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1,3-Dipolar Cycloaddition of Pyridazinium Ylides with Perhalocycloalkenes and Thermal Decomposition of the Adducts

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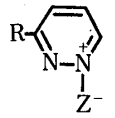
Some pyridazinium *N*-ylides underwent 1,3-dipolar cycloaddition with perhalocyclopropenes and with a perhalocyclobutene. Thermal decomposition and chemical transformations of the pyrolyzed products afforded various hitherto unknown 2-chloropyrazolo[1,5-*b*]pyridazine derivatives.

Keywords——pyridazinium *N*-ylide; pyridazine *N*-acylimine; *N*-acyliminopyridazine; 1,3-dipolar cycloaddition; thermal ring-opening; diazaindolizine; pyrazolo[1,5-*b*]pyridazine; 2-chloropyrazolopyridazine

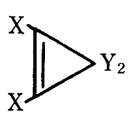
Cyclopropenes and their analogues are well known to give cycloadducts with linear 1,3-dipoles such as diazoalkanes.[1] On the other hand, exocyclic 1,3-dipoles such as heteroaromatic *N*-ylides commonly undergo nucleophilic addition with cyclopropenones and their analogues,[2] and little is known about the 1,3-dipolar cycloaddition of heteroaromatic *N*-ylides with cycloalkenes.

Matsumoto *et al.*[3] and Kascheres *et al.*[4] reported that pyridinium *N*-ylides underwent 1,3-dipolar cycloaddition with cyclopropenones and that the tricyclic adducts were unstable, bicyclic products being obtained as a result of ring opening of the three-membered ring of the adducts and elimination of neutral molecules from the adducts.

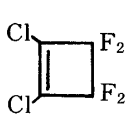
We have described the isolation of 1,3-dipolar cycloadducts between pyridazinium *N*-ylides (**1**)[5] and perhalocycloalkenes (**2** and **3**) in a previous communication.[6] This paper reports experimental details of the cycloaddition and further findings on the pyrolysis of the adducts.



1a: R=H, Z=NCOMe
1b: R=Ph, Z=NCOMe
1c: R=OEt, Z=NCOMe
1d: R=H, Z=NCOPh
1e: R=H, Z=NCO_2Et
1f: R=Ph, Z=NCO_2Et
1g: R=H, Z=$C(CN)_2$



2a: X=Y=H
2b: X=Y=Cl
2c: X=Br, Y=F



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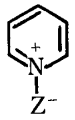


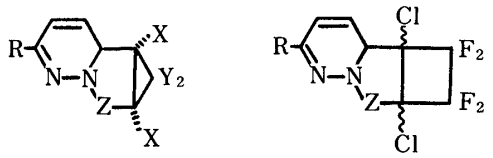
4a: Z=NCOMe
4b: Z=O

Chart 1

First, cyclopropene (**2a**), a strained olefin, failed to react with either pyridazinium *N*-ylides (**1a—g**) or pyridinium *N*-ylides (**4a** and **4b**) under any conditions tested, the starting materials being recovered quantitatively. On the other hand, tetrachlorocyclopropene (**2b**), an

electron-deficient highly strained olefin, reacted with pyridine *N*-acetylimine (**4a**)[7] and pyridine *N*-oxide (**4b**)[8] to give only hydrophilic products which are presumed to be mixtures of quaternary pyridinium salts, and no products derived from the 1,3-dipolar cycloaddition were obtained.[9]

However, when a solution of pyridazine *N*-acetylimine (**1a**) and **2b** in tetrahydrofuran (THF) was allowed to stand at room temperature for 12 h (under N_2), an ether-soluble substance was obtained. It was a crystalline material of mp 151.5 °C (dec.) whose elemental analysis showed the composition of the 1:1 adduct ($C_9H_7Cl_4N_3O$). The infrared (IR) spectrum showed an absorption at 1700 cm^{-1}: (KBr) due to the amide carbonyl, whereas the carbonyl absorption of the acetylimine **1a** was at 1570 cm^{-1}. The ^{1}H-nuclear magnetic resonance (^{1}H-NMR) spectrum (shown in Table I) supported the 1,3-dipolar cycloadduct structure, and an X-ray crystallographic study revealed the compound to be the sterically preferred *exo*-adduct (**5a**; X=Y=Cl, Z=NCOMe) (4aα,4bβ,5aβ)-6-acetyl-4b,5,5,5a-tetrachloro-4a,4b,5a,6-tetrahydro-5*H*-cyclopropa[3,4]pyrazolo[1,5-*b*]pyridazine, as described in the previous communication.[6] The steric isomer (*endo*-adduct) was not obtained. Other combinations of pyridazine *N*-acylimines (**1a—f**) and perhalocyclopropenes (**2b** and **2c**) also afforded the corresponding 1,3-cycloadducts (**5** and **6**). Although the perhalocyclobutene (**3**), which is electron-deficient but whose ring strain is less than that of **2**, showed only low reactivity with **1a—g** as well as with **4a** and **4b**, the reaction of some imines with **3** under reflux



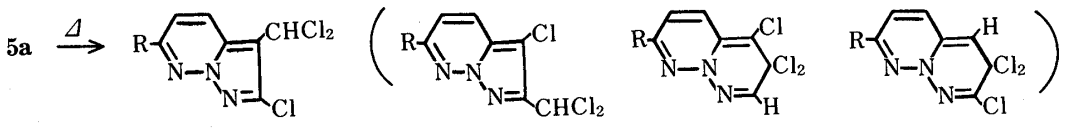
5: X=Y=Cl
6: X=Br, Y=F

7

Chart 2

in benzene gave the adduct (**7**) in low yields (in some cases, large amounts of the starting materials were recovered).[10] Moreover, the reaction of pyridazinium *N*-dicyanomethylide (**1g**) and **2b** afforded the similar adduct 4b,5,5,5a-tetrachloro-4a,4b,5a,6-tetrahydro-5*H*-cyclopropa[3,4]pyrrolo[1,2-*b*]pyridazine 6,6-dicarbonitrile (**5g**; X=Y=Cl, Z=C(CN)$_2$). The yields and some properties of the adducts obtained here are summarized in Table I. The ^{1}H-NMR spectral patterns of these compounds are suggestive of the same configuration (*i.e.*, the *exo* ring junction).

As shown in Table I, some of the adducts were rather unstable and most of **5** and **6** were decomposed at their melting points. Each of the adducts **5** and **6** bears halogen atoms and an acylamide group as eliminatable moieties and is assumed to retain a strain due to the presence of the cyclopropane ring. When **5a** (R=H, X=Y=Cl, Z=NAc) was refluxed in xylene, it afforded a compound (**8a**) as the major product whose composition was $C_7H_4Cl_3N_3$ (*i.e.*, **5a**–CH_3COCl), and the same compound was obtained from the similar decomposition of **5d**. The structures **8$_1$a**, **8$_2$a**, **8$_3$a**, and **8$_4$a** may be considered for **8a**.



8$_1$a: R=H
8$_1$b: R=Ph
8$_1$c: R=OEt

8$_2$a **8$_3$a** **8$_4$a**

Chart 3

TABLE I. 1,3-Dipolar Cycloadducts of Pyridazinium *N*-Ylids with Perhalocycloalkenes

	R	Z	X	Y	Yield (%)[a]	mp (°C)	NMR (δ, J in Hz)[b] 3-H	4-H	4a-H	Other signals		IR (cm^{-1})[c]	Formula	Analysis (%) Calcd (Found) C	H	N
5a	H	NCOMe	Cl	Cl	41	151.5 (dec.)	6.20 (m)	6.20 (m)	4.61 (d, 3.8)	2.24 (CH_3CO)	7.08 (dd, 3.8 and 3.5, 2-H)	1700	$C_9H_7Cl_4N_3O$	34.31 (34.68	2.24 2.24	13.34 13.42)
5b	Ph	NCOMe	Cl	Cl	38	162 (dec.)	6.83 (d, 10.0)	6.44 (dd, 10.0 and 6.0)	4.71 (d, 6.0)	2.33 (CH_3CO)	7.4—7.8 (Ph-H)	1700	$C_{15}H_{11}Cl_4N_3O$	46.06 (45.82	2.84 2.71	10.75 10.69)
5c	OEt	NCOMe	Cl	Cl	27	158 (dec.)	6.13 (d, 11.0)	6.42 (dd, 11.0 and 6.0)	4.59 (d, 6.0)	1.31 and 4.14 (OCH_2CH_3)	2.37 (CH_3CO)	1700	$C_{11}H_{11}Cl_4N_3O_2$	36.39 (36.61	3.09 3.03	11.70 11.76)
5d	H	NCOPh	Cl	Cl	19	150 (dec.)	6.25 (m)	6.25 (m)	4.68 (d, 3.4)	7.4—8.0 (Ph-H)	7.26 (dd, 3.5 and 3.4, 2-H)	1695	$C_{14}H_9Cl_4N_3O$	44.59 (44.60	2.41 2.38	11.15 11.18)
5e	H	NCO_2Et	Cl	Cl	14	Unstable oil	6.21 (m)	6.21 (m)	4.67 (d, 5.0)	1.37 and 4.38 (OCH_2CH_3)	7.10 (br m, 2-H)	1735	$C_{10}H_9Cl_4N_3O_2$	*m/e* Calcd for M^+: 342.945 (Found: 342.944)		
5f	Ph	NCO_2Et	Cl	Cl	5	143.5 (dec.)	6.73 (d, 11.0)	6.36 (dd, 11.0 and 6.0)	4.69 (d, 6.0)	1.40 and 4.38 (OCH_2CH_3)	7.3—7.9 (Ph-H)	1745	$C_{16}H_{13}Cl_4N_3O_2$	45.63 (45.23	3.11 3.05	9.98[d] 10.05)
6a	H	NCOMe	Br	F	44	143 (dec.)	6.25 (m)	6.25 (m)	4.40 (d, 3.0)	2.25 (CH_3CO)	7.14 (dd, 4.0 and 3.0, 2-H)	1700	$C_9H_7Br_2F_2N_3O$	29.13 (29.00	1.90 1.91	11.32 11.11)
6b	Ph	NCOMe	Br	F	34	142.5	6.84 (d, 10.0)	6.38 (dd, 10.0 and 6.0)	4.43 (d, 6.0)	2.31 (CH_3CO)	7.3—7.8 (Ph-H)	1700	$C_{15}H_{11}Br_2F_2N_3O$	40.29 (40.50	2.46 2.00	9.40 9.11)
7a	H	NCOMe			5	108	6.27 (m)	6.27 (m)	4.68 (d, 4.5)	2.34 (CH_3CO)	7.06 (dd, 3.0 and 2.0, 2-H)	1710	$C_{10}H_7Cl_2F_4N_3O$	36.16 (36.08	2.12 2.11	12.65 12.33)
7b	Ph	NCOMe			2	153 (dec.)	6.87 (d, 10.0)	6.32 (dd, 10.0 and 5.5)	4.69 (d, 5.5)	2.37 (CH_3CO)	7.3—7.7 (Ph-H)	1720	$C_{16}H_{11}Cl_2F_4N_3O$	*m/e* Calcd for M^+: 407.022 (Found: 407.024)		
7e	H	NCO_2Et			2	Unstable oil	6.23 (m)	6.23 (m)	4.68 (d, 5.2)	1.38 and 4.38 (OCH_2CH_3)	7.02 (dd, 3.2 and 2.0, 2-H)	1730	$C_{11}H_9Cl_2F_4N_3O_2$	*m/e* Calcd for M^+: 361.001 (Found: 361.002)		
7f	Ph	NCO_2Et			1	Unstable solid	6.86 (d, 10.0)	6.32 (dd, 10.0 and 6.0)	4.72 (d, 6.0)	1.41 and 4.41 (OCH_2CH_3)	7.3—7.9 (Ph-H)	1730	$C_{17}H_{13}Cl_2F_4N_3O_2$	—		
5g	H	$C(CN)_2$	Cl	Cl	67	98 (dec.)	6.12 (m)	6.12 (m)	5.15 (m)	7.07 (dd, 2.8 and 2.0, 2-H)		2250	$C_{10}H_4Cl_4N_4$	37.30 (37.48	1.25 1.24	17.40 17.61)

a) Isolation yields (conditions are described in the experimental section). *b*) In $CDCl_3$. *c*) KBr disc. *d*) High mass M^+ *m/e*: 418.975 (Calcd: 418.976).

Compound **8a** was labile to moisture and was readily hydrolyzed to give an aldehyde (**9a**; $\nu_{C=O}$: 1668 cm^{-1}, δ: 10.10). Thus, the dihydropyridazinopyridazine structures (**8_3a** and **8_4a**, which could be derived from the cleavage of the interior bond of the cyclopropane ring [*i.e.*, C(4b)–C(5a) bond] were ruled out; this conclusion was also supported by the observations described below.

Although **9a** resisted catalytic reduction (with Pd–C or Raney-Ni), lithium aluminum hydride reduction (in THF) gave a carbinol **10a**, and hydrolysis of **9a** with hydrochloric acid afforded the deformylated product **11a**. In addition, dechlorination of **8a** by using tributyltin hydride (in benzene, with azobisisobutyronitrile (AIBN) as a radical initiator) gave **12a**, which contains a methyl group.

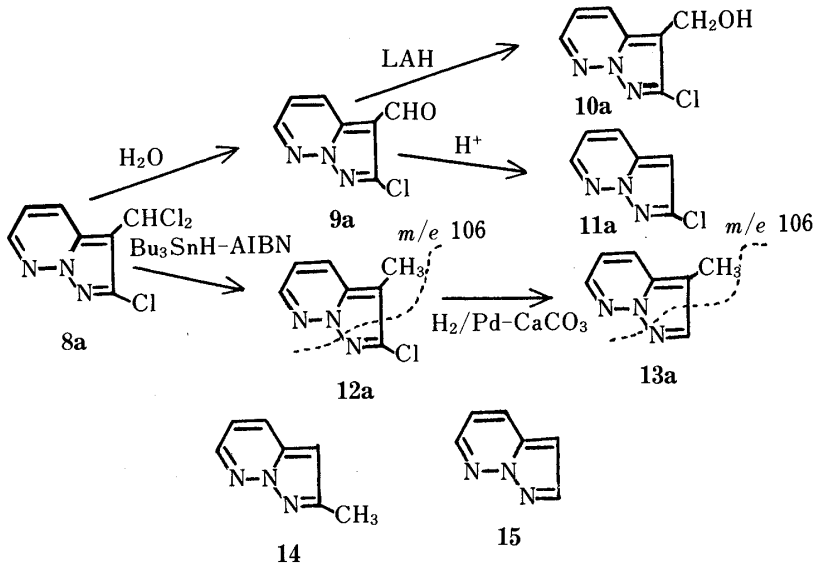


Chart 4

All these data and the ^{1}H-NMR spectral data (see Table II) support the pyrazolo[1,5-*b*]pyridazine structure (**8_1a** or **8_2a**), which could be derived by way of the exterior bond cleavage of the cyclopropane ring of **5a**. The mass spectrum (MS) of **12a** showed a peak (4% of the base peak due to $M^+ - 1$) at *m/e* 106.052 due to $[M - ClCN]^+$ (Calcd for $C_6H_6N_2$: 106.053) while the peak of $[M - MeCN]^+$ was absent, suggesting the structure whose methyl group is at the 3-position rather than the 2-position.

Moreover, catalytic reduction of **12a** using Pd–$CaCO_3$ in alkaline methanol gave a dechlorinated product **13a** whose spectral data showed features analogous to those of 2-methylpyrazolo[1,5-*b*]pyridazine[11] (**14**) and the unsubstituted compound[12] (**15**), though it was not identical with **14** (see Table II).

The MS of **13a** showed a peak at *m/e* 106.054 (9% of the base peak due to $M^+ - 1$) which is attributable to $[M - HCN]^+$ ($C_6H_6N_2$), although the $[M - MeCN]^+$ was not observed. These data support the structure of **13a** with the methyl group in the 3-position, hence the structure of **12a** with the chlorine atom in the 2-position.

Next, to confirm synthetically the positions of the substituents of the aforesaid pyrazolopyridazines, the aldehyde **9a** was oxidized by Delépine's method[13] to give a carboxylic acid **16**, which was then methylated with diazomethane to give an ester **17**. The ester was dechlorinated by catalytic hydrogenation on Pd–$BaSO_4$ under alkaline conditions to give **18**,[14] which was again methylated to give an ester **19**. The ester was identical with the known compound.[15] Thus, the structure of the initially obtained trichloro compound **8a** was decided to be 2-chloro-3-dichloromethylpyrazolo[1,5-*b*]pyridazine (**8_1a**), derived from the

TABLE II. Pyrazolo[1,5-*b*]pyridazines

	Yield (%)[a]	mp (°C)	NMR (δ, J in Hz)[b] Positions 2-	3-	4-	5-	6-	Formula	Analysis (%) Calcd (Found) C	H	N
8a	50[c,d]	123	—	6.98 (s, $CHCl_2$)	8.50 (m)	7.22 (dd, 8.0 and 4.0)	8.50 (m)	$C_7H_4Cl_3N_3$	35.55	1.70	17.77[g]
	50[e]								(36.03	1.82	18.44)
8b	64[c,d]	130	—	6.98 (s, $CHCl_2$)	8.44 (d, 9.5)	7.70 (d, 9.5)	7.50 and 8.00 (m, Ph-H)	$C_{13}H_8Cl_3N_3$	49.94	2.58	13.44
									(49.98	2.65	13.28)
8c	53[c,d]	92.5	—	6.94 (s, $CHCl_2$)	8.28 (d, 10.0)	6.90 (d, 10.0)	1.46 and 4.49 (OEt)	$C_9H_8Cl_3N_3O$	38.53	2.87	14.98
									(38.80	2.99	14.84)
9a	73[f]	139.5	—	10.10 (s, CHO)	8.55 (dd, 4.5 and 2.2)	7.43 (dd, 9.0 and 4.5)	8.68 (dd, 9.0 and 2.2)	$C_7H_4ClN_3O$	46.30	2.22	23.14
	45[e]								(46.47	2.29	23.34)
9b	62	151	—	10.09 (s, CHO)	8.65 (d, 10.0)	7.84 (d, 10.0)	7.52 and 8.05 (m, Ph-H)	$C_{13}H_8ClN_3O$	60.59	3.13	16.31
									(60.40	3.22	16.55)
9c	86	169	—	10.00 (s, CHO)	8.45 (d, 10.0)	7.05 (d, 10.0)	1.51 and 4.50 (OEt)	$C_9H_8ClN_3O_2$	47.90	3.57	18.62
									(48.13	3.48	18.81)
11a	71	88.5	—	6.54 (s)	7.86 (dd, 9.0 and 2.0)	7.03 (dd, 9.0 and 4.0)	8.27 (dd, 4.0 and 2.0)	$C_6H_4ClN_3$	46.92	2.63	27.36
									(47.18	2.40	27.46)
11b	74	158	—	6.51 (s)	7.90 (d, 9.5)	7.35 (d, 9.5)	7.50 and 8.00 (m, Ph-H)	$C_{12}H_8ClN_3$	62.75	3.51	18.30
									(62.44	3.42	18.61)
11c	91	159	—	6.42 (s)	7.68 (d, 9.5)	6.68 (d, 9.5)	1.41 and 4.42 (OEt)	$C_8H_8ClN_3O$	48.62	4.08	21.26[h]
									(48.68	4.16	21.72)
10a	73	130	—	4.28 (s, CH_2) 1.95 (s, OH)	7.95 (dd, 9.5 and 1.9)	6.96 (dd, 9.5 and 4.0)	8.20 (dd, 4.0 and 1.9)	$C_7H_6ClN_3O$	45.79	3.29	22.89[i]
									(45.88	3.26	23.35)
12a	27	133.5	—	2.28 (s, Me)	7.80 (dd, 10.0 and 2.0)	6.98 (dd, 10.0 and 4.0)	8.22 (dd, 4.0 and 2.0)	$C_7H_6ClN_3$	50.16	3.61	25.07
									(50.48	3.58	24.84)
13a	80	62.5	7.84 (s)	2.32 (s, Me)	7.86 (dd, 9.5 and 2.0)	6.87 (dd, 9.5 and 4.5)	8.19 (dd, 4.5 and 2.0)	$C_7H_7N_3$	63.14	5.30	31.56
									(63.22	5.52	31.41)
14[4]		Oil	3.84 (s, Me)	6.34 (s)	7.77 (d, 8.0)	6.85 (dd, 8.0 and 5.0)	8.10 (d, 5.0)				
15[5]		Oil	8.02 (s)	6.62 (d)	7.95 (dd)	6.95 (dd)	8.25 (dd)				
16	Quant.	290.5	—	13.00 (s, CO_2H)	8.50 (dd, 10.0 and 1.9)	7.86 (dd, 10.0 and 4.5)	8.67 (dd, 4.5 and 1.9)	$C_7H_4ClN_3O_2$	42.55	2.04	21.27
									(42.37	2.01	21.02)
17	88	169.5	—	3.97 (s, CO_2CH_3)	8.42 (dd, 4.0 and 2.0)	7.27 (dd, 9.0 and 4.0)	8.48 (dd, 9.0 and 2.0)	$C_8H_6ClN_3O_2$	45.40	2.86	19.86
									(45.45	2.78	19.81)
19	38	126 (Lit.[8] 126)	8.37 (s)	3.90 (s, CO_2CH_3)	8.40 (dd, 4.0 and 1.9)	7.19 (dd, 8.5 and 4.0)	8.58 (dd, 8.5 and 1.9)				

a) Isolation yields. *b*) In $CDCl_3$ except **16** d_6-DMSO. *c*) Lower yields of **8** than of **9** are due to the instability of **8**. *d*) From **5**. *e*) From **5d**. *f*) From **5**. *g*) High mass M^+ *m/e*: 234.947 (Calcd: 234.947). *h*) High mass M^+ *m/e*: 197.037 (Calcd: 197.036). *i*) High mass M^+ *m/e*: 183.019 (Calcd: 183.020).

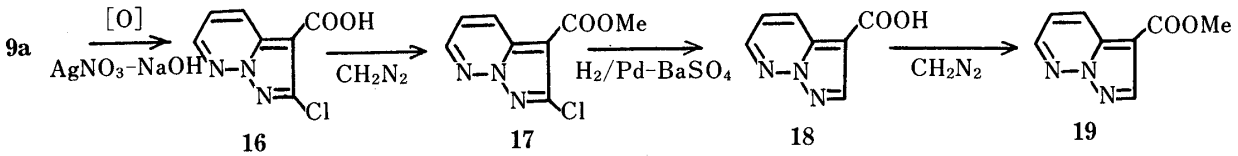


Chart 5

cleavage of the C(5)–C(5a) bond. This mode of cleavage is in contrast with that in the thermal decompositions of other heterocyclic [4.1.0.0] tricyclo compounds, where the cleavages generally occur at the interior C–C bond of the three-membered rings.[16]

The transformations **5**→**8**→**9**→**11** of the phenyl and ethoxy derivatives (**b** and **c**, respectively) were carried out similarly, and their yields and the ^{1}H-NMR spectral data are summarized in Table II. All the 2-chloropyrazolo[1,5-*b*]pyridazines described here are new compounds, and their syntheses would be interesting, because it has been reported that electrophilic substitutions, *e.g.*, halogenation, nitration, *etc.*, usually take place at the 3-positions of pyrazolo[1,5-*b*]pyridazines.[11] Further, the thermolysis of **5g** did not give a major product, a complicated mixture being obtained owing to decomposition.

Finally, to return to the initial transformation **5**→**8**, we wished to determine whether the hydrogen atom in the dichloromethyl group of **8** arose intermolecularly or intramolecularly. To investigate this problem, tetradeuterated **5a** (d_4-**5a**) was synthesized from d_4-**1a** and pyrolyzed in xylene (C_8H_{10}) (Chart 6). The incorporations of hydrogen atoms into the 4-, 5-, and 6-positions of **9a** were negligible, and the incorporation into the aldehyde group was only trace, when d_4-**5a** was refluxed in C_8H_{10} followed by transformation to the aldehyde **9a**. However, when a mixture of d_4-**5a** (R=D) and **5c** (R=OEt) in 2:1 molar ratio was thermolyzed in xylene, hydrogen was incorporated into the aldehydic moiety of d_3-**9a** to the extent of approximately 29%, and incorporation of deuterium into the aldehyde group of **9c** occurred concurrently, to the extent of about 66% (by NMR).[17]

From these observations, it was concluded that the aldehyde proton of **9** and hence the dichloromethyl proton of **8** arose from the intermolecular abstraction of hydrogen at the 4a-position of **5**, and that the hydrogen was far more easily abstracted than those of a xylene

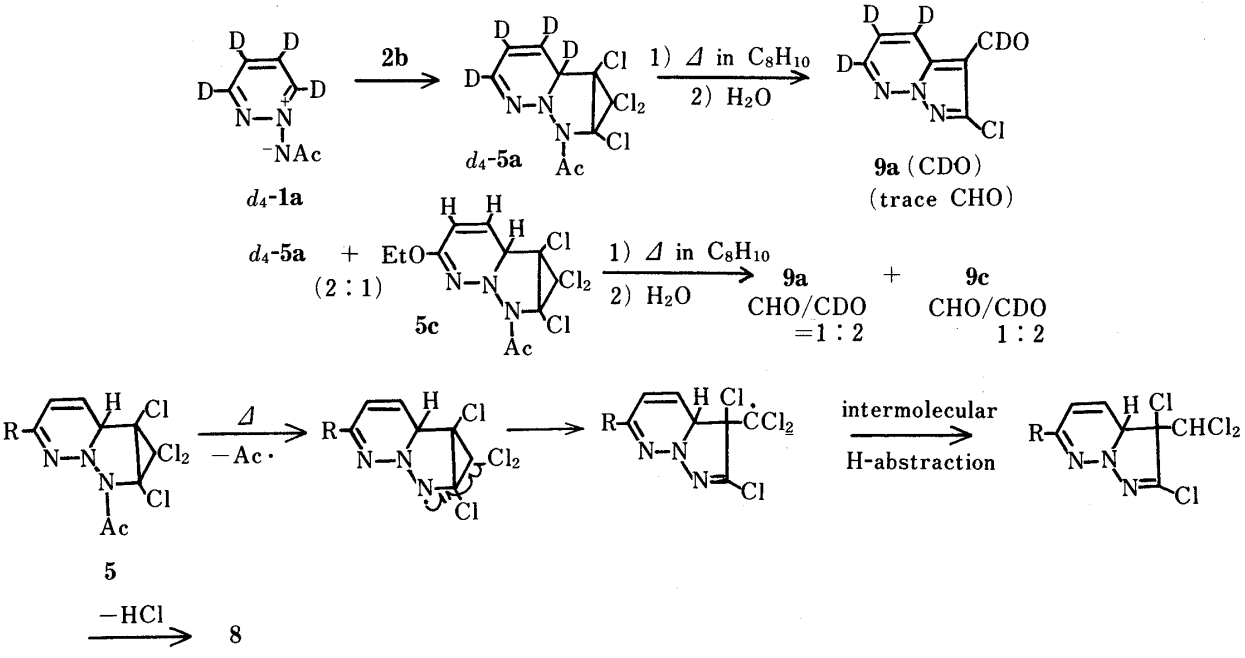


Chart 6

molecule. The ease of the transformation **5**→**8** in a solvent of low polarity (xylene), and the fact that the reaction was scarcely enhanced by addition of dimethylformamide and/or dimethylsulfoxide, polar solvents, suggest that the reaction may proceed *via* a radical mechanism.

Thus, the mechanism shown in Chart 6 is proposed for the transformation **5**→**8**, where the dichloromethyl hydrogen of **8** arises through intermolecular hydrogen-abstraction in an intermediary radical, although a detailed examination of the mechanism is still in progress.

Experimental

IR spectra and ^{1}H-NMR spectra were measured with JASCO IRA-2 and Hitachi R-22 instruments, respectively. High-resolution mass spectra were measured on a JEOL JMS D-300.

Cycloaddition of Pyridazinium *N*-Ylides (1) with Perhalocycloalkenes (2 and 3)——The starting materials **1a—g** were synthesized according to the published procedures.[5] Compound **2b** (7 g) was added to a solution of the acetylimine **1a** (5.1 g) in 50 ml of THF during 0.5 h with cooling on an ice bath. The solution was stirred for 12 h under N_2 at room temperature. The THF was distilled off under reduced pressure and the residue was extracted with hot ether. The extract was evaporated *in vacuo* to dryness and the residue was chromatographed on an aluminum oxide column (hexane–ether) to give 4.85 g (41%) of **5a**: colorless prisms from hexane–benzene. Other adducts were obtained by similar procedures. Reaction conditions for the runs in Table I (all runs were carried out under N_2), and the appearances of the products are described below. In THF at room temperature for 12 h to give **5b**: colorless needles from benzene–ether. In THF at room temperature for 12 h to give **5c**: colorless needles from benzene–ether. In benzene at 55 °C for 10 h to give **5d** (silica-gel column chromatography; hexane–ether): colorless plates from CCl_4–CH_2Cl_2 (11% of benzoic acid and 20% of **1d** were also obtained from the chromatographic eluates. In CH_2Cl_2 at room temperature for 0.5 h to give an unstable oil **5e**. In THF at room temperature for 0.5 h to give **5f** (silica gel thick layer chromatography; hexane–ether): colorless needles from hexane–ether. In THF at room temperature for 12 h to give colorless needles (from benzene–ether) of **6a** (the same conditions were employed to prepare **6b**): colorless plates (from ether). Reflux in benzene for 3.5 h to give **7a**: colorless plates from benzene–ether. Reflux in benzene for 46 h to give **7b**: colorless plates from hexane–ether. Reflux in benzene for 3 h to give **7e**: an unstable oil (silica gel column chromatography; hexane–ether). Reflux in benzene for 12 h to give **7f** as an unstable glassy solid, whose purification was difficult (silica gel thick layer chromatography; benzene–CH_2Cl_2) because it decomposed into a tarry mixture during the work-up. Compound **2b** (0.88 g) was added to a solution of **1g** (0.7 g) in THF and the mixture was allowed to stand for 3 d at room temperature. A residue, obtained after the described work-up, was subjected to a silica gel column chromatography (hexane–ether) and 1.05 g of **5g** was obtained: colorless prisms from hexane–ether. Upon aluminum oxide chromatography, a cyano group of **5g** was readily hydrolyzed to give 6-carbamoyl-6-cyano-4b,5,5,5a-tetrachloro-4a,4b,5a,6-tetrahydro-5*H*-cyclopropa[3,4]pyrazolo[1,5-*b*]pyridazine: colorless needles from benzene–$CHCl_3$–THF of mp 180 °C (dec.). *Anal.* Calcd for $C_{10}H_6Cl_4N_4O$: C, 35.34; H, 1.78; N, 16.49. Found: C, 35.39; H, 1.73; N, 16.60. ^{1}H-NMR (d_6-DMSO) δ: 5.48 (1H, m), 6.89 (1H, dd, J=3.0, 2.8 Hz), 6.08 (2H, m), 8.21 (2H, br s). IR (KBr) $\nu_{C=O}$: 1720 cm^{-1}.

Reaction of 4a with 2b——The acetylimine **4a**[7] (0.4 g) was dissolved in 10 ml of THF, and **2b** (0.5 g) was added to the solution during 10 min at 0 °C. The mixture was stirred for 1 h under N_2 at room temperature. The solvent was evaporated off under reduced pressure, and the residue was extracted with hot ether. The amount of the ether-soluble part was only 0.05 g and the ^{1}H-NMR spectrum and the result of thin layer chromatography (TLC) of the extract showed that it was a complex mixture. The ^{1}H-NMR spectrum (in D_2O) of the ether-insoluble part showed a typical pattern of signals of quaternary pyridinium salts in the δ 8.2—9.5 region.

Reaction of 4b with 2b——The oxide **4b**[8] was treated with **2b** (0.375 g) as described above. After the work-up, the ether-soluble part was negligible and the ^{1}H-NMR spectrum (in D_2O) of the ether-insoluble material (approx. 0.57 g) showed signals only in the δ 8.2—9.5 region.

Thermal Decomposition of Adducts (5a—d)——An adduct **5** (1 mmol) was dissolved in 3—5 ml of dry xylene and heated at 150—160 °C under N_2 until most of the starting material had decomposed (checked by TLC). The mixture was evaporated *in vacuo* (0.01 mmHg) and the residue was extracted with ether. The extract was evaporated and recrystallized to give pure **8**. Compounds **8a—c** were unstable to moisture and decomposed to give mixtures of products upon being exposed to the atmosphere. Crystal appearances of compounds **8** are as follows. **8a**: pale yellow needles from ether. **8b**: pale yellow needles from hexane–ether. **8c**: colorless needles from hexane.

Preparation of the Aldehydes 9——The adduct **5** (1 mmol) was decomposed in xylene as described above. The residue, obtained after the evaporation of the xylene, was subjected to aluminum oxide thick layer chromatography (benzene–ether) to give the corresponding **9**. **9a**: pale yellow granules from benzene–ether. **9b**: colorless needles from benzene–ether. **9c**: colorless fibers from benzene–ether.

Thermolysis of the Mixture of d_4-5a and 5c——A mixture of 270 mg of d_4-**5a** and 150 mg of **5c** was heated in

xylene, and worked up as above to give a mixture of **9a** and **9c**. The mixture was separated by aluminum oxide column chromatography followed by silica gel thick layer chromatography. The aldehydes **9a** and **9c** were purified by recrystallization, and the H/(H+D) ratio of each compound was decided by ^{1}H-NMR spectroscopy in $CDCl_3$ containing $CHCl_3$ as an internal standard, and in CCl_4 containing xylene as an internal standard. The tetradeuterated **5a** was derived from pyridazine-d_4 by the same method as described for **5**. The pyridazine-d_4 was obtained next: 15 g of pyridazine was heated with 2 g of 99% NaOD and 50 g of D_2O, for 27 h at 170 °C in a sealed Pyrex tube. After cooling and addition of NaCl (5 g), the mixture was extracted with CH_2Cl_2 and the extract was dried over $MgSO_4$. The solvent was distilled off and the remaining oil was distilled to give partially deuterated pyridazine. The pyridazine was further treated twice with NaOD–D_2O in a similar manner to give approximately 98% deuterated pyridazine (as judged from the ^{1}H-NMR spectrum).

Deformylation of 9——The aldehyde (0.25 mmol) was dissolved in a mixture of conc. HCl (5 ml) and EtOH (5 ml), and refluxed for 5 h, and then the EtOH and HCl were evaporated off. The residue was suspended in 20% NaOH and extracted with CH_2Cl_2 (50 ml × 3). The extract was dried over $MgSO_4$ and evaporated to dryness *in vacuo*, then the residue was chromatographed on an aluminum oxide column (ether) or a thick layer of aluminum oxide (benzene–CH_2Cl_2) to give **11**. **11a**: colorless plates from cyclohexane. **11b**: colorless fibers from hexane–$CHCl_3$. **11c**: colorless needles from hexane–$CHCl_3$.

Reduction of 9a with Lithium Aluminum Hydride (LAH)——A THF (2 ml) solution containing 200 mg of **9a** was added dropwise to a suspension of LAH (420 mg) in THF (2 ml), during 5 min with stirring under N_2. The mixture was filtered and the filtrate was evaporated to dryness. The residue was recrystallized from ethyl acetate to give the carbinol **10a**: colorless needles.

Reductive Dechlorination of 8a——A mixture of **8a** (2 mmol), 2.5 molar excess of Bu_3SnH, and 100 mg of azobisisobutyronitrile (AIBN) was refluxed in benzene (10 ml) for 3 h under N_2. One ml of water, 200 mg of KBr, and 50 ml of CH_2Cl_2 were added to the mixture, and the whole was shaken and filtered. The filtrate was dried over $MgSO_4$ and the solvent was evaporated off *in vacuo*. The residue was chromatographed over silica gel (hexane–ether) and recrystallized from cyclohexane to give yellow needles (**12a**). MS *m/e*: 167.025 (70%, Calcd for M^+: 167.025), 166.017 (base peak, M^+-1: 166.017), 132.055 (7%, M^+-Cl: 132.056), 106.052 (4%, M^+-ClCN: 106.053).

Catalytic Reduction of 12a——Compound **12a** (0.6 mmol) was dissolved in 20 ml of MeOH containing 50 mg of NaOH and reduced under H_2 (atmospheric pressure) over Pd(5%)–$CaSO_4$ until almost all of **12a** was consumed (about 6 h). The mixture was filtered and evaporated to dryness. The residue was extracted with CH_2Cl_2, evaporated, and chromatographed on an aluminum oxide thick layer (CH_2Cl_2). The major band afforded **13a**: colorless needles from isopropyl ether. MS *m/e*: 133.061 (95%, Calcd for M^+: 133.064), 132.051 (base peak, M^+-1: 132.056), 106.054 (9%, M^+-HCN: 106.053).

Oxidation of the Aldehyde 9a——Compound **9a** (110 mg) was dissolved in 25 ml of EtOH. $AgNO_3$ (228 mg) in H_2O (1 ml) and NaOH (116 mg) in H_2O (5 ml) were added to the solution with stirring. The whole was stirred for 25 min, then acidified with dil. HCl, and the resulting precipitate was filtered off and recrystallized from MeOH–H_2O to give 110 mg of **16**: colorless granules.

Methylation of the Carboxylic Acid 16——The acid **16** was methylated with an ethereal solution of diazomethane. The mixture was evaporated to dryness and the residue was recrystallized from acetone to give the ether **17**: pale yellowish crystals.

Reductive Dechlorination of the Ester 17——The ester **17** (in methanolic solution containing NaOH to make pH 8—9) was hydrogenated (atmospheric pressure) over Pd(5%)–$BaSO_4$. The mixture was filtered and evaporated to dryness. Diluted HCl was added to the residue (to acidify the mixture) and the mixture was extracted with CH_2Cl_2. The extract was dried and evaporated, then the residue was dissolved in ether and treated with ethereal diazomethane. After evaporation of the solvent, the residue was subjected to alumina thick layer chromatography (benzene–CH_2Cl_2) and the product was recrystallized from ether to give 16 mg of **19**, which was identical with an authentic sample.[15]

References and Notes

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9) Pyridazine *N*-oxide (**1**, Z=O) and pyridinium dicyanomethylide (**4**, Z=$C(CN)_2$) scarcely reacted with **2a**, the starting materials being recovered almost quantitatively.
10) Compound **1d** did not react with **3** under conditions similar to those applied to the reaction of other **1** and **3**.
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13) J. C. Sheehan and C. A. Robinson, *J. Am. Chem. Soc.*, **73**, 1207 (1951).
14) Hydrogenation of **16** was unsuccessful; hydrogenation of **17** under neutral conditions was unsuccessful; hydrogenation of **17** in alkaline methanol was accompanied with hydrolysis of the ester.
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16) For example, *a*) R. Barlet and Y. Vo-Quang, *Bull. Soc. Chim. Fr.*, **10**, 3729 (1969); *b*) R. M. Acheson, "An Introduction to the Chemistry of Heterocyclic Compounds," 3rd ed., J. Wiley, New York, 1976, p. 199; *c*) K. Matsumoto and T. Uchida, *Synthesis*, **1978**, 207; see also ref. 2*a*.
17) Hydrogen–deuterium exchange was not observed at the ring protons.