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Studies of Acyl and Thioacyl Isocyanates. X.[1] The Cycloaddition Reaction of Benzoyl and Thiobenzoyl Isocyanates with Benzaldazines

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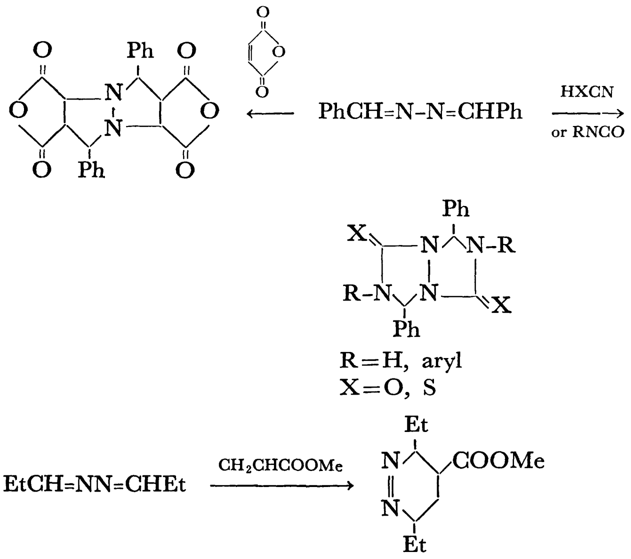
Although benzoyl isocyanates do not react with benzaldazines at room temperature, the criss-cross cycloadducts are formed if the reaction is carried out in refluxing xylene. On the other hand, thiobenzoyl isocyanate behaves quite differently toward the same azines. It reacts easily with azines at room temperature to afford to mono- or the bis(4+2) cycloadducts depending on the nature of the substituent in the azines. We found that the mono (4+2) cycloadduct can be thermally dissociated into its components. Neither benzoyl isocyanate nor thiobenzoyl isocyanate react with aromatic ketazines.

Azines having the conjugated system C=N–N=C exhibit a curious behavior toward cycloaddition reactions. Benzaldazines react with cyanic acid,[2] thiocyanic acid,[2,3] isocyanates,[3] maleic anhydride[4,5] and methyl acrylate[6] to form the corresponding criss-cross cycloadducts. On the other hand, the reaction of propionaldazine with methyl acrylate affords a Diels-Alder type adduct;[6] in this case the aldazine behaves as a diene (Scheme 1).



Scheme 1

Benzoyl (I) and thiobenzoyl isocyanates (II) react with the C=N bonds of anils[7,8] and carbodiimides[9] to give the (4+2) and/or (2+2) cycloadducts. Accordingly, in the reaction of acyl isocyanate with azines, we might expect the formation of a criss-cross cycloadduct or Diels-Alder adduct, besides mono- or bis(4+2) or (2+2) cycloadduct of C=N bonds of azines. However, no study has been reported on the addition of acyl isocyanate to azines. As part of the investigation of the chemistry of I and II with compounds having a C=N bond, their reaction with aromatic azines was studied.

Results and Discussion

Reaction of Benzoyl Isocyanates with Benzaldazines. Although no reaction of benzoyl isocyanate (Ia) with benzaldazine (IIIa) took place at room temperature, Ia reacted with IIIa in refluxing xylene to afford a 2 : 1 adduct IVa in 58% yield. The IR spectrum of IVa showed bands ascribable to $\nu_{C=O}$ at 1760 and 1680 cm^{-1}. The NMR spectrum in deuteriochloroform ($CDCl_3$) exhibited a singlet (2H) assignable to two equivalent methine protons at δ 7.20 ppm, besides signals of aromatic protons. The mass spectrum showed the parent peak (M^+) at *m/e* 502, together with major peaks at *m/e* 397 (M^+—PhCO), 355 (M^+—PhCONCO), 278 (355^+—Ph), 250 (278^+—CO), 208 ([Ph-CH=N-N=CH-Ph]$^+$), 147 ([PhCONCO]$^+$) and 105 ([PhCO]$^+$).

Hydrolysis of IVa with hydrochloric acid afforded hydrazodicarbonamide (V) and benzaldehyde. The structure of V was confirmed by spectral data and elemental analysis as well as by comparison with an authentic sample prepared from urea and hydrazine hydrate;[10] benzaldehyde was identified as its 2,4-dinitrophenylhydrazone (Scheme 2). It is thus deduced that the most reasonable structure for IVa of the possible 2 : 1 cycloadducts, including bis (2+2), (4+2) and mixed cycloadducts, is the criss-cross cycloadduct.

Benzoylation of the criss-cross cycloadduct VI[2] prepared from IIIa and cyanic acid, with benzoyl chloride in pyridine afforded perhydro-2,6-dibenzoyl-1,5-diphenyltriazolo[1,2-a]triazole-3,7-dione (IVa), as shown in Scheme 2.

Similar reactions of benzoyl isocyanates (Ia-Id) with benzaldazines (IIIa—IIIe) gave the corresponding criss-cross cycloadducts IV. The yields, physical properties and results of elemental analyses of IV are summarized in Table 1.

We see that the yield of IV is affected by the nature of the substituents R^1 and R^2. The stronger the

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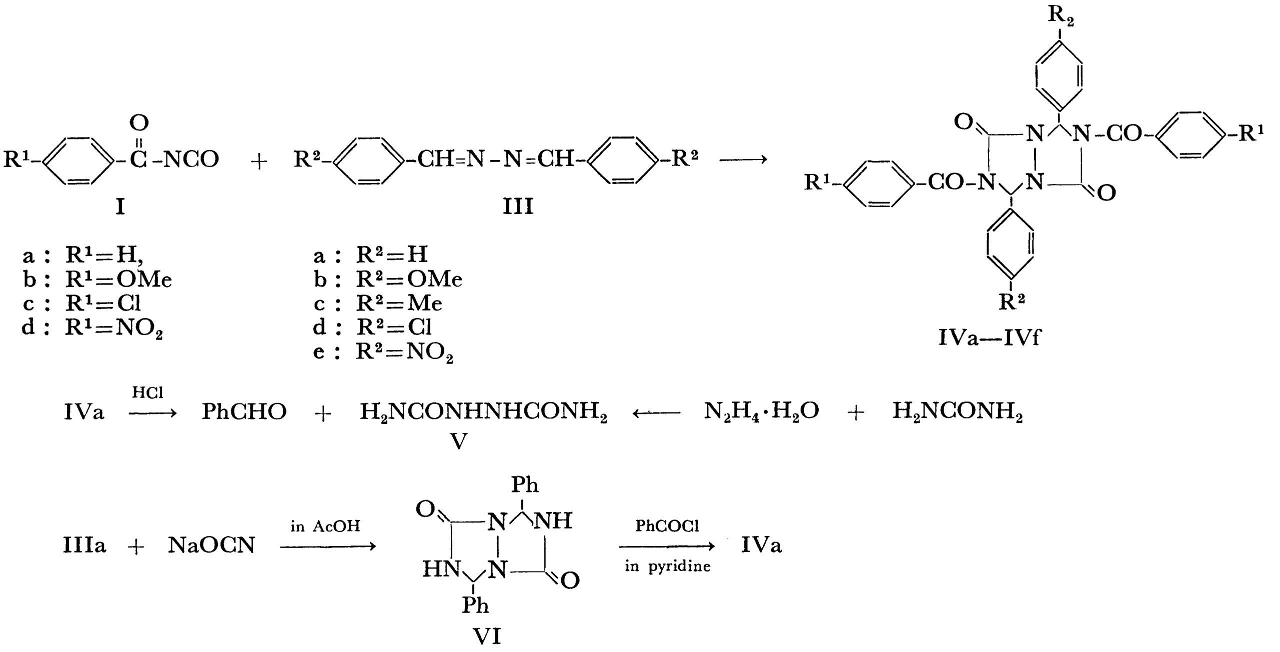


Scheme 2

Table 1. Perhydro-2,6-diaroyl-1,5-diaryltriazolo[1,2-a]triazole-3,7-diones IV[a)]

IV			Reaction time,[b)] hr	Yield, %	Mp, °C	IR, cm^{-1} $\nu_{C=O}$	NMR (CDCl$_3$) >CH δ ppm	Microanalysis, %					
								Found			Calcd		
	R¹	R²						C	H	N	N	N	N
a	H	H	23	58	130.5—131 (decomp.)	1760, 1680	7.20	71.68	4.59	11.03	71.78	4.41	11.15
b	H	OMe	20	82	202—203	1760, 1690	7.11	68.52	4.75	9.95	68.32	4.66	9.96
c	H	Me	24	72	193—193.5	1760, 1680	7.15	72.51	5.04	10.74	72.44	4.94	10.56
d	H	Cl	48	34	200.5—201	1770, 1680	7.19	63.29	3.37	9.43	63.10	3.54	9.81
e	Cl	H	24	62	224—225	1770, 1690	7.21	63.43	3.47	9.69	63.10	3.54	9.81
f	NO$_2$	H	26	92	240—241 (decomp.)	1770, 1690	7.13	61.15	3.52	13.96	60.81	3.40	14.19

a) All the compounds are colorless prisms. b) Reaction temperature: 140°C. Reaction of Ia with IIIe (24 hr) and of Ib with IIIa (48 hr) did not take place.

electron-donating nature of substituent R² in III, the higher the yield of IV, while the effect of substituent R¹ in I on the yield is the reverse: although Ia and Ib did not react with IIIe and IIIa, respectively, the reactions of Ia with IIIb and of Id with IIIa gave excellent yields of IV. On the other hand, I did not react with aromatic ketazines such as acetophenone and benzophenone azines under similar conditions.

Reaction of Thiobenzoyl Isocyanate with Benzaldazines. In contrast with benzoyl isocyanates (I), thiobenzoyl isocyanate (II) reacted easily with benzaldazine (IIIa) at room temperature to afford a quantitative yield of the 1 : 1 adduct VIIa. The IR spectrum of VIIa showed no bands assignable to ν_{NH}, but displayed bands of $\nu_{C=O}$ and $\nu_{C=N}$ at 1680, 1660 and 1650 cm^{-1} respectively; it is very similar to that of the (4+2) cycloadduct[8)] of II to benzylidenaniline. In the NMR spectrum (CDCl$_3$) singlets appeared at δ 6.42 (1H, >CH) and 9.48 ppm (1H, –CH=N–), besides signals of aromatic protons.

Thus, VIIa was deduced to be 3-benzylidenamino-2,6-diphenyl-2*H*-1,3,5-thiadiazin-4(3*H*)-one, whose structure corresponds to the (4+2) cycloadduct of II to one C=N bond of IIIa.

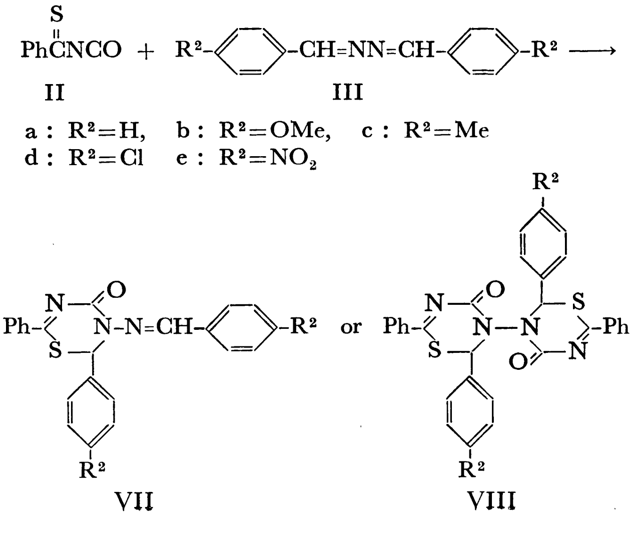


Table 2. Mono- and bis-2*H*-1,3,5-thiadiazin-4(3*H*)-ones VII and VIII.[a)]

	R^2	Mp, °C	Yield, %	IR, cm^{-1}		Microanalysis, %					
						Found			Calcd		
				$\nu_{C=O}$	$\nu_{C=N}$	C	H	N	C	H	N
VIIa	H	148—149 (decomp.)	100	1680 1660	1650	71.05	4.45	11.24	71.15	4.61	11.32
VIIIb-1	OMe	181 (decomp.)	50	1690 1670	1645	64.96	4.11	9.08	64.64	4.41	9.42
VIIIb-2	OMe	141—142	39	1700 1670	1650	65.13	4.26	9.22	64.64	4.41	9.42
VIIIc	Me	201 (decomp.)	62	1690 1675	1650	68.28	4.68	9.72	68.32	4.66	9.96
VIId[b)]	Cl	165—168 (decomp.)	80	1670	1655	60.31	3.11	9.27	60.00	3.41	9.55

a) All the compounds are colorless needles. b) NMR δ ppm: 6.41 (1H, singlet, >**CH**), 9.52 (1H, singlet, -**CH**=N-) in $CDCl_3$; 7.07 (1H, singlet, >**CH**), 8.75 (1H, singlet, -**CH**=N-) in CF_3COOH.

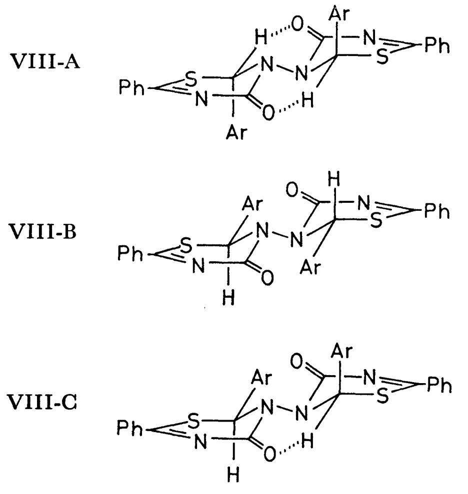
In similar reactions of II with azines IIIb—IIId, a 1 : 1 or a 2 : 1 adduct was formed, depending on the nature of substituent R^2 in III. When R^2 is electron-donating such as methoxy or methyl, the 2 : 1 adduct VIII was obtained, while the 1 : 1 adduct VIId was only formed if R^2 is electron-withdrawing such as chlorine. However, the reaction with IIIe having nitro groups did not take place even under forced conditions. The results are summarized in Table 2.

The structures of 1 : 1 adduct VIId, and of 2 : 1 adducts VIIIb and VIIIc were confirmed to be those of the corresponding mono(4+2) and bis(4+2) cycloadducts of II to one and both C=N bonds in III on the basis of spectral studies. In spite of having a second C=N bond to which to add, II did not react further with the 1 : 1 adduct VII under more forced conditions (at 50°C for 5 min and then at room temperature for 3 hr); instead the unchanged 1 : 1 adduct was recovered almost quantitatively.

The NMR spectrum of VIIIc indicated that its configuration is symmetrical; singlets attributable to two equivalent methyl and methine protons appeared at δ 2.25 and 6.22 ppm in $CDCl_3$, and at δ 2.35 and 6.79 ppm in trifluoroacetic acid (CF_3–COOH), respectively.

On the other hand, two stereoisomers VIIIb-1 and VIIIb-2 were obtained in the reaction with IIIb. Their NMR spectra could not be measured in the same solvent, because VIIIb-1 is insoluble in $CDCl_3$ and VIIIb-2 decomposed in CF_3COOH. The NMR spectrum of VIIIb-1 in CF_3COOH showed two singlets at δ 3.89 (6H, OCH_3) and 6.81 ppm (2H, >**CH**), while four singnlets appeared at δ 3.77, 3.81 (each 3H, OCH_3) and 5.35, 6.59 ppm (each 1H, >**CH**) in the NMR spectrum of VIIIb-2 ($CDCl_3$). This indicates that the configuration of VIIIb-1 is symmetrical, while that of VIIIb-2 is asymmetrical.

Dreiding models of VIII show that the free rotation of N^3–$N^{3'}$ bond is hindered by the steric interaction between the 2- or 2′-aryl group and 4′- or 4-carbonyl group. Thus, two isomers resulting from the configurations of 2- and 2′-aryl groups are possible for symmetrical 2 : 1 adduct VIIIb-1 or VIIIc: one (VIII-A) in which both 2- and 2′-aryl groups are quasi-axial, and the other (VIII-B) in which they are quasi-equatorial. However, it is conceivable that VIII-A is more favorable since there is a significant repulsion between 2- or 2′-aryl group and 4′- or 4-carbonyl group in VIII-B (Fig. 1).


VIII-A

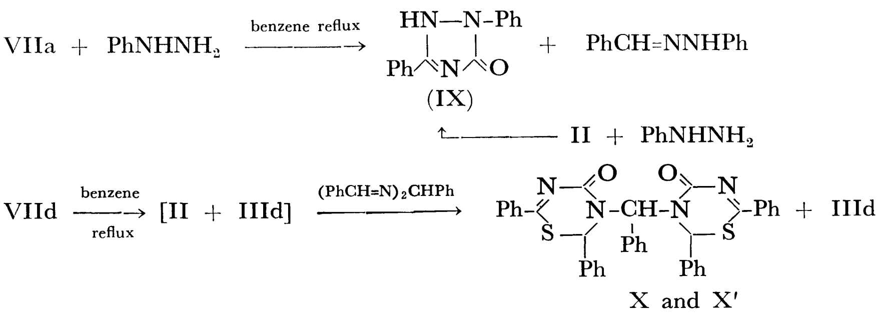
VIII-B

VIII-C

Fig. 1.

On the other hand, the configuration VIII-C in which 2- and 2′-aryl groups are quasi-equatorial and quasi-axial, respectively, is only possible for asymmetrical 2 : 1 adduct VIIIb-2. In this case, there is a steric interaction between 2-aryl group and 4′-carbonyl group, and the rotation of N^3–$N^{3'}$ bond should occur to attain minimum steric hindrance.

The singlet of methine protons of VIIIc is shifted to a lower field by about 0.6 ppm, in changing from $CDCl_3$ to CF_3COOH. If the value of the shift is applied to the methine protons of VIIIb-1, a singlet should appear at δ ca. 6.2 ppm in $CDCl_3$. Consequently, the singlets at 5.35 and 6.59 ppm in VIIIb-2 could be assigned to the 2-quasi-axial and 2′-quasi-equatorial hydrogens, respectively. The shift of equatorial hydrogens to a lower field can be explained in terms of hydrogen bonding with the carbonyl group in the adjacent ring as shown in Fig. 1. Isolation of the 2 : 1 adduct of type VIIIb-2 was unsuccessful, probably owing to its instability.



Scheme 3.

It is of interest to note that II behaves quite differently from I toward benzaldazines, although just as in the case of I, no reaction took place with aromatic ketazines.

Thermal Dissociation of Mono(4+2) Cycloadducts VII. The 1 : 1 adducts VII decomposed at their melting points and changed to reddish violet substances. When a solution of VII in dry benzene was heated to reflux, it gradually turned red. Upon cooling, the red color disappeared, the solution becoming colorless. This suggests that VII could be thermally dissociated into its components, since the benzene solution of II is reddish violet. We established thermal dissociation by the following experiments.

Phenylhydrazine reacted with VIIa in refluxing benzene to give 2,3-dihydro-2,5-diphenyl-1,2,4-triazol-3(1*H*)-one (IX) and the phenylhydrazone of benzaldehyde,[11] although hardly any reaction took place at room temperature. The structure of IX was confirmed by comparison with an authentic sample prepared from II and phenylhydrazine.[12] When VIId was treated with hydrobenzamide in refluxing benzene, two isomeric bis(4+2) cycloadducts X and X′[8] of II to hydrobenzamide and *p*-chlorobenzaldazine IIId were obtained (Scheme 3).

Experimental

All melting points are uncorrected. The IR spectra were measured as KBr pellets on a JASCO IR-S spectrophotometer; the NMR spectra were determined at 60 MHz on a Hitachi R-20 NMR spectrometer with TMS as an internal reference. The mass spectra were obtained on a Hitachi RMS-4 mass spectrometer with a direct inlet and an ionization energy of 70 eV. Elemental analyses were carried out by Miss M. Akita.

Materials. Benzoyl isocyanates (Ia–Id) were prepared by the method reported previously.[13] Thiobenzoyl isocyanate (II):[12] a solution of 1.0 g of 2-phenylthiazoline-2,4-dione[14] in 10 m*l* of xylene was heated at 120°C, producing a reddish violet solution of II. This is referred as the standard solution of II. Benzaldazines were prepared from the corresponding aldehydes and hydrazine hydrate in acetic acid. Benzaldazine (IIIa), mp 93°C (lit,[15] mp 93°C); *p*-methoxy- (IIIb), mp 169—170°C (lit,[16] mp 170—172°C); *p*-methyl- (IIIc), mp 153°C (lit,[17] mp 153°C); *p*-chloro- (IIId), mp 207—208°C (lit,[16] mp 208°C); *p*-nitrobenzaldazine (IIIe), mp 296—297°C (lit,[18] mp 297—298°C).

Reaction of Benzoyl Isocyanates (I) with Benzaldazines (III). The procedure is illustrated by a reaction of benzoyl isocyanate (Ia) with benzaldazine (IIIa).

A solution of 2.0 g of Ia and 1.4 g of IIIa in 15 m*l* of dry xylene was refluxed in an atmosphere of nitrogen for 23 hr, and the reaction mixture was allowed to stand at room temperature for 2 days, during which time crystals deposited. Filtration gave 1.18 g of colorless crystals. The filtrate was evaporated *in vacuo* to leave resinous materials, which solidified on trituration with petroleum ether to yield 0.78 g of crystals. Recrystallization of the combined crystals (1.96 g (58%)) from petroleum ether (bp 45—65°C) gave perhydro-2,6-dibenzoyl-1,5-diphenyltriazolo[1,2-b]triazole-3,7-dione (IVa), mp 130.5—131°C (decomp.), as colorless prisms.

Similarly, the reaction of benzoyl isocyanates (Ia—Id) with benzaldazines (IIIa—IIIe) gave the corresponding criss-cross cycloadduct IV. However, Ia and Ib did not react with IIIe and IIIa, respectively. The reaction conditions and yields, physical porperties and results of elemental analyses are summarized in Table 1.

Hydrolysis of Criss-cross Cycloadduct IVa. A suspension of 0.4 g of IVa in 20 m*l* of concentrated hydrochloric acid was stirred at 100°C for 3 hr. After cooling, it was filtered to recover 0.17 g (40%) of unreacted IVa. Evaporation of the filtrate *in vacuo* left a residue, which was washed with a small amount of water and then recrystallized from water to afford 55 mg (58%) of hydrazodicarbonamide (V), mp 255.5°C (decomp.) (lit,[10] mp 244—245°C (decomp.)), as colorless prisms. The compound was identical with an authentic sample prepared from hydrazine hydrate and urea.[10]

Found: C, 20.10; H, 4.90; N, 47.71%. Calcd for $C_2H_6N_4O_2$: C, 20.34; H, 5.12; N, 47.44%.

From the washings, benzaldehyde was identified to be its 2,4-dinitrophenylhydrazone.

Preparation of IVa. To a stirred solution of 4.5 g of IIIa in 30 m*l* of acetic acid was added 5.25 g of sodium cyanate at room temperature over a period of 15 min. After the reaction mixture had been stirred for 30 min at the same temperature, it was then poured into 100 m*l* of water. Filtration gave 4.8 g (76%) of perhydro-1,5-diphenyltriazolo[1,2-a]triazole-3,7-dione (VI), mp 235°C (decomp.) (lit,[2]

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[11] The formation of the hydrazone indicates that benzaldazine IIIa generated by dissociation was hydrolyzed to benzaldehyde.

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mp 234°C (decomp.)), as pale yellow prisms. A mixture of 0.5 m*l* of benzoyl chloride and 0.5 g of VI in 10 m*l* of pyridine was stirred at room temperature for 18 hr. It was then poured into water to precipitate a colorless solid, which on recrystallization from petroleum ether (bp 45—65°C) afforded 0.85 g (99.5%) of IVa, mp 130.5—131°C (decomp.).

Reaction of Thiobenzoyl Isocyanate (II) with p-*Methoxybenzaldazine (IIIb).* The standard solution of II was stirred with 0.7 g of IIIb at 50°C for 30 min. Filtration gave 0.78 g (50%) of bis(4+2) cycloadduct VIIIb-1. The analytical sample was prepared by recrystallization from xylene.

The filtrate was evaporated *in vacuo* to leave isomeric bis(4+2) cycloadduct VIIIb-2, which was recrystallized from benzene-petroleum ether (bp 45—65°C).

Similarly, the reaction of II with IIIa, IIIc and IIId gave the corresponding mono(4+2) cycloadducts VIIa, VIId and bis(4+2) cycloadduct VIIIc, respectively, while II did not react with IIIe. The yields, physical properties and results of elemental analyses of VII and VIII are given in Table 2.

Reaction of VIIa with Phenylhydrazine. A solution of 0.1 g of VIIa and 5 drops of phenylhydrazine in 10 m*l* of dry benzene was refluxed for 30 min, during which time 40 mg (63%) of 2,3-dihydro-2,5-diphenyl-1,2,4-triazol-3(1*H*)-one (IX), mp 230—231°C, precipitated. Compound IX was identical with an authentic sample, mp 230–231°C,[12] prepared from II and phenylhydrazine. The filtrate was concentrated *in valuo* to give 0.11 g (95%) of phenylhydrazone of benzaldehyde, identical with an authentic sample.

Reaction of VIId with Hydrobenzamide. A solution of 0.2 g of VIId and 0.1 g of hydrobenzamide in 15 m*l* of dry benzene was refluxed for 1 hr. The crystalline precipitate was filtered and washed with hot benzene to leave 80 mg (30%) of bis(4+2) cycloadduct X, mp 208—209°C (decomp.).[8] The filtrate was evaporated *in vacuo* to give a mixture of 40 mg of azine IIId and 80 mg (30%) of isomeric bis(4+2) cycloadduct X', mp 186°C,[8] which were separated by extraction with carbon tetrachloride. Evaporation of benzene washings afforded 50 mg of azine IIId; the total yield of azine IIId is 90 mg (72%).

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