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A Photochemical Preparation of N-Substituted Pyrroles from Pyridazine N-Oxides[1,2]

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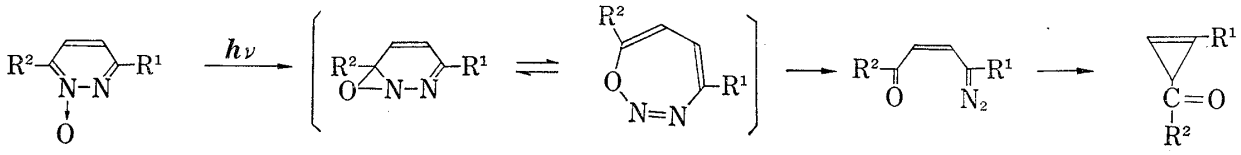
Irradiation of a mixture of pyridazine N-oxide (I) and primary amine dissolved in dichloromethane resulted in the formation of the corresponding N-substituted pyrrole. Thus, from pyridazine 1-oxide (IA), N-substituted pyrroles (VIIAa—d) were obtained. From 6-methylpyridazine 1-oxide (IB), N-substituted 2-methylpyrroles (VIIBa—d) were obtained. From 3-methylpyridazine 1-oxide (IC), 2-methylpyrroles (VIIB) and their isomers, 3-methylpyrroles (VIIIC) were obtained.

We have reported[4,5] that the photolysis of the pyridazine N-oxides resulted in the formation of oxaziridine (II), followed by the ring fission to give diazoketone intermediate (IV), which was then converted into cyclopropenyl ketone (V) by elimination of molecular nitrogen and ring closure. In the case of this reaction, irradiation of the N-oxide in the presence of *n*-butylamine afforded N-*n*-butylpyrrole, a part of which was outlined in a preliminary communication.[4]

We now report the general preparative method of N-substituted pyrroles from pyridazine N-oxides according to the above-mentioned procedure.



I II III IV V

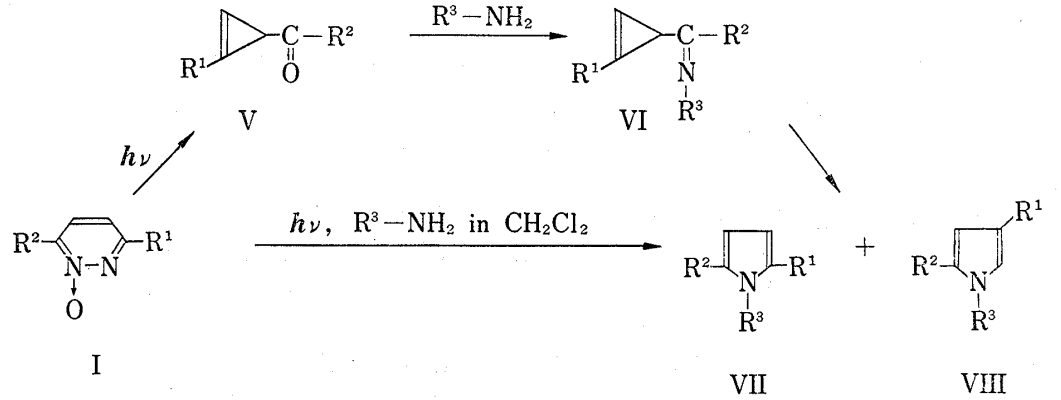
Chart 1

A solution of pyridazine N-oxide (I) and primary amine (3—5 equivalent moles) dissolved in dichloromethane was irradiated internally for 3—4 hr under nitrogen atmosphere. A reaction mixture was worked up as usual, affording the corresponding N-substituted pyrrole in 7—15% yield based on the N-oxide. On the other hand, irradiation of the N-oxide without the amine, the corresponding cyclopropenyl ketone (V) was obtained in 6—10% yield. Heating V with the primary amine under reflux for 30 min or stirring them for 3—4 hr afforded the corresponding N-substituted pyrrole in the yield of *ca.* 80% based on V. Furthermore, after irradiation of the N-oxide (I) in dichloromethane, without isolation of the product, the amine was added and the mixture was stirred for 3—4 hr to afford the same result in spite of the low yield.

1) This work was presented at the 92 nd Annual Meeting of the Pharmaceutical Society of Japan, Osaka, April 1972.
2) This paper consitutes Part VIII in the series entitled "Photochemistry." Part VII: T. Tsuchiya, H. Arai, T. Tonami, and H. Igeta, *Chem. Pharm. Bull.* (Tokyo), **20**, 300 (1972).
3) Location: *1-5-8, Hatanodai, Shinagawa-ku, Tokyo.*
4) T. Tsuchiya, H. Arai, and H. Igeta, *Chem. Commun.*, **1972**, 550.
5) T. Tsuchiya, H. Igeta, and H. Arai, The 5 th Symposium of Chemistry on Heterocyclic Compounds, Gifu, Novemver 1972, Abstracts of Paper, p. 97.

Irradiation of a mixture of the N-oxide and the amine gave a better yield and was so easy to perform that according to this procedure, syntheses of various N-substituted pyrroles were carried out.

As the primary amines, a) *n*-butylamine, b) cyclohexylamine, c) phenethylamine, and d) aniline were used. From pyridazine 1-oxide (IA), N-substituted pyrroles (VIIAa—d)



A: R^1=R^2=H
B: R^1=H, R^2=Me
C: R^1=Me, R^2=H
D: R^1=R^2=Me

R^3: a; *n*-butyl
b; cyclohexyl
c; phenethyl
d; phenyl

Chart 2

Table I. NMR Spectral Data (CCl_4, δ)

Compound VIIA	Yield (%)	2-H (m)	3-H (m)	4-H (m)	5-H (m)	N-Substituted group
a) 7)[a]	8— 9	6.48	5.92	5.92	6.48	N–CH_2–: 3.82 (t); –$(CH_2)_2$–: 1.00—1.95 (m); –CH_3: 0.95 (t)
b) 6)	12	6.52	5.92	5.92	6.52	1′–H: 3.5—3.9 (m); others: 1.1—1.8 (m. 10H)
c)	13	6.45	5.95	5.95	6.45	N–CH_2–: 3.65 (t); –CH_2–: 2.99 (t); C_6H_5: 6.9—7.3 (m)
d) 8)	7	6.95	6.20	6.20	6.92	C_6H_5: 7.2—7.45 (m)

Compound VIIB	Yield (%)	2-CH_3 (s)	3-H (m)	4-H (t)	5-H (m)	N-Substituted group
a)	9—10	2.15	5.66	5.80	6.35	N–CH_2–: 3.73 (t); –$(CH_2)_2$–: 1.0—1.9 (m) –CH_3: 0.94 (t)
b) 6)	11	2.20	5.65	5.84	6.50	1′–H: 3.72 (m); others: 1.0—2.1 (m. 10H)
c)	13—15	2.20	5.64	5.82	6.33	N–CH_2–: 3.92 (t); –CH_2–: 2.37 (t); C_6H_5: 6.8—7.2 (m)
d)	7— 8	2.18	5.88	6.00	6.60	C_6H_5: 7.3 (m)

Compound VIIIC	Yield (%)	2-H (m)	3-CH_3 (s)	4-H (m)	5-H (t)	N-Substituted group
a)	4— 5	6.21	2.04	5.72	6.30	N–CH_2–: 3.71 (t); –$(CH_2)_2$–: 1.0—1.95 (m) –CH_3: 0.90 (t)
b)	6— 7	6.75	2.00	6.10	6.85	C_6H_5: 7.24 (m)

a) references

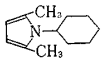
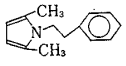
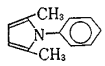
were obtained. From 6-methylpyridazine 1-oxide (IB), N-substituted 2-methylpyrroles (VIIBa—d) were obtained. The yields of them were 7—15%, as shown in the Table I. From 3-methylpyridazine 1-oxide (IC), 2-methylpyrroles (VIIB) and their isomers, 3-methylpyrroles (VIIIC) were obtained in a ratio of *ca.* 1:1. VIIIC was also obtained from 4- or 5-methyl-pyridazine 1-oxide in 12% yield. From 3,6-dimethylpyridazine 1-oxide (ID) two kinds of the products, *i.e.*, 2,5-dimethylpyrrole (VIID) and 2,4-dimethylpyrrole (VIIID) were obtained in the yields shown in Table II.

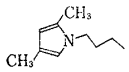
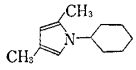
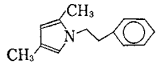
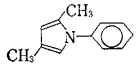
NMR spectra and analytical data of the pyrroles thus obtained were shown in Table I—III. Some of the products are the compounds known in the literatures.[6-8] The structures of the novel compounds were confirmed in comparison with the data of the known compounds.[6,9]

In the case of 3-substituted pyridazine 1-oxide ($R^1 \neq H$), two kinds of pyrroles were obtained, suggesting that the nitrogen atom of the base intermediate (VI) attacked at 1-position (carbon atom having substituent R^1) of the cyclopropenyl group to give VII, at 2-position to form VIII.[10]

Many synthetic methods of N-substituted pyrroles by thermal reactions are known,[11] but photochemical methods are scarcely known except for the formation of pyrroles from furans and thiophens in 5—8% yields, which are reported recently.[6]

Table II. NMR Spectral Data (CCl_4, δ)

Compound VIID	Yield (%)	2-CH_3 (s)	3-H (s)	4-H (s)	5-CH_3 (s)	N-Substituted group
a) 	6	2.13	5.50	5.50	2.13	N-CH_2-: 3.58 (t); -$(CH_2)_2$-: 1.1—1.95 (m); -CH_3: 0.95 (t)
b) 	3—4	2.10	5.54	5.54	2.10	1'-H: 3.4—3.8 (m); others: 1.1—1.9 (m, 10H)
c) 	7	2.03	5.50	5.50	2.03	N-CH_2-: 3.90 (t); -CH_2-: 2.89 (t); C_6H_5: 6.9—7.3 (m)
d) 	4	2.11	5.70	5.70	2.11	C_6H_5: 7.11—7.45 (m)

Compound VIIID	Yield (%)	2-CH_3 (s)	3-H (s)	4-CH_3 (s)	5-H (s)	N-Substituted group
a) 	5—6	2.12	5.50	1.95	6.18	N-CH_2-: 3.58 (t); -$(CH_2)_2$-: 1.1—1.95 (m); -CH_3: 0.95 (t)
b) 	3—4	2.10	5.45	1.95	6.23	1'-H: 3.4—3.8 (m); others: 1.1—1.9 (m, 10H)
c) 	4	2.03	5.46	1.95	6.16	N-CH_2-: 3.87 (t); -CH_2-: 2.84 (t); C_6H_5: 6.9—7.3 (m)
d) 	3	2.11	5.70	2.02	6.40	C_6H_5: 7.1—7.45 (m)

6) A. Couture and A. Lablache-Combier, *Tetrahedron*, **27**, 1059 (1971).
7) H. Gross, *Chem. Ber.*, **95**, 2270 (1962).
8) M.F. Fegley, N.M. Bortnick, and C.H. McKeever, *J. Am. Chem. Soc.*, **79**, 4144 (1957).
9) F.Y. Perveev, V.Y. Statsevich, and L.P. Gavryuchenkova, *Zh. Org. Khim.*, **2**, 397 (1966).
10) A. Couture and A. Lablache-Combier, *Chem. Commun.*, **1971**, 891.
11) E. Baltazzi and L.I. Kreimen, *Chem. Rev.*, **63**, 511 (1963), and Ref. 7) and references cited therein.

Besides cyclopropenyl ketones, depending on the reaction conditions and the substituents, the formation of furans,[5,12] pyrazoles,[13,14] and deoxygenated pyridazines[15] is already known from the diazoketone intermediate[13] and details are now under investigation. Although the yields of cyclopropenyl ketones are not satisfactory at present, efforts to improve the yield will lead to the facile synthetic method of the N-substituted pyrroles.

Experimental

General Procedure for Syntheses of N-Substituted Pyrroles——A solution of pyridazine N-oxide (IA—IB, 3—4 g) and the primary amine (3—5 equivalent moles) dissolved in dichloromethane (250—300 ml) was irradiated at room temperature under nitrogen atmosphere (200 W, high pressure Hg lamp, Nikko Sekiei Co., Tokyo). The reaction mixture was evaporated *in vacuo* below 40°. The products were separated by column chromatography on silica gel. From the eluate with benzene, N-substituted pyrroles (VII and VIII) were obtained. In cases of IA and IB, they were purified by distillation. In cases of IC and ID, two kinds of pyrroles (VII and VIII) were obtained as a mixture, so they were again separated by column chromatography on silica gel, eluting with a mixture of *n*-hexane–benzene. Each fraction was purified by distillation, respectively. From the eluate with dichloromethane, a small amount of the starting material was obtained.

From the eluate with CH_2Cl_2–MeOH, deoxygenated pyridazine (20—35%) and the excess amine were obtained. The yields, bp, and analytical data of the products are shown in Table III.

Table III

Compound	bp°C/mmHg (bath temp.)	Formula	Alalyses (%) Calcd. C	H	N	Found C	H	N
VIIA-a	75/10	$C_8H_{13}N$	77.99	10.64	11.37	78.21	10.40	10.99
VIIA-b	85/5	$C_{10}H_{15}N$	80.48	10.13	9.39	80.38	9.87	9.01
VIIA-c	100/3	$C_{12}H_{13}N$	84.17	7.65	8.18	83.85	7.62	7.82
VIIA-d	110/5	$C_{10}H_9N$	83.88	6.34	9.78	83.50	5.96	9.94
VIIB-a	70/10	$C_9H_{15}N$	78.77	11.02	10.21	78.59	10.53	10.33
VIIB-b	110/5	$C_{11}H_{17}N$	80.92	10.50	8.58	81.26	10.20	8.19
VIIB-c	140/5	$C_{13}H_{15}N$	84.28	8.16	7.56	84.03	7.77	7.15
VIIB-d	100/4	$C_{11}H_{11}N$	84.04	7.05	8.91	83.80	7.39	8.90
VIIIC-a	80/10	$C_9H_{15}N$	78.77	11.02	10.21	78.59	10.72	9.89
VIIIC-d	80/5	$C_{11}H_{11}N$	84.04	7.05	8.91	84.24	7.03	9.11
VIID-a	80/10	$C_{10}H_{17}N$	79.40	11.34	9.26	79.02	11.51	9.35
VIID-b	105/3	$C_{12}H_{19}N$	81.30	10.80	7.90	81.22	11.20	7.83
VIID-c	130/3	$C_{14}H_{17}N$	84.37	8.60	7.03	83.85	8.75	6.88
VIID-d	120/5	$C_{12}H_{13}N$	84.17	7.65	8.18	84.01	7.44	8.20
VIIID-a	80/10	$C_{10}H_{17}N$	79.40	11.34	9.26	79.70	11.13	9.49
VIIID-b	105/3	$C_{12}H_{19}N$	81.30	10.80	7.90	81.11	10.54	8.26
VIIID-c	130/3	$C_{14}H_{17}N$	84.37	8.60	7.03	84.25	8.84	6.97
VIIID-d	120/5	$C_{12}H_{13}N$	84.17	7.65	8.18	83.80	7.65	8.37

12) T. Tsuchiya, H. Arai, T. Tonami, and H. Igeta, *Chem. Pharm. Bull.* (Tokyo), **20**, 300 (1972).
13) P.L. Kumler and O. Buchardt, *J. Am. Chem., Soc.*, **90**, 5640 (1968).
14) M. Ogata and H. Kano, *Chem. Commun.*, **1967**, 1176.
15) There are many reports on the deoxygenation of the N-oxides, including those of pyridazine N-oxides. *cf.* Ref. 4), 12), 13), and T. Tsuchiya, H. Arai, and H. Igeta, *Tetrahedron Letters*, **1969**, 2479; **1970**, 2213.