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Studies on Indolizines and Azaindolizines. I. The 1,3-Dipolar Cycloaddition of Acetylenic Compounds to Pyridazinium Ylides

Yukio Masaki, Hideo Ōtsuka, Yoshie Nakayama, and Masaharu Hioki

Gifu College of Pharmacy[1]

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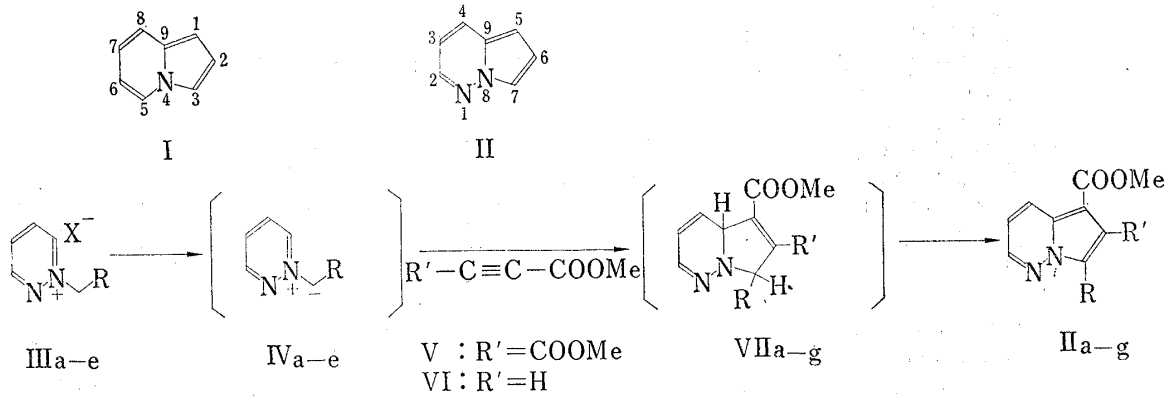
Indolizine (I) is a bicyclic 10-π-electron heterocycle containing a bridge-head nitrogen and frequently found as a ground skeleton of some classes of alkaloids. From the viewpoints of chemical and biological interests, the chemistry of azaindolizines closely related to indolizine (I) merits attention.

Among many synthetic studies on pyrrolo(1,2-*b*)pyridazines (5-azaindolizines) (II),[2] the 1,3-dipolar cycloaddition of acetylenic compounds to pyridazinium ylides[2c,d] is one of the best one-step synthesis of this system. Systematic studies concerning the effects of substituents of the ylides on the cycloaddition, however, have not been reported.

This paper describes some results demonstrating that the substituents (R) of the ylides (IV) influence the 1,3-dipolar cycloaddition of dimethyl acetylenedicarboxylate (V) and methyl propiolate (VI) to several pyridazinium ylides (IVa—e) leading to II (Chart 1).

Pyridazinium ylides (IVa—e) were prepared upon treatment of the corresponding pyridazinium salts (IIIa—e) with triethyl amine and employed without purification as 1,3-dipolar species. Pyridazinium salts (IIIa—e) were obtained by the reaction of pyridazine with alkyl-



a: X=I, R=H, R′=COOMe
b: X=Cl, R=phenyl, R′=COOMe
c: X=Cl, R=*p*-nitrophenyl, R′=COOMe
d: X=Br, R=benzoyl, R′=COOMe
e: X=Br, R=acetyl, R′=COOMe
f: R=benzoyl, R′=H
g: R=acetyl, R′=H

Chart 1

1) Location: 36–492, *Mitahora*, *Gifu*.

2) *a*) R.L. Letsinger and R. Lasco, *J. Org. Chem.*, **21**, 764 (1956); *b*) R.M. Acheson and M.W. Foxton, *J. Chem. Soc.* (*C*), **1966**, 2218; W. Flitsch and U. Krämer, *Ann.*, **735**, 35 (1970); *idem*, *Tetrahedron Letters*, **1968**, 1479; M. Zupan, B. Stanovnik and M. Tisler, *J. Heterocycl. Chem.*, **8**, 1 (1971); *c*) D.G. Farnum, R.J. Alaimo and J.M. Dunston, *J. Org. Chem.*, **32**, 1130 (1967); *d*) T. Sasaki, K. Kanematsu, Y. Yukimoto, and S. Ochiai, *idem*, **36**, 813 (1971); Y. Kobayashi, T. Kutsuma, and K. Morinaga, *Chem. Pharm. Bull.* (Tokyo), **19**, 2106 (1971); M. Petrovanu, E. Stefanescu and I. Druta, *Rev. Roum. Chim.*, **16**, 1107 (1971).

halides, *i.e.*, methyl iodide, benzyl chloride, *p*-nitrobenzyl chloride, phenacyl bromide, and bromoacetone in the usual way. The present 1,3-dipolar cycloaddition were conveniently carried out by addition of a slight excess of triethyl amine to the mixture of salts (IIIa—e) and V or VI in appropriate solvents. In most cases, the oxidative post-treatment with chloranil was made to complete the oxidation of primary adducts to pyrrolo(1,2-*b*)pyridazines (II). Table I summarizes the results of the cycloaddition. The structures of IIa—g thus obtained were established by mass, infrared (IR), and nuclear magnetic resonance (NMR) spectral data and microanalytical results (Table II).

Table I clearly points out that the substituents (R) of ylides (IVa—e) affect the ease of the 1,3-dipolar cycloaddition in the order as follows; benzoyl>acetyl>*p*-nitrophenyl>

Table I. Synthetic Data of Pyrrolo (1,2-*b*) pyridazines (II a—g)

Solvent	Temp. °C	Time hr	Oxidation[a]	Yield, %						
				IIa	IIb	IIc	IId	IIe	IIf	IIg
DMF	100	1	b	6.3[b]	24	38	42	36	57	24
DMF	100	1	a	9.5[b]	28	41	82	75	—	—
DMF	20	3	a	—	12	32	84	66	56[c]	22[c]
Benzene	80	1	b	—	27	23	44	27	50	46
Benzene	80	1	a	—	28	21	77	74	—	—
Benzene	20	3	a	—	6	16	68	75	58[c]	43[c]

a) "a" represents that the oxidative post-treatment with chloranil was carried out. "b" stands for no the oxidative post-treatment.
b) Potassium carbonate was used as a base because the employment of triethyl amine gave no satisfactory results.
c) The oxidative post-treatment was not made.

Table II. Physical Properties of Pyrrolo (1,2-*b*) pyridazines (II a—g)

Compound	mp (°C)	Mass Spectrum M^+ *m/e*	IR (KBr) cm^{-1} $\nu_{C=O}$	NMR ($CDCl_3$) τ Aromatic-H (*J*: Hz)	NMR ($CDCl_3$) τ O-Methyl or acetyl	Formula	Analysis (%) Found (Calcd.)
IIa	65— 67	234	1735 1683	C_2:1.78(dd), $J_{2,3}$:4.5 C_3:3.13(dd), $J_{3,4}$:9.5 C_4:1.60(dd), $J_{2,4}$:2.1 C_7:1.97(s)	6.07(s) (two O-Me)	$C_{11}H_{10}O_4N_2$	C:56.13(56.41) H: 4.56(4.30) N:11.78(11.96)
IIb	178—180	310	1727 1712	C_2:1.80(dd), $J_{2,3}$:4.5 C_3:3.10(dd), $J_{3,4}$:9.5 C_4:1.51(dd), $J_{2,4}$:2.5	6.08(s) 6.15(s) (O-Me)	$C_{17}H_{14}O_4N_2$	C:65.73(65.80) H: 4.64(4.55) N: 9.02(9.03)
IIc	205—207	355	1735 1697	C_2:1.70(dd), $J_{2,3}$:4.5 C_3:2.98(dd), $J_{3,4}$:9.5 C_4:1.42(dd), $J_{2,4}$:2.2	6.05(s) 6.10(s) (O-Me)	$C_{17}H_{13}O_6N_3$	C:57.60(57.46) H: 3.76(3.69) N:11.90(11.83)
IId	157—159	338	1745 1705 1650	C_2:1.72(dd), $J_{2,3}$:4.5 C_3:2.96(dd), $J_{3,4}$:9.5 C_4:1.45(dd), $J_{2,4}$:2.2	6.10(s) 6.43(s) (O-Me)	$C_{18}H_{14}O_5N_2$	C:63.93(63.90) H: 4.22(4.17) N: 8.32(8.28)
IIe	203—205	276	1740 1705 1660	C_2:1.55(dd), $J_{2,3}$:5.0 C_3:2.87(dd), $J_{3,4}$:9.1 C_4:1.37(dd), $J_{2,4}$:2.1	5.97(s) 6.10(s) (O-Me) 7.17(s) (Ac)	$C_{13}H_{12}O_5N_2$	C:56.56(56.52) H: 4.51(4.38) N:10.24(10.14)
IIf	143—144	280	1705 1635	C_2:1.45(dd), $J_{2,3}$:4.5 C_3:2.85(dd), $J_{3,4}$:9.5 C_4:1.33(dd), $J_{2,4}$:2.1 C_6:2.24(s),	6.06(s) (O-Me)	$C_{16}H_{12}O_3N_2$	C:68.35(68.56) H: 4.30(4.32) N:10.01(10.00)
IIg	136—139	218	1700 1655	C_2:1.54(dd), $J_{2,3}$:4.5 C_3:2.92(dd), $J_{3,4}$:9.5 C_4:1.40(dd), $J_{2,4}$:2.1 C_6:2.02(s),	6.03(s) (O-Me) 7.25(s) (Ac)	$C_{11}H_{10}O_3N_2$	C:60.37(60.54) H: 4.64(4.62) N:12.73(12.84)

phenyl>hydrogen. This finding is parallel to the stability of IVa—e. Less stable ylides (IVa,b,c) may be accompanied by unfavorable side reactions to decrease the yields of IIa,b,c. It has been well demonstrated that in the 1,3-dipolar cycloaddition of acetylenic compounds, they play a role as an oxidizing reagent of the initially formed 1,3-dipolar adduct.[2c,3] In the present cases of less stable ylides (IVa,b,c), however, the efficient increase of yields was not observed even by using excess amounts of V and VI.

A few examples of isolation of the primary adducts in the 1,3-dipolar cycloaddition of quaternary ammonium ylides of heteroaromatics have been reported.[4] Although attempts to isolate the primary adducts in the present study were unsuccessful, the oxidations of the cycloaddition products with chloranil resulted in the formation of some pyrrolo(1,2-*b*)pyridazines (IId,e) in strikingly improved yields, suggesting the relative stability of those primary adducts (VIId,e).

It is concluded that the choice of substituents at the anion part of ylides is quite significant for the formation of the pyrrolo(1,2-*b*)pyridazine system by the 1,3-dipolar cycloaddition.

Experimental[5]

Methylpyridazinium Iodide (IIIa)——This salt was prepared from pyridazine and methyl iodide in ether at room temperature according to the literature.[2a,6]

Benzylpyridazinium Chloride (IIIb)——A solution of pyridazine (6 g) and benzyl chloride (9 g) in MeOH (60 ml) was refluxed for 1 hr. After evaporation of MeOH *in vacuo* from the reaction mixture, a crude crystalline mass was obtained by washing with acetone. Recrystallization of the crude product from *n*-PrOH–acetone (1:1) afforded IIIb (9.4 g), mp 180—182°. *Anal.* Calcd. for $C_{11}H_{11}N_2Cl$; C, 63.92; H, 5.37; N, 13.55. Found: C, 63.80; H, 5.23; N, 13.44.

***p*-Nitrobenzylpyridazinium Chloride (IIIc)**——A solution of pyridazine (2.3 g) and *p*-nitrobenzyl chloride (4.9 *g*) in EtOH (22 ml) was refluxed for 1 hr. After evaporation of EtOH *in vacuo* from the reaction mixture, a crude crystalline mass was obtained by washing with ether. Recrystallization of the crude product from EtOH afforded IIIc (3.3 g), mp 206—210°. *Anal.* Calcd. for $C_{11}H_{10}O_2N_3Cl$: C, 52.49; H, 4.01; N, 16.70. Found: C, 52.75; H, 4.30; N, 16.54.

Phenacylpyridazinium Bromide (IIId)——A mixture of pyridazine (1 g) and phenacyl bromide (2.5 g) in CH_2Cl_2 (15 ml) was allowed to stand overnight at room temperature to deposit crystalline mass. Filtration and recrystallization of the crude product from EtOH afforded IIId (3.1 g), mp 238—241° (decomp.). *Anal.* Calcd. for $C_{12}H_{11}ON_2Br$: C, 51.63; H, 3.97; N, 10.04. Found: C, 51.75; H, 4.12; N, 9.80.

Acetonylpyridazinium Bromide (IIIe)——A mixture of pyridazine (2 g) and bromoacetone (3.5 g) in CH_2Cl_2 (40 ml) was allowed to stand overnight at room temperature to deposit crystalline mass. Filtration and recrystallization of the crude product from EtOH afforded IIIe (4.0 g), mp 185—187°. *Anal.* Calcd. for $C_7H_9ON_2Br$: C, 38.73; H, 4.18; N, 12.91. Found: C, 38.96; H, 4.38; N, 12.83.

1,3-Dipolar Cycloaddition of Acetylenic Compounds (V) and (VI) to Pyridazinium Ylides (IVa—e) (Synthesis of Pyrrolo-(1,2-*b*)pyridazines (IIa—g)). General Procedure——To a mixture of pyridazinium salt (III) (500 mg) and acetylenic compound (V or VI) (1.2 equiv.) in DMF (10—20 ml) or benzene (50 ml), triethyl amine (K_2CO_3 in the case of IIa) (1.2 equiv.) was added under stirring at room temperature. The mixture was stirred under the reaction conditions listed in Table I. The reaction products were extracted with benzene and the benzene layer was washed with water, 2% HCl, 5% $NaHCO_3$ and then with water, and dried over anhyd. K_2CO_3. Evaporation of the solvent *in vacuo* afforded the crude cycloadduct, which was submitted to the oxidative post-treatment with chloranil. To the crude reaction product dissolved in benzene (35 ml) was added chloranil (400 mg). The mixture was refluxed for 1 hr. The reaction mixture was washed with 2% NaOH and with water, and dried. Evaporation of the solvent left pyrrolo-(1,2-*b*)pyridazines (IIa—

3) T. Sasaki, K. Kanematsu, and Y. Yukimoto, *J. Chem. Soc.* (*C*), **1970**, 481.
4) T. Kutsuma, K. Fujiyama, Y. Sekine, and Y. Kobayashi, *Chem. Pharm. Bull.* (Tokyo), **20**, 1558 (1972); T. Kutsuma, K. Fujiyama, and Y. Kobayashi, *ibid.*, **20**, 1809 (1972); Y. Kobayashi, T. Kutsuma, and Y. Sekine, *Tetrahedron Letters*, **1972**, 3325; N. Basketter and A.O. Plunkett, *Chem. Commun.*, **1971**, 1578.
5) Melting points were determined on a Yanagimoto Micro Melting Point Apparatus and are uncorrected. Mass spectra were measured on a Hitachi RMS-4 instrument. IR spectra were run on a Hitachi EPI-S2 instrument in KBr disk. NMR spectra were taken on a Hitachi R-20B instrument at 60 Mc in $CDCl_3$ with TMS as an internal reference, and chemical shifts are presented in τ values.
6) A.E. Blood and C.R. Noller, *J. Org. Chem.*, **22**, 844 (1957).

e), which were recrystallized from EtOH. In the case of no the oxidative post-treatment, pyrrolo(1,2-*b*)-pyridazines (IIa—g) were obtained directly by recrystallization of the crude cycloaddition products. The melting points and IR, NMR, and mass spectral data and microanalytical results of pyrrolo(1,2-*b*)pyridazines (IIa—g) are summarized in Table II.

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Synthesis of Active Forms of Vitamin D. IV.[1] Synthesis of 24,25- and 25,26-Dihydroxycholesterols[2]

Masao Seki, Julieta Rubio-Lightbourn, Masuo Morisaki, and Nobuo Ikekawa

Laboratory of Chemistry for Natural Products, Tokyo Institute of Technology[3]

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Recently, in the studies carried out on the activity of vitamin D, special attention has been paid to the metabolites, such as 25-hydroxy-, 1,25-, 24,25- and 25,26-dihydroxycholecalciferols. Among these compounds, it was found that 1,25-dihydroxycholecalciferol is the metabolically active form in the stimulation of intestinal calcium absorption and in the mobilization of calcium from bone, being considered as the hormonal form of vitamin D responsible for the maintenance of serum calcium at the expense of either bone or diet.[4] However, hitherto a complete determination of the biological significance of another metabolites, 24,25-dihydroxycholecalciferol (I)[5] and 25,26-dihydroxycholecalciferol (II)[6] have been hampered due to minuteness of available sample, obtained from the natural source. Therefore, it is of big need to find the method of synthesizing these compounds.

We describe in this paper on a synthesis of 24,25- and 25,26-dihydroxycholesterols which should be easily transformed to the corresponding vitamin D derivatives by the established procedures.[7] As described in the previous series, a characteristic aspect of our synthetic method is the ready availability of starting material. Thus, fucosterol which is abundant in brown algae is simply converted by our method[8] to desmosterol acetate (III), from which all the presently known active metabolites of vitamin D_3 could be obtained by rather brief processes.

Reaction of desmosterol acetate (III) with *m*-chloroperbenzoic acid gave in 54% yield, 24,25-epoxide,[9] which was then converted to 24ξ,25-diol (IVa),[10] mp 153.5—154.5°, by treatment with sulfuric acid in 79% yield. The same glycol (IVa) was obtained from III by oxidation with one equivalent of osmium tetroxide in a nearly quantitative yield. The structure of IVa was further characterized by transformation into diacetate (IVb).

1) Part III: J. Rubio-Lightbourn, M. Morisaki, and N. Ikekawa, *Chem. Pharm. Bull.* (Tokyo), **21**, 1854 (1973). This is also Part IX in the series of "Studies on Steroids." Part VIII: *Idem*, *ibid.*
2) Presented to the 93rd Annual Meeting of Pharmaceutical Society of Japan, Tokyo, April 1973.
3) Location: *2–12–1, Ohokayama, Meguro-ku, Tokyo.*
4) Y. Tanaka, H. Frank, and H.F. DeLuca, *J. Nutrition*, **102**, 1569 (1972); A.W. Norman and R.G. Wong, *ibid.*, **102**, 1709 (1972).
5) M.F. Holick, H.K. Schnoes, H.F. DeLuca, R.W. Gray, I.T. Boyle, and T. Suda, *Biochemistry*, **11**, 4251 (1972). This compound was formerly reported as 21,25-dihydroxycholecalciferol.
6) T. Suda, H.F. DeLuca, H.K. Schnoes, Y. Tanaka, and M.F. Holick, *Biochemistry*, **9**, 4776 (1970).
7) L.F. Fieser and M. Fieser, "Steroids" Reinhold, New York, 1959, Chapter 4.
8) N. Ikekawa, M. Morisaki, H. Ohtaka, and Y. Chiyoda, *Chem. Commum.*, **1971**, 1498; H. Ohtaka, M. Morisaki, and N. Ikekawa, *J. Org. Chem.*, **38**, 1688 (1973).
9) M. Morisaki, J. Rubio-Lightbourn, and N. Ikekawa, *Chem. Pharm. Bull.* (Tokyo), **21**, 457 (1973).
10) Determination of stereochemistry of C_{24} position is under investigation.