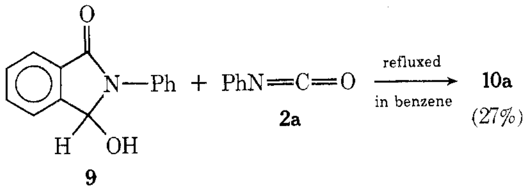


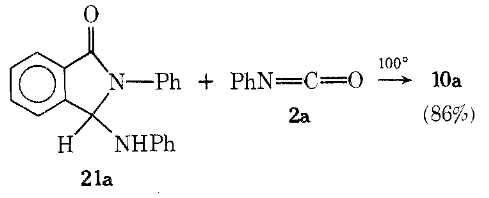
R	Yield, % 15	9	13
CH_3	81	Trace	98
C_2H_5	69	9	87

Chart V

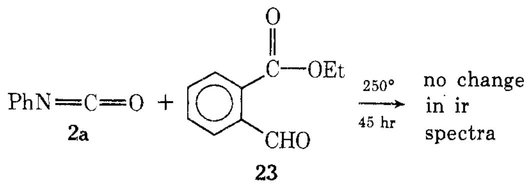


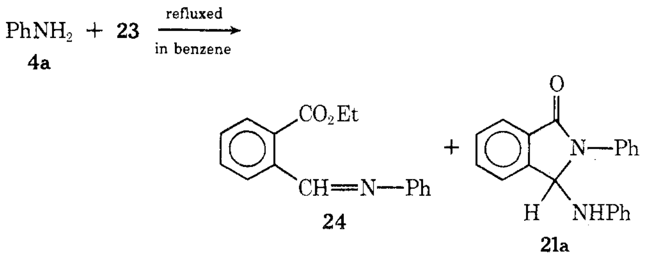
benzene gave **10a** in 27% yield. Furthermore, when **2a** was heated with 3-anilino-2-phenylphthalimidine (**21**) prepared independently,[6] at 100° for 3 hr, **10a** was isolated in 86% yield.





Ethylphthalaldehydate. Phenylisocyanate was found not to react with ethylphthalaldehydate (**23**). No change in ir spectra was observed, even when the two were mixed and allowed to stand at 250° for 45 hr.





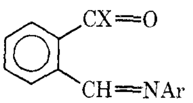
Although phenylisocyanate did not react with **23**, a fast reaction was observed with equimolar amounts of aniline (**4a**) and **23**, isolating the imine **24** and phthalimidine **21a** in 83 and 7% yields, respectively.

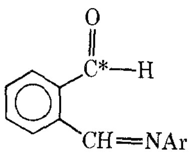
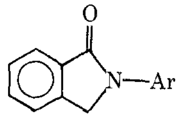
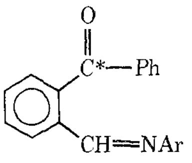
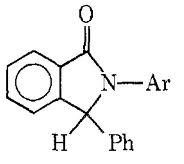
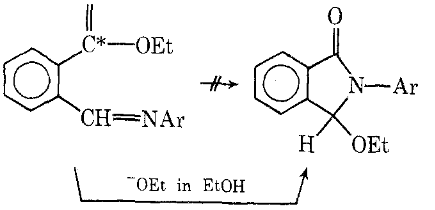
Pojer and his coworkers[6] obtained **21a** in their reaction of *"excess"* aniline with **23** but did not isolate **24**. They gave no discussion regarding the formation mechanism of **21a**.

On the other hand, Henderson and Dahlgren reported that aniline was not reactive toward **23** in dioxane at 21°.[7] Therefore we studied the reaction between **4a** and **23** in more detail. When the imine **24** was heated with aniline at 100° for 10 hr, **21a** was obtained in 64% yield. From this fact we could conclude that the formation of **21a** in the reaction between **23** and **4a** would involve the initial formation of **24**, followed by the nucleophilic attack of **4a** toward the CH=N bond.

A cyclization analogous to that involved in the formation of **21a** from **4a** and **24** was also observed when the imine **24** was heated with methanol or ethanol in the presence of sodium alkoxide to form **15a,b**. The reaction between **1a** and

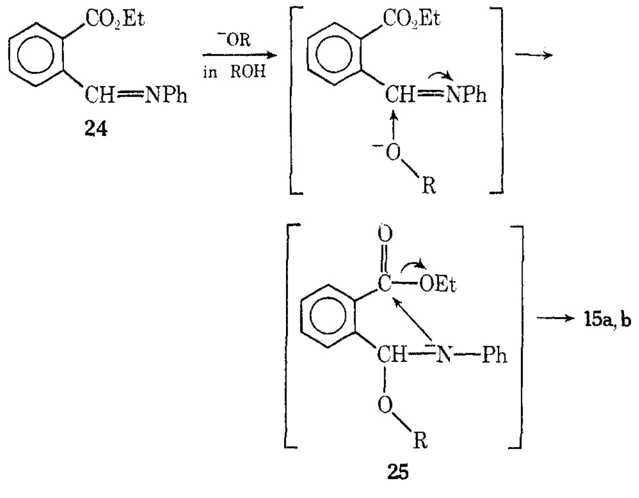
Table III
Cyclization of the Compounds of the Type



Reactant	Product	δ_c
		190.7[a]
		194.8[b]
		164.9[c]

[a–c] The chemical shifts of carbonyl groups were approximated by those of (*a*) PhC*HO, (*b*) $Ph_2C^*{=}O$, (*c*) PhC^*O_2Et.

2a would imply the analogous isolation of **15b** from the thermolysis of **24**. Our attempt was, however, unsuccessful.



In summary, the cyclization of *o*-carbonylbenzylideneaniline seems to be initiated by the nucleophilic attack of nitrogen to carbonyl carbon; the electrophilicity of carbonyl carbon would make an important contribution. The electron density of carbonyl carbon affected by its environment is correlated with the chemical shift of C-13 nmr. As shown in Table III, the chemical shift of carbethoxy carbon is displayed at δ 164.9 ppm,[8a] but both aldehyde[8b] and ketone carbon[8c] are at lower fields than δ 190 ppm. These facts should support the above discussion. When the imine **24** was heated with the alkoxide ion, the nucleophilicity of imino nitrogen would increase by formation of intermediate **25**, resulting in a cyclization product.

Experimental Section[9]

Reaction of *o*-Benzoylbenzaldehyde (1a) with Aromatic Isocyanates 2a–d. General Procedure. A mixture of **1a** (4.0 g, 0.019 mol) and phenylisocyanate (**2a**) (2.5 g, 0.019 mol) was heated at 200° for 15 hr. The resulting dark brown cake was dissolved in benzene (10 ml), and chromatographed on neutral alumina (benzene was used as eluent) to afford 2,3-diphenylphthalimidine (**3a**) in 67% (3.6 g) yield, mp 192–194°; mass spectrum (70 eV) *m/e* 285 (M^+), 208 ($M^+ - Ph$), 180 (208 − CO). The spectral and analytical data are summarized in Table I.

Reaction of *o*-(*p*-Toluoyl)benzaldehyde (1b) with 2a. A Mixture of **1b** (2.2 g, 0.01 mol) and **2a** (1.2 g, 0.01 mol) was treated in a similar manner as the above. After similar work-up, the yield of **3e** was 1.5 g (52%), mp 190–190.5°.

Reaction of 1a with Aniline (4a). To a solution of **1a** (4.2 g, 0.01 mol) in benzene was added **4a** (1.9 g, 0.02 mol), and the resulting mixture was refluxed for 5 hr using a Dean-Stark trap. The solvent was evaporated *in vacuo* and the residue was chromatographed on alumina to give 3.7 g (65%) of **3a**.

Reaction of Phthalaldehydic Acid (8) with 2a. A mixture of **8** (4.5 g, 0.03 mol) and **2a** (3.07 g, 0.03 mol) in benzene (20 ml) was refluxed for 8 hr. The solvent was removed *in vacuo* and the resulting brown cake was chromatographed on neutral alumina using benzene, benzene–ethanol (99:1), and ethanol as eluents. The first fraction was concentrated and the residue was recrystallized from benzene–hexane to give a trace amount (0.01 g) of phthalic anhydride, mp 129–130 (lit.[10] 131.2°). Similar treatment of the second fraction afforded 1.0 g (15%) of *N*-phenylphthalimide (**12**), mp 208° (lit.[11] 208°). Similar treatment of the third fraction afforded 2.0 g (30%) of 3-hydroxy-2-phenylphthalimidine (**9**), mp 171.5–172.5° (lit.[12] 171–172°). The fourth fraction gave a trace amount of 3,3′-oxidiphthalide (**14**), mp 233–235° (lit.[13] 234–236°). The fifth fraction afforded 1.55 g (12%) of 3-(*N,N′*-diphenylureido)-2-phenylphthalimidine (**10a**), mp 203–203.5°: ir (Nujol) 3300 (NH), 1700 (C=O), 1670 (C=O) cm^{-1}; nmr (acetone-d_6) δ 6.37 (s, 1, CH), 6.48–7.8 (m, 9, aromatic protons), 8.8 (s, 1, NH); mass spectrum (70 eV) *m/e* 419 (M^+), 300, 299, 208.

Anal Calcd for $C_{27}H_{21}O_2N_3$: C, 77.31; H, 5.05; N, 10.02. Found: C, 77.33; H, 5.08; N, 9.77.

The sixth fraction gave a trace amount (0.008 g) of *N,N′*-diphenylurea (**13**), mp 234–235° (lit.[14] 235°).

Reaction of 8 with *m*-Tolylisocyanate (2b). The reaction was carried out at the boiling temperature of benzene for 8 hr as described above using **8** (5.6 g, 0.037 mol) and **2b** (2.5 g, 0.042 mol). After similar work-up, the residue obtained was chromatographed on alumina using benzene–ethanol (98:2) to give 3-(*N,N′*-di-*m*-tolylureido)-2-*m*-tolylphthalimidine (**10b**) (4.5 g, 23%), which was the only product isolated, mp 166–168°: ir (Nujol) 3320 (NH), 1740 (C=O), 1640 (C=O) cm^{-1}; nmr (acetone-d_6) δ 2.1 (s, 3, CH_3), 6.0 (s, 1, CH), 6.2–7.9 (m, 16, aromatic protons), 8.05 (s, 1, NH).

Anal. Calcd for $C_{30}H_{27}O_2N_3$: C, 78.06; H, 5.83; N, 9.47. Found: C, 77.87; H, 5.90; N, 9.11.

Acid-Catalyzed Hydrolysis of 10a. A solution of **10a** (1.0 g, 0.0024 mol) in acetone (50 ml) was refluxed with concentrated hydrochloric acid (1.5 ml) for 3 hr. After removal of solvent, the residue was extracted with chloroform, washed with water, and dried over sodium sulfate. The chloroform layer was chromatographed on alumina to afford 0.25 g (47%) of **9**, 0.2 g (38%) of **13**, and 0.5 g (50% recovered) of **10a**.

Acid-Catalyzed Methanolysis of 10a. A solution of 1.0 g (0.0024 mol) of **10a** in 30 ml of aqueous methanol was refluxed with concentrated hydrochloric acid (1.0 ml) for 3 hr. The solvent was removed *in vacuo* and the residue was chromatographed on alumina to afford a trace of **9**, 0.5 g (87%) of 3-methoxy-2-phenylphthalimidine (**15a**), and 0.5 g (96%) of **13**.

15a had mp 79–80°: ir (Nujol) 1710 (C=O) cm^{-1}; nmr (CCl_4) δ 2.77 (s, 3, CH_3), 6.26 (s, 1, CH), 6.95–7.90 (m, 9, aromatic protons).

Anal. Calcd for $C_{15}H_{13}O_2N$: C, 75.30; H, 5.48; N, 5.85. Found: C, 75.25; H, 5.30; N, 6.05.

Acid-Catalyzed Ethanolysis of 10a. A solution of **10a** (2.0 g, 0.0048 mol) in 50 ml of 99% ethanol containing concentrated hydrochloric acid (1.0 ml) was refluxed for 3 hr. After similar work-up, the yield of **9** was 0.1 g (9%), that of **13** was 0.9 g (87%), and that of 3-ethoxy-2-phenylphthalimidine (**15b**) was 0.8 g (69%).

15b had mp 76–77°: ir (Nujol) 1710 cm^{-1}; nmr (CCl_4) δ 0.93 (t, 3, CH_3), 2.93 (m, 2, CH_2), 6.22 (s, 1, CH), 6.75–7.93 (m, 9, aromatic protons); mass spectrum (70 eV) *m/e* 253 (M^+), 224, 208, 180.

Anal. Calcd for $C_{16}H_{15}O_2N$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.78; H, 5.82; N, 5.66.

Reaction of 9 with 2a. A mixture of **9** (1.0 g, 0.0045 mol) and **2a** (1.1 g, 0.0093 mol) in benzene (20 ml) was refluxed for 6 hr. After removal of solvent, the residue was chromatographed on alumina to afford 0.5 g (27%) of **10a**.

Reaction of 3-Anilino-2-phenylphthalimidine (21a) with 2a. A mixture of **21a** (0.5 g, 0.0017 mol) and **2a** (0.5 g, 0.004 mol) was heated at 100° for 3 hr. Then the resulting mixture was chilled by ether, and filteration gave 0.6 g (86%) of **10a.**

Reaction of Ethylphthalaldehydate (23) with 4a. A mixture of **23** (5.34 g, 0.03 mol) and **4a** (2.8 g, 0.03 mol) in benzene (50 ml) was refluxed for 6 hr using a Dean-Stark trap. After removal of solvent, the residue was distilled under reduced pressure to afford 6.30 g (83%) of *o*-carbetoxybenzylideneaniline (**24**), bp 159° (2 mm): ir (Neat) 1720 (C=O), 1620 (C=N), 1260 ($-CO_2-$) cm^{-1}; nmr (CCl_4) δ 1.38 (t, 3, CH_3), 4.33 (q, 2, CH_2), 7.05–8.5 (m, 9, aromatic protons), 9.25 (s, 1, CH=N); mass spectrum (70 eV) *m/e* 253 (M^+), 224, 208, 280.

Anal. Calcd for $C_{16}H_{15}O_2N$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.94; H, 5.90; N, 5.59.

The residue after distillation was chromatographed on alumina to afford 0.63 g (7%) of **21a,** mp 160–161° (lit.[6] 162°).

Reaction of 24 with 4a. A mixture of **24** (3.0 g, 0.012 mol) and **4a** (1.12 g, 0.012 mol) was heated at 100° for 10 hr. Then the resulting mixture was chromatographed on alumina to afford 2.3 g (64%) of **21a.**

Reaction of 24 with *o*-Toluidine (4b). The reaction between **24** (3.0 g, 0.012 mol) and **4b** (1.29, 0.012 mol) was carried out in a similar manner as described for the reaction of **24** with **4a.** After similar work-up, the yield of 2-phenyl-3-(*o*-toluidino)phthalimidine (**21b**) was 3.75 g (*ca.* 100%), mp 167–168°: ir (Nujol) 3390 (NH), 1700 (C=O) cm^{-1}; nmr ($CDCl_3$) δ 1.90 (s, 3, CH_3), 5.90–7.95 (m, 15).

Anal. Calcd for $C_{21}H_{18}ON_2$: C, 80.23; H, 5.77; N, 8.91. Found: C, 80.14; H, 5.62; N, 8.91.

Base-Catalyzed Methanolysis of 24. A solution of **24** ((3.00 g, 0.0012 mol) in absolute methanol was refluxed for 6 hr in the presence of sodium methoxide (0.3 g). After removal of solvent, the residue was extracted with ethylacetate, washed with water, and dried over sodium sulfate. The ethylacetate layer gave 2.35 g (82%) of **15a.**

Base-Catalyzed Ethanolysis of 24. A solution of **24** (3.0 g, 0.0012 mol) in ethanol was treated in the presence of sodium ethoxide (0.3 g) in a similar manner as the above. After similar work-up, the yield of **15b** was 1.70 g (56%).

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Registry No.—**1a,** 16780-82-8; **1b,** 52920-19-1; **2a,** 103-71-9; **2b,** 621-29-4; **2c,** 86-84-0; **2d,** 2243-54-1; **3a,** 36149-34-5; **3b,** 53778-18-0; **3c,** 53779-19-1; **3d,** 53778-20-4; **3e,** 52920-23-7; **4a,** 62-53-3; **4b,** 621-29-4; **8,** 119-67-5; **9a,** 18167-15-2; **10a,** 52920-24-8; **10b,** 52920-27-1; **15a,** 52920-25-9; **15b,** 25770-48-3; **21a,** 19339-69-6; **21b,** 52920-26-0; **23,** 34046-43-0; **24,** 52920-28-2; 2-phenylphthalimidine, 5388-42-1.

Supplementary Material Available. Full carbon-13 nmr data for compounds 2-phenylphthalimidine, 2,3-diphenylphthalimidine, and 2-phenyl-2-(*p*-tolyl)phthalimidine will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the paters in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-74-3924.

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Acylation of Amino Acid Schiff Bases

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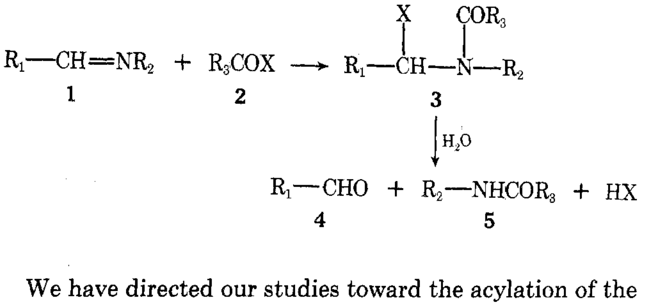
Acylating agents react with amino acid Schiff bases to form intermediates that can be hydrolyzed to acylated amino acids or dipeptides. This procedure offers a new method for preparing semisynthetic penicillins.

Previously, we had found it advantageous to isolate and purify 6-aminopenicillanic acid (6-APA), the basic intermediate for the production of semisynthetic penicillins, as its Schiff base.[1] We now wish to report that it is possible to acylate the Schiff base directly to form the desired penicillin derivative without the necessity of generating the free amino acid for use as the starting material.

It has long been known that the Schiff bases of amines (**1**) could readily be acylated with acid halides (**2**) or anhydrides.[2] The reaction involves an addition across the —CH=N bond to form a stable compound (**3**). Subsequent hydrolysis of the acid halide adduct yields the simple acylation product (**5**) of the original amine.



$$\underset{1}{R_1{-}CH{=}NR_2} + \underset{2}{R_3COX} \longrightarrow \underset{3}{R_1{-}\overset{X}{\overset{|}{C}H}{-}\overset{COR_3}{\overset{|}{N}}{-}R_2} \xrightarrow{H_2O} \underset{4}{R_1{-}CHO} + \underset{5}{R_2{-}NHCOR_3} + HX$$

We have directed our studies toward the acylation of the Schiff bases of 6-APA salts and esters. The syntheses of penicillin V (**7a**) and its methyl ester (**7b**) were investi-