Chemical Properties of *N*-Benzoylimines of Quinazoline, Quinoxaline, and Phthalazine

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Reactions of 1-benzoylimino-4-phenylquinazolinium (I), 1-benzoylimino-3-phenylquinoxalinium (II), and 3-benzoylimino-1-phenylphthalazinium betaines (III) with nucleophiles (hydroxide and cyanide ions) and 1,3-dipolarophiles (acetylenic esters and maleimides) were investigated. Heating I in aqueous alkali gave 3-phenylindazole, while similar treatment of II and III resulted in the formation of 1-benzoylamino-2-oxo-3-phenylquinoxaline and 2-benzoylamino-1-oxo-4-phenylphthalazine, respectively. Reaction of II and III with cyanide ion afforded 2-cyano-3-phenylquinoxaline and 1-cyano-4-phenylphthalazine in high yields, respectively. 1,3-Dipolar cycloaddition reactions of I and III with dimethyl acetylenedicarboxylate and ethyl propiolate afforded primary 1:1 cycloadducts, while the reaction of II with dimethyl acetylenedicarboxylate gave a product which is formed by ring opening of a primary adduct. The reaction of I-III with *N*-methyl and *N*-phenylmaleimides afforded the corresponding primary 1:1 cycloadducts in high yields, whose stereochemical assignment was made on the basis of nmr spectroscopy.

Whereas the chemical properties of the *N*-oxides of benzodiazines have been well defined (1), little work has appeared on the chemistry of the isoelectronic *N*-imines and their *N*-acyl derivatives. Because the syntheses of *N*-benzoylimines of quinazolines, quinoxalines and phthalazines have recently been achieved (2) and these compounds are now readily available, we have been led to a study of the chemical properties of this new class of compounds. In this paper, we describe the reactions of 1-benzoylimino-4-phenylquinazolinium (I), 1-benzoylimino-3-phenylquinoxalinium (II), and 3-benzoylimino-1-phenylphthalazinium betaines (III) with nucleophiles (hydroxide and cyanide ions) and with 1,3-dipolarophiles (acetylenic esters and maleimides).

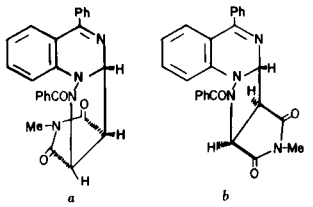
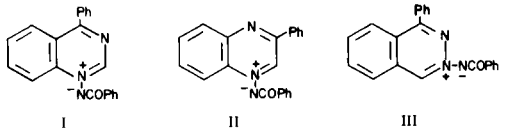


Figure 1

Reactions with Hydroxide Ion.

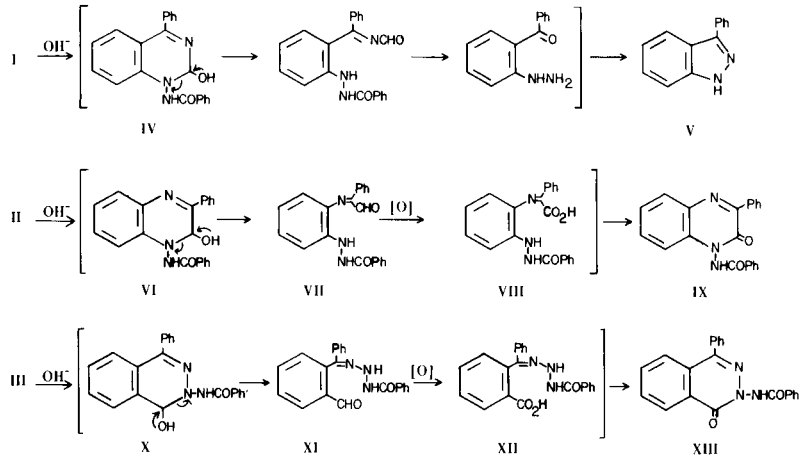
When a solution of *N*-benzoylimine I in 10% aqueous potassium hydroxide was heated at 90° for 3 hours, 3-phenylindazole (V) was obtained in 86% yield. In contrast, *N*-benzoylimines II and III were converted under the similar conditions into 1-benzoylamino-2-oxo-3-phenylquinoxaline (IX) and 2-benzoylamino-1-oxo-4-phenylphthalazine (XIII) in 27 and 49% yields, respectively. It



Scheme 1

should be noted that expected 2-oxo-3-phenylquinoxaline and 1-oxo-4-phenylphthalazine were not detected in the reaction mixture. The structures of IX and XIII are based on the elemental and spectral data. The principal features of the mass, nmr, and ir spectra of compounds IX and XIII were markedly similar. For example, compound IX has the molecular formula $C_{21}H_{15}N_3O_2$ and exhibits a band at 3300 cm^{-1} (NH) and two strong carbonyl bands at 1680 and 1645 cm^{-1} in its ir spectrum. The nmr spectrum shows the disappearance of the signal due to 2-H and the appearance of a broad singlet at δ 9.44 (NH).

These transformation reactions may involve the initial formation of hydrate intermediates (IV, VI, and X). This step is analogous to that proposed for the first step in the alkaline induced transformations of quinazoline 1-oxides into 2-quinazolinones (3), 3-phenylquinoxaline 1-oxide into 3-phenyl-2(1*H*)quinoxalinone (4a), and 4-phenylphthalazine 2-oxide into 4-phenyl-1-phthalazinone (4b). The inter-

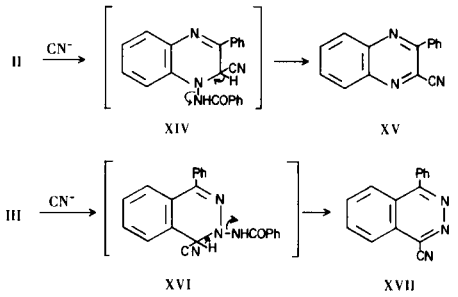


Scheme 2

mediate IV is presumed to undergo base catalyzed ring opening followed by hydrolysis and recrylization to afford aromatized product V. On the other hand, the intermediates VI and X may initially undergo ring opening to aldehydes VII and XI, but this step is presumably followed by oxidation by the air to carboxylic acids VIII and XII, which cyclize to IX and XIII, respectively. In fact, when II was treated with alkali under a stream of oxygen, the yield of IX increased to 40%. However, the possibility that IX and XIII are produced directly from VI and X, respectively, by the air oxidation, can not be eliminated at this time.

Reaction with Cyanide Ion.

Compounds II and III, when treated with aqueous potassium cyanide at room temperature, were smoothly converted into 2-cyano-3-phenylquinoxaline (XV) (4) and 1-cyano-4-phenylphthalazine (XVII) (5) in 93 and 75% yields, respectively. Benzamide was also isolated. The behavior of II and III is similar to those reported for the corresponding *N*-oxides (4) and for the formation of 2-cyanoquinoline and 1-cyanoisoquinoline from quinoline and isoquinoline Reissert compounds prepared from sulfonic acid halides, respectively (5). Consequently, it may be reasonable to consider that the transformations (II→XV and III→XVII) proceed *via* intermediates XIV and XVI as shown in Scheme 3. In contrast, I did not give a clear cut result under the similar conditions. Thus, although tlc analysis of the reaction mixture showed the disappearance of the starting material and the appearance of the new products, usual work-up procedure resulted in the recovery of the starting material as the major product (21%), accompanied by the formation of many other products.



Scheme 3

1,3-Dipolar Cycloadditions.

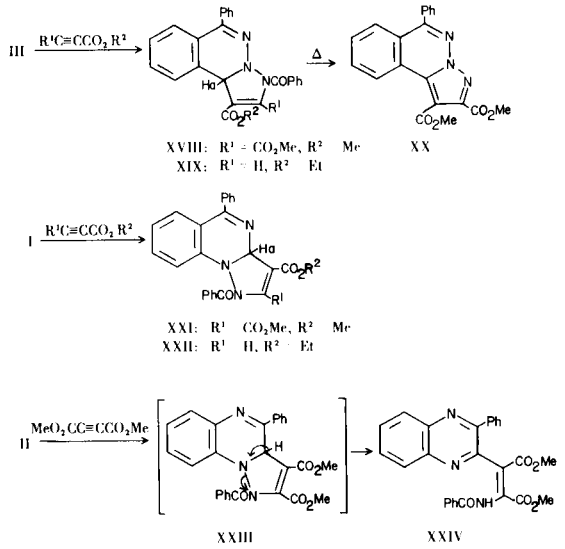
A previous study revealed that *N*-imines of 3-phenylquinoxaline and 4-phenylphthalazine undergo 1,3-dipolar cycloaddition reactions with acetylenic esters to give fully aromatized cycloadducts (6). The primary cycloadducts could not be isolated. We were then led to examine the behavior of *N*-benzoylimines I-III towards acetylenic esters and found that primary cycloadducts could be isolated as stable products from the reactions of I and III. *N*-Methyl- and *N*-phenylmaleimides were also found to react with I-III to give the corresponding primary cycloadducts.

Thus, *N*-benzoylimine III gave adducts XVIII and XIX in 75 and 69% yields, when heated with dimethyl acetylenedicarboxylate and ethyl propiolate in refluxing toluene, respectively. The structures of the adducts were assigned on the basis of spectral and chemical evidence. For example, the mass spectrometry (M^+, 467) and elemental analysis confirmed that XVIII is a 1:1 cycloadduct. The ir spectrum shows three carbonyl bands at 1745, 1710, and 1660 cm^{-1}. The nmr spectrum shows a singlet at δ 5.59 (1H, Ha), two methoxyl singlets at δ 3.89 and 3.68, and a multiplet (14H) in the aromatic region. Refluxing XVIII in mesitylene gave XX (6) in 26% yield, providing conclusive evidence for the assigned structure.

N-Benzoylimine I reacted with dimethyl acetylenedicarboxylate and ethyl propiolate in refluxing toluene,

giving cycloadducts XXI and XXII in 58 and 78% yields, respectively. The principal features of the ir and nmr spectra of these cycloadducts were similar to those observed with XVIII and XIX, except for the low field shift of the nmr signal due to Ha which appeared at δ 8.40 for XXI and δ 8.23 for XXII. The adducts XXI and XXII were rather stable and recovered unchanged after refluxing in mesitylene. Presumably, a major contributing factor to the isolation of the stable 1:1 cycloadducts (XVIII, XIX, XXI, and XXII) is the fact that loss of the resonance energy due to destruction of the aromaticity of the diazine ring is small enough to be counterbalanced by the energy gained in the formation of the two sigma bonds.

In sharp contrast to the cases of I and III, the *N*-benzoylimine II gave a ring opened product XXIV on reacting with dimethyl acetylenedicarboxylate in refluxing toluene. The structure of XXIV (7) followed from its spectra. The ir spectrum shows strong carbonyl bands at 1745 and 1680 cm^{-1} and the nmr spectrum reveals the presence of a broad singlet at δ 12.01 (NH) (disappeared by deuterium oxide treatment at 35° after 1 week), two methoxyl singlets at δ 3.73 and 3.31, and a multiplet (14H) in the aromatic region. Attempts to isolate a possible intermediate XXIII were unsuccessful, although tlc analysis at the early stage of the reaction showed the appearance of a new spot (presumably due to XXIII) which disappeared with increasing amount of XXIV. Instability of the primary adduct derived from II may be attributed to activation of hydrogen at the 2-position in XXIII by the C=N group as well as by the C=C double bond, so that the rearomatization reaction to XXIV is considered to be facilitated.

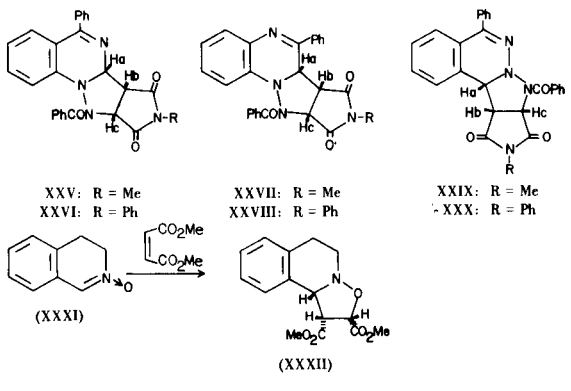


Scheme 4

N-Methyl- and *N*-phenylmaleimides were also found to react with *N*-benzoylimines I-III to produce stereospecifically the corresponding 1:1 cycloadducts XXV-XXX in high yields. The ir and nmr spectra (Table II) of the adducts were strikingly similar. For example, the ir spectrum of XXV shows two carbonyl bands at 1715 and 1660 cm^{-1}, and the nmr spectrum of XXV reveals an AMX pattern consisting of two doublets due to Ha and Hc and a triplet due to Hb with $J_{ab} = J_{bc} = 8$ Hz. The stereochemical relationship of Ha and Hb in these adducts was ascertained by an examination of the nmr spectra. In the adducts XXV, XXVII, and XXIX, *N*-methyl signals appear at 0.50-0.63 ppm higher field than that of *N*-methylsuccinimide (δ 2.98). An inspection of models (Figure 1) reveals that the *N*-methyl group can be oriented in the shielding cone of the benzene ring, and this can occur only when the Ha and Hb are *cis* (Figure 1a). The coupling constants (8 Hz) between Ha and Hb observed in all the cycloadducts (XXV-XXX) are also reasonable as the values for *cis* vicinal couplings in pyrrolidines (8), and thus *N*-phenyl derivatives XXVI, XXVIII, and XXX have the same stereochemistry as the *N*-methyl derivatives XXV, XXVII, and XXIX.

Huisgen (9) have studied the 1,3-dipolar cycloaddition reactions of 3,4-dihydroisoquinoline *N*-oxide (XXXI) with dimethyl maleate and obtained cycloadduct XXXII which has all *cis*-stereochemistry. His interpretation of the formation of XXXII is based on the premise that there are favorable π-overlap interactions between the carbonyl group and benzene ring in the transition state leading to the observed all *cis*-adduct.

An intriguing alternative would involve the transition state depicted in Figure 2a (compare with Figure 2b). This orientation closely resembles that proposed for the Diels-Alder reaction (10), in which there is a favorable secondary orbital interaction between occupied diene (HOMO) and unoccupied olefin molecular orbitals (LUMO) or between unoccupied diene (LUMO) and occupied olefin molecular orbitals (HOMO). In the 1,3-dipolar cyclo-



Scheme 5

Table I

1,3-Dipolarcycloaddition Reaction of *N*-Benzoylimines I-III with Acetylenic Esters and Maleimides

Compound	M.p. °C	Recrystallized from	Yield %	Reaction Time hours	Formula	Anal.	C%	H%	N%
XVIII	222-224	Ethyl acetate	75	7	$C_{27}H_{21}N_3O_5$	Calcd.	69.37	4.53	8.99
						Found	69.16	4.52	9.07
XIX	114-116	Ethanol	69	0.5	$C_{26}H_{21}N_3O_3$	Calcd.	73.74	5.00	9.92
						Found	73.45	5.04	9.89
XXI	125-127	Ether	58	8	$C_{27}H_{21}N_3O_5$	Calcd.	69.37	4.53	8.99
						Found	69.20	4.42	8.99
XXII	116-117	Ether	78	17	$C_{26}H_{21}N_3O_3$	Calcd.	73.74	5.00	9.92
						Found	73.83	5.09	9.92
XXV	236-240	Ethyl acetate	81	5	$C_{26}H_{20}N_4O_3$	Calcd.	71.55	4.62	12.84
						Found	71.47	4.64	12.68
XXVI	251-255	Chloroform-ether	98	27 (a)	$C_{31}H_{22}N_4O_3$	Calcd.	74.68	4.45	11.24
						Found	74.50	4.50	11.17
XXVI	238-240	Ethyl acetate	85	5.5	$C_{26}H_{20}N_4O_3$	Calcd.	71.55	4.62	12.84
						Found	71.25	4.66	12.50
XXVIII	292-294	DMF-ether	82	2	$C_{31}H_{22}N_4O_3$	Calcd.	74.68	4.45	11.24
						Found	74.46	4.60	11.19
XXIX	226-228	Chloroform-ether	30	3.5	$C_{26}H_{20}N_4O_3$	Calcd.	71.55	4.62	12.84
						Found	71.61	4.59	12.93
XXX	276-279	Chloroform-ether	71	16 (a)	$C_{31}H_{22}N_4O_3$	Calcd.	74.68	4.45	11.24
						Found	74.78	4.23	11.27

(a) Reaction was performed with stirring at room temperature.

Table II

Spectral Data for Cycloadducts

Compound	Ir (chloroform) cm^{-1}	Nmr (deuteriochloroform) δ
XVIII	1745, 1710, 1660	7.2-8.2 (m, 14H, aromatic H), 5.59 (s, 1H, Ha), 3.89 (s, 3H, $-CO_2CH_3$), 3.68 (s, 3H, $-CO_2CH_3$)
XIX	1700, 1660	7.2-8.3 (m, 15H, H-2 and aromatic H), 5.58 (d, 1H, Ha, J = 3 Hz), 4.15 (q, 2H, $-CH_2CH_3$, J = 7 Hz), 1.27 (t, 3H, $-CH_2CH_3$, J = 7 Hz)
XXI	1740, 1660	8.40 (s, 1H, Ha), 7.2-8.1 (m, 14H, aromatic H), 3.90 (s, 3H, $-CO_2CH_3$), 3.70 (s, 3H, $-CO_2CH_3$)
XXII	1710, 1660	8.63 (s, 1H, Ha), 7.2-8.0 (m, 15H, H-2 and aromatic H), 4.25 (q, 2H, $-CH_2CH_3$, J = 7 Hz), 1.31 (t, 3H, $-CH_2CH_3$, J = 7 Hz)
XXV	1715, 1660	7.2-8.1 (m, 14H, aromatic H), 5.99 (d, 1H, Hc or Hb, J = 8 Hz), 4.50 (d, 1H, Ha, J = 8 Hz), 3.54 (t, 1H, Hb or Hc, J = 8 Hz), 2.48 (s, 3H, N-CH_3)
XXVI	1720, 1660	6.9-8.2 (m, 19H, aromatic H), 6.13 (d, 1H, Hc or Hb, J = 8 Hz), 4.57 (d, 1H, Ha, J = 8 Hz), 3.89 (t, 1H, Hb or Hc, J = 8 Hz)
XXVII	1715, 1665	7.0-8.1 (m, 14H, aromatic H), 6.05 (d, 1H, Hc or Hb, J = 8 Hz), 4.56 (d, 1H, Ha, J = 8 Hz), 3.77 (t, 1H, Hb or Hc, J - 8 Hz), 2.37 (s, 3H, N-CH_3)
XXVIII	1720, 1670	6.8-8.2 (m, 19H, aromatic H) (a), 5.87 (d, 1H, Hc or Hb, J = 8 Hz), 5.18 (d, 1H, Ha, J = 8 Hz), 4.23 (t, 1H, Hb or Hc, J = 8 Hz)
XXIX	1715, 1660	6.8-8.0 (m, 14H, aromatic H), 5.97 (d, 1H, Hc or Hb, J = 8 Hz), 5.55 (d, 1H, Ha, J = 8 Hz), 3.83 (t, 1H, Hb or Hc, J = 8 Hz), 2.35 (s, 3H, N-CH_3)
XXX	1720, 1670	6.8-8.0 (m, 19H, aromatic H), 6.11 (d, 1H, Hc or Hb, J = 8 Hz), 5.69 (d, 1H, Ha, J = 8 Hz), 4.02 (t, 1H, Hb or Hc, J = 8 Hz)

(a) Dimethylsulfoxide-d_6 was used as solvent.

addition reaction, the secondary interaction in Figure 2c must be negligible, but that in Figure 2d is bonding. Consequently the transition state shown in Figure 2a is anticipated to be prefered.

We are now engaged in a more detailed investigation on the stereochemistry of the 1,3-dipolar cycloaddition reactions.

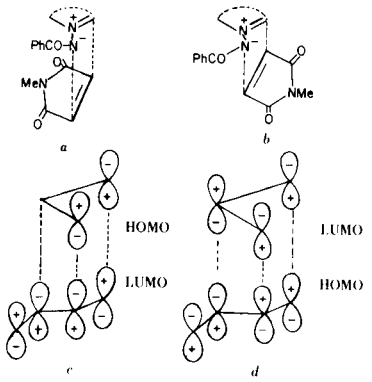


Figure 2

EXPERIMENTAL

All melting points are uncorrected. Ir spectra were recorded on a Hitachi EPI G-2 spectrophotometer, uv spectra on a Hitachi 124 spectrophotometer, nmr spectra on a Hitachi R-20A spectrometer, and mass spectra on a Hitachi RMU-6D mass spectrometer operating at 70 eV. Preparative tlc was carried out on Merck Alumina PF_{254}.

3-Phenylindazole (V).

A solution of I (107 mg.) in ethanol (5 ml.) and 10% potassium hydroxide (5 ml.) was heated under reflux for 3 hours. The solution was concentrated to about 5 ml., neutralized with acetic acid, and extracted with chloroform. The extract was dried over sodium sulfate, concentrated, and the residual solid was purified by preparative tlc on alumina with chloroform followed by recrystallization from petroleum ether (b.p. 60-80°) to give white crystals of V, yield, 55 mg. (86%), m.p. 118-118.5° [lit. (11) 115-116°], which was identified by mixed melting point determination and the ir spectral comparison with an authentic sample.

1-Benzoylamino-2-oxo-3-phenylquinoxaline (IX).

Using a similar procedure as described above for V, II (103 mg.) gave white crystals of IX, m.p. 221-222° (from benzene), yield, 29 mg. (27%); ir (potassium chloride) cm^{-1} 3300, 1680, 1645; nmr (deuteriochloroform) δ 9.46 (s, 1H, NHCOPh), 7.20-8.75 (m, 14H, aromatic H). The mass spectrum showed the parent peak at m/e 341 (Calcd. 341).

Anal. Calcd. for $C_{21}H_{15}N_3O_2$: C, 73.89; H, 4.43; N, 12.31. Found: C, 74.10; H, 4.12; N, 12.15.

Similar treatment of II (103 mg.) under a stream of oxygen increased the yield of IX to 40%.

2-Benzoylamino-1-oxo-4-phenylphthalazine (XIII).

Using a similar procedure as described for V, III (103 mg.) gave white crystals of XIII, m.p. 258-260° (from benzene), yield, 53 mg. (49%); ir (potassium chloride) cm^{-1} 3200, 1680, 1650; nmr (deuteriochloroform) δ 9.22 (s, 1H, NHCOPh), 7.20-8.60 (m, 14H, aromatic H). The mass spectrum showed the parent peak at m/e 341 (Calcd. 341).

Anal. Calcd. for $C_{21}H_{15}N_3O_2$: C, 73.89; H, 4.43; N, 12.31. Found: C, 73.94; H, 4.05; N, 12.38.

2-Cyano-3-phenylquinoxaline (XV).

To a stirred solution of II (112 mg.) in methanol (10 ml.) was added dropwise a solution of potassium cyanide (112 mg.) in water (1 ml.) and one drop of 10% potassium hydroxide solution. After stirring for 3 hours at room temperature, the mixture was concentrated and extracted with chloroform and the dried extract was evaporated. The residue was passed through a short column of alumina with benzene and the eluate was concentrated to give white crystals which were recrystallized from benzene-petroleum ether (b.p. 60-80°) to give XV, 75 mg. (93%), m.p. 163-164° [lit. (2) 163°].

1-Cyano-4-phenylphthalazine (XVII).

Using a similar procedure as described for XV, III (105 mg.) gave white crystals of XVII, yield, 63 mg. (75%), m.p. 185-185.5° [lit. (3) 180-182°].

General procedure for 1,3-Dipolar Cycloaddition with Acetylenic Esters. Formation of (XVIII, XIX, XXI, and XXII).

A solution of I or III (0.33 mmole) and dimethyl acetylenedicarboxylate or ethyl propiolate (0.66 mmole) in toluene (5 ml.) was heated under reflux. The mixture was evaporated under reduced pressure and the residue was purified by preparative tlc on alumina using benzene or chloroform as solvent followed by recrystallization. The elemental analysis, yield, reaction time and physical data are summarized in Tables I and II.

2,3-Dimethoxycarbonyl-8-phenylpyrazolo[5,1-*a*]phthalazine (XX).

A solution of XVIII (30 mg.) in mesitylene (5 ml.) was heated under reflux for 25 hours and concentrated under reduced pressure. The residue was recrystallized from benzene-petroleum ether (b.p. 60-80°) to give white crystals of XX, yield, 6 mg. (26%), m.p. 203-204° [lit. (6) 203-204°].

2-Phenyl-3-(1,2-dimethoxycarbonyl-2-benzamido)ethenylquinoxaline (XXIV).

A solution of II (108 mg.) and dimethyl acetylenedicarboxylate (71 mg.) in toluene (5 ml.) was heated under reflux for 5 hours. The mixture was evaporated to dryness under reduced pressure and the residue was purified by preparative tlc on alumina with ether-petroleum ether (b.p. 30-60°) (1:1). The product was recrystallized from benzene-petroleum ether (b.p. 60-80°) to give white crystals of XXIV (55 mg., 35%), m.p. 150-151°; ir (chloroform): cm^{-1} 1745 and 1680; nmr (deuteriochloroform): δ 12.01 (br. s., 1H, NHCOPh), 7.20-8.30 (m, 14H, aromatic H), 3.73 and 3.31 (2 x s, 2 x 3H, 2 x CO_2CH_3). The mass spectrum showed the parent peak at m/e 467 (Calcd. 467).

Anal. Calcd. for $C_{27}H_{21}N_3O_5$: C, 69.37; H, 4.53; N, 8.99. Found: C, 69.27; H, 4.63; N, 9.01.

General Procedure for 1,3-Dipolar Cycloaddition with Maleimides. Formation of (XXV-XXX).

A solution of I-II (0.3 mmole) and *N*-phenyl- or *N*-methylmaleimide (0.4 mmole) in chloroform (10 ml.) was heated under reflux. The reaction mixture was evaporated under reduced pressure and the residue was recrystallized to give XXV-XXX. The elemental analysis, yield, reaction time, and physical data are summarized in Tables I and II.

N-Methylsuccinimide.

To an ice-cooled solution of succinimide (2 g.) and potassium hydroxide (1.2 g.) in water (10 ml.) was added methyl iodide (3.4 g.). After stirring for 2 hours at room temperature the reaction mixture was extracted with chloroform and the extract was dried over sodium sulfate and concentrated. The residue was purified by chromatography (alumina-chloroform) followed by recrystallization from petroleum ether (b.p. 60-80°) to give white needles of *N*-methylsuccinimide, yield, 400 mg. (18%), m.p. 70-70.5° [lit. (12) 66°]; nmr (deuteriochloroform): δ 2.22 (s, 4H, CH_2 x 2), 2.98 (s, 3H, NCH_3).

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