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Studies on Pyridazines. XXVI.[1] The Reaction of Substituted N-Acetyliminopyridazinium Ylides with Benzyne

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Reaction of N-acetyliminopyridazinium ylide (3) with benzyne afforded 1,3-dipolarcycloadduct (4). Photolysis of the cycloadduct (4), having alkoxy group in the 3-position of the pyridazine ring, afforded α-alkoxynaphthalene (5), and 3-(2-acetoamidophenyl)pyridazine (7). Photolysis of **4a** did not give naphthalene, but afforded indazolo[2,3-*b*]pyridazine (**6**). Reaction of **4** with base afforded 3-vinylindazole (**8**), indazolo[2,3-*b*]4,5-dihydropyridazine (**9**). Reaction of 2H-pyridazinone 1-oxide (**22**) with benzyne afforded the 1,3-cycloadduct (**23**), followed by fission of N–O bond to give pyridazinone substituted with 2-hydroxyphenyl group (**24**). The reaction mechanisms are also discussed.

Keywords——1,3-dipolarcycloadduct of N-acetyliminipyridazinium ylide with benzyne; photolysis of the 1,3-cycloadduct; reaction of the 1,3-cycloadduct with base; reaction of 2H-pyridazinone 1-oxide with benzyne; reaction mechanisms

Though the 1,3-dipolarcycloaddition of pyridazinium ylides with acetylene dicarboxylate[3-5] and tetracyanoethylene[3,6] have been extensively studied, the addition with benzyne has not yet been known.

In a previous paper we have reported that the reaction of pyridazine N-oxides with benzyne afforded 1-benzoxepines in moderate yields, by elimination of molecular nitrogen. Also, we have presented the interesting results that the reaction of N-acetylimino ylide and dicyanomethylide of unsubstituted pyridazine with benzyne gave 1,3-cycloadducts, not obtained previously in pyridazine series, and described their behavior towards photolysis and thermolysis.

In present paper we describe the reaction of various N-acetylimino ylides of substituted pyridazines with benzyne, affording the 1,3-cycloadducts. Then, the photolysis and the reaction with base of the 1,3-adduct, having alkoxy group in the 3-position of the pyridazine ring, showed different reactivity from those having hydrogen atom or methyl group in the 3-position of the pyridazine ring.[7]

Synthesis of N-Acetyliminopyridazinium Ylide (3) and the 1,3-Cycloadduct (4)

Various substituted pyridazines (**1**) were N-aminated with O-mesitylenesulfonylhydroxylamine in methylene chloride, followed by acetylation with acetic anhydride. Treatment of the acetates with base (K_2CO_3) afforded N-acetyliminopyridazinium ylides (**3**) in 50—70% yields. Reaction of **3** with benzyne,[8] prepared from anthranilic acid, afforded the 1,3-adducts (**4**) in high yields.

However, the reaction of the ylides (**3e, f**) with benzyne failed to isolate the cycloadducts (**4e, f**). In case of **3e**, nitrogen atom of the substituent piperidine group in the 3-position of

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1) Part XXV: H. Igeta, C. Kaneko, and T. Tsuchiya, *Chem. Pharm. Bull.* (Tokyo), 23, 2797 (1975).
2) Location: *Hatanodai 1-5-8, Shinagawa-ku, Tokyo, 142, Japan.*
3) Y. Kobayashi, T. Kutsuma, and K. Morinaga, *Chem. Pharm. Bull.* (Tokyo), 19, 2106 (1971).
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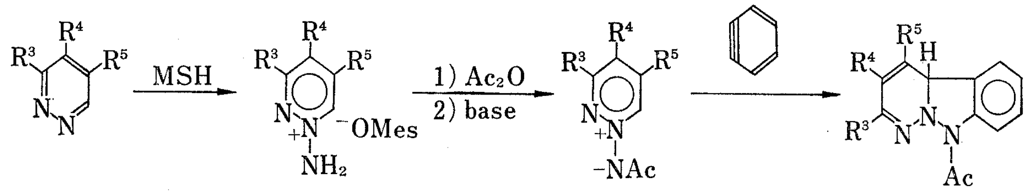
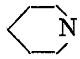
6) T. Sasaki, K. Kanematsu, Y. Yukimoto, and S. Ochiai, *J. Org. Chem.*, 36, 813 (1971).
7) H. Igeta, H. Arai, H. Hasegawa, and T. Tsuchiya, *Chem. Pharm. Bull.* (Tokyo), 23, 2971 (1975).
8) G.A. Reynolds, *J. Org. Chem.*, 29, 3733 (1964).

Table I. Yields of Reaction Products (2), (3) and (4) (%)



1 2 3 4

	R^3	R^4	R^5	2	3	4
a	Me	H	H	89	50	90
b	OMe	H	H	85	75	91
c	OEt	H	H	79	77	83
d	Ph	H	H	75	67	89
e		H	H	74	70	—[a]
f	OMe	Me	H	50	45	—[b]
g	OMe	H	Me	87	60	87

a) 3-Piperidino-6-(2-acetanilino)-pyridazine was yielded with 8%

b) recovery of the starting material (**3f**) and polymeric mixture

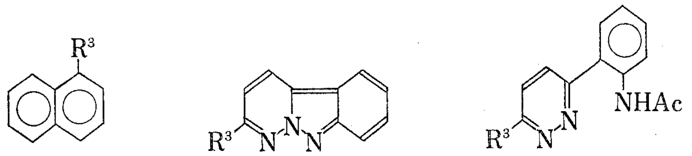
the pyridazine ring might be stronger electron donor than alkoxy group in the same position, producing predominently 3-(2-acetoamidophenyl)-pyridazine (**7**). In case of **3f**, the dipolar character might be reduced by a contribution of hyperconjugation of the methylgroup,hence the reactivity of the ylide might be diminished, resulting in the difficulty of the reaction with benzyne. Actually the reaction of 4-methyl- and 3,6-dimethyl-N-acetyliminopyridazinium ylides with benzyne resulted in the recovery of the starting materials, similar to the case of **3f.**

Reaction of the 1,3-Cycloadduct (4)

We have reported that photolysis of the unsubstituted 1,3-cycloadduct afforded indazolo-[2,3-*b*]pyridazine, 2,3-cyclobutenyl-1-acetyl-2,3-dihydroindole, and 1-acetylindole.[7]

Now, we carried out the photolysis of the 1,3-cycloadduct, having alkoxy groups **4b**: R^3=OMe and **4c**: R^3=OEt). The reaction proceeded by elimination of molecular nitrogen to give α-alkoxynaphthalene (**5**) and by aromatization to give 3-(2-acetoamidophenyl)-pyridazine (**7**) in the yields shown in Table II. Photolysis of **4a** did not give the compound corresponding to **5**, but afforded **6** as a major product.

Table II. Photolysis Products of Cycloadducts (4) (%)



5 6 7

Compound	5	6	7
4b	37	2	27
4c	15	16	37

Reaction of the cycloadducts (**4b** and **4d**) with sodium methoxide in methanol at 0—5° for 1 hr afforded 3-vinylindazole (**8**),[9] indazolo[2,3-*b*]4,5-dihydropyridazine (**9**), and **7**. In

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9) J. Kurita and T. Tsuchiya, *J.C.S. Chem. Comm.*, 1974, 936.

addition, the nitrile (**4d**: Ph–CN) was obtained.[10] These facts would support the mechanism for the formation of **8** as shown in Chart 2.

Furthermore, **9b** could be readily oxidized by DDQ (2,3-dichloro-5,6-dicyano-*p*-benzoquinone) to give **6b**.

Table III. Reaction Products of Cycloadducts (**4**) with Sodium Methoxide

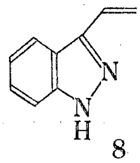
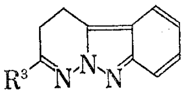
Compound	 8	 9	**7**	R^3-CN
4b	8	82	1—2	—
4d	45	7	35	*ca.* 20

Table IV. Spectral and Analytical Data of **4**

	IR ν_{CO} (cm^{-1})	MS(M$^+$) *m/e*	Analysis Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
4a	1690	227	68.70	5.77	18.49	68.89	5.81	18.27
4b	1670	243	64.18	5.39	17.28	64.01	5.31	17.40
4c	1690	257	65.35	5.88	16.33	65.15	5.81	15.14
4d	1690	289	74.72	5.23	14.53	74.86	5.27	14.41
4g	1680	257	65.35	5.88	16.33	65.56	5.72	16.11

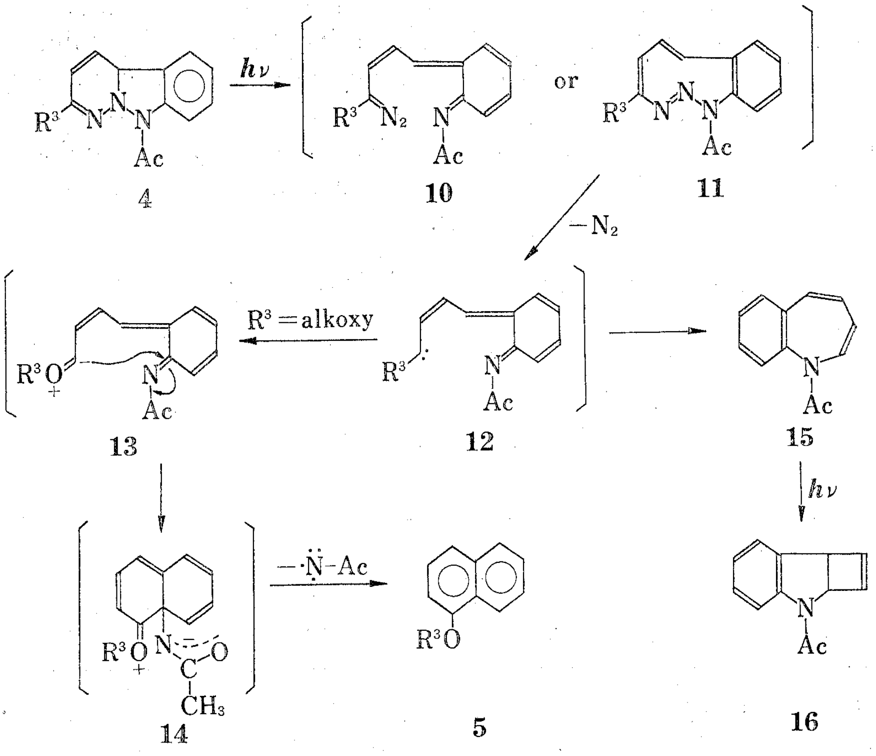


Chart 1

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[10] Cycloadduct of unsubstituted pyridazinium ylide (R^3=H) gave indazole (**8**) and also HCN.[7]

The formation mechanisms of the compounds, obtained by photolysis and reaction with base were shown in Chart 1 and 2, respectively. We have already reported that photolysis of the cycloadduct (**4**) of unsubstituted pyridazinium ylide gave benzazepine (**15**) and dihydroindole (**16**).[7] When R^3 was alkoxy group, the contribution of intermediate (**13**) might be predominent to give another intermediate (**14**), followed by elimination of acetyl nitrene and by aromatization to give α-alkoxynaphthalene (**5**). Concerning the formation of **8** and **9** with base, the intermediate (**17**) might be formed by deacetylation with base, followed by fission of N–N bond of the pyridazine ring to give vinylindazole *via* **18**, by elimination of R–CN. Formation of benzonitrile from **4d** suggests the validity of the mechanism through path A. When R^3 was alkoxy group, path B might be preferred to path A on account of predominant contribution of an electronic structure shown as **19**, followed by initial abstraction of the proton from 6-position of the pyridazine ring to form **20** and 1,5-shift of hydrogen atom of NH group to give the dihydrocompound (**9**).

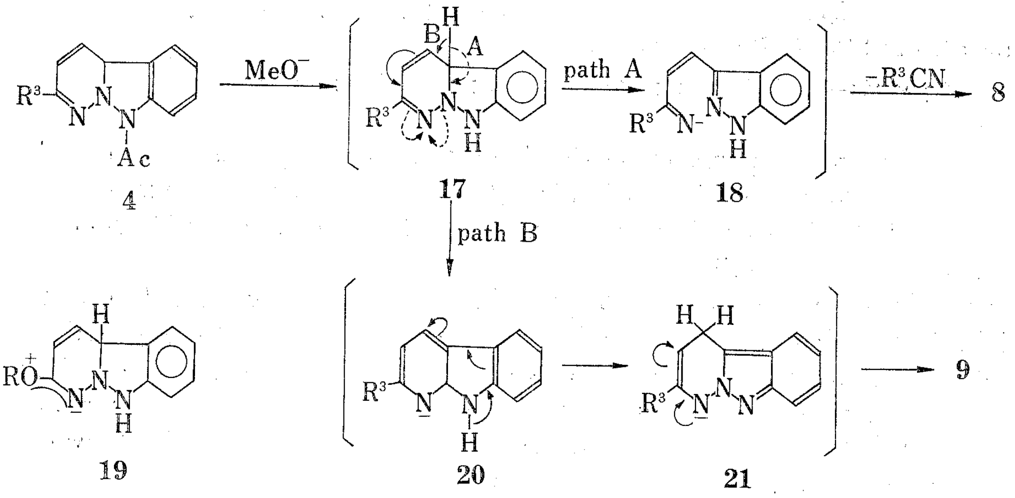
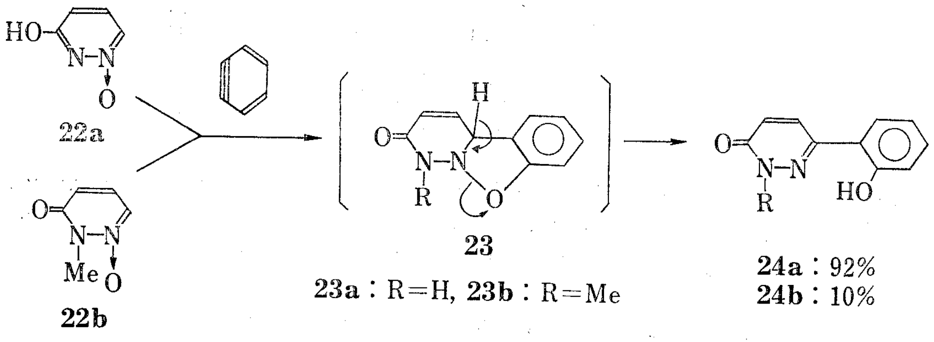


Chart 2

Reaction of 2H-Pyridazinone 1-Oxide (22) with Benzyne

In a previous paper we have reported that reaction of pyridazine 1-oxides with benzyne afforded benzoxepines in fairly high yields.[7] Present paper shows reactions of 3-hydroxypyridazine 1-oxide (**22a**), having hydroxy form,[11] and 2-methylpyridazin-3(2H)-one 1-oxide (**22b**), having keto form, with benzyne. The reaction afforded the cycloadducts (**23**), followed by fission of N–O bond to give pyridazinones substituted with 2-hydroxyphenyl groups (**24a**: 92% and **24b**: 10%), respectively, while the compounds corresponding to benzoxepines and their derivatives were not obtained in these cases.



23a : R=H, **23b** : R=Me

24a : 92%
24b : 10%

Chart 3

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[11] H. Igeta, T. Tsuchiya, M. Nakajima, and H. Yokogawa, *Chem. Pharm. Bull.* (Tokyo), 17, 763 (1969).