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Studies on the Heterocyclic Compounds. XXI.[1] A New Alkylation of Pyridazines with Nitromethane and Nitroethane[2]

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Pyridazine derivatives (I, III, V, VII, IX, XI, XIII, XV, XVII, and XIX) were treated with nitromethane and nitroethane in the presence of a basic catalyst to give the corresponding 5-methyl (IIa, IVa, VIa, VIIIa, Xa, XIIa, XIVa, XVIa, XVIIIa, and XXa) and 5-ethyl derivatives (IVb, VIb, VIIIb, Xb, XIIb, XIVb, XVIb, and XVIIIb). Namely, in these reactions nuclear alkylation occurred instead of nitroalkylation.

Keywords——pyridazines; new alkylation; nuclear alkylation; nitroalkane; 5-alkylated pyridazines

In the previous paper,[1] the authors described an interesting finding that in the reaction of 4-cyano-3,6-dichloropyridazine (I) with primary amines, the 5-position of I was nucleophilic activity. In the course of the study on such a nucleophilic reaction, nitromethane and nitroethane were applied as nucleophile in the presence of a basic catalyst.

When I and nitromethane (three equivalents) in absolute tetrahydrofuran (THF) was refluxed for three hours in the presence of anhydrous potassium carbonate, IIa of colorless needles, mp 99—99.5° was obtained in 50% yield. The elementary analysis of IIa was equivalent to $C_6H_3Cl_2N_3$; infrared absorption (IR) spectrum showed at 2230 cm^{-1} (for cyano group); and nuclear magnetic resonance (NMR) spectrum showed the singlet peak at 2.64 ppm (3H) which was assignable to methyl group and no peak as ring proton. Therefore, the product IIa was proved to be 4-cyano-3,6-dichloro-5-methylpyridazine in which nuclear alkylation occurred instead of nitroalkylation at 5-position. When absolute dioxane was used as solvent, IIa was obtained in low yield of 12%. In the case of similar reaction of I with nitroethane in absolute THF or absolute dioxane the corresponding 5-ethyl derivative was not obtained.

Further, various pyridazine derivatives having electron-withdrawing group at 4-position were treated with nitromethane and nitroethane.

When a solution of 6-chloro-4-ethoxycarbonyl-3 (2*H*)-pyridazinone[4] (III) and nitromethane (five equivalents) in dimethyl sulfoxide (DMSO) was stirred in the presence of anhydrous potassium carbonate (one equivalent) at room temperature for 24 hours, the corresponding 5-methyl derivative (IVa) was obtained in colorless columns, mp 173—175° in 63% yield. In the similar reaction of III with nitroethane, the corresponding 5-ethyl derivative (IVb) was obtained in colorless columns, mp 131—132° in 70% yield. Structure assignments of IVa and IVb were based on the elementary analyses and the NMR spectra(Table I and II). When triethylamine (one equivalent) was used as base, IVa and IVb were obtained in good yields of 96% and 84%, respectively. As described above, DMSO was found to be favorable as solvent, DMSO was used in subsequent reactions.

In the reaction of 4-carboxy-6-chloro-3(2*H*)-pyridazinone[4] (V) with nitromethane and nitroethane in the presence of triethylamine, the decarboxylated methyl (VIa) and ethyl

1) Part XX: M. Yanai, S. Takeda, and T. Mitsuoka, *Chem. Pharm. Bull.* (Tokyo), **25**, 1708 (1977).
2) Presented at the Meeting of Chugoku-Shikoku and Kyushu Branch, the Chemical Society of Japan, Nagasaki, Feb. 1976; short communication was presented to *Heterocycles*, **4**, 1331 (1976).
3) Location: *1–14 Bunkyo-machi, Nagasaki, 852, Japan.*
4) T. Kuraishi, *Pharm. Bull.* (Tokyo), **5**, 587 (1957).

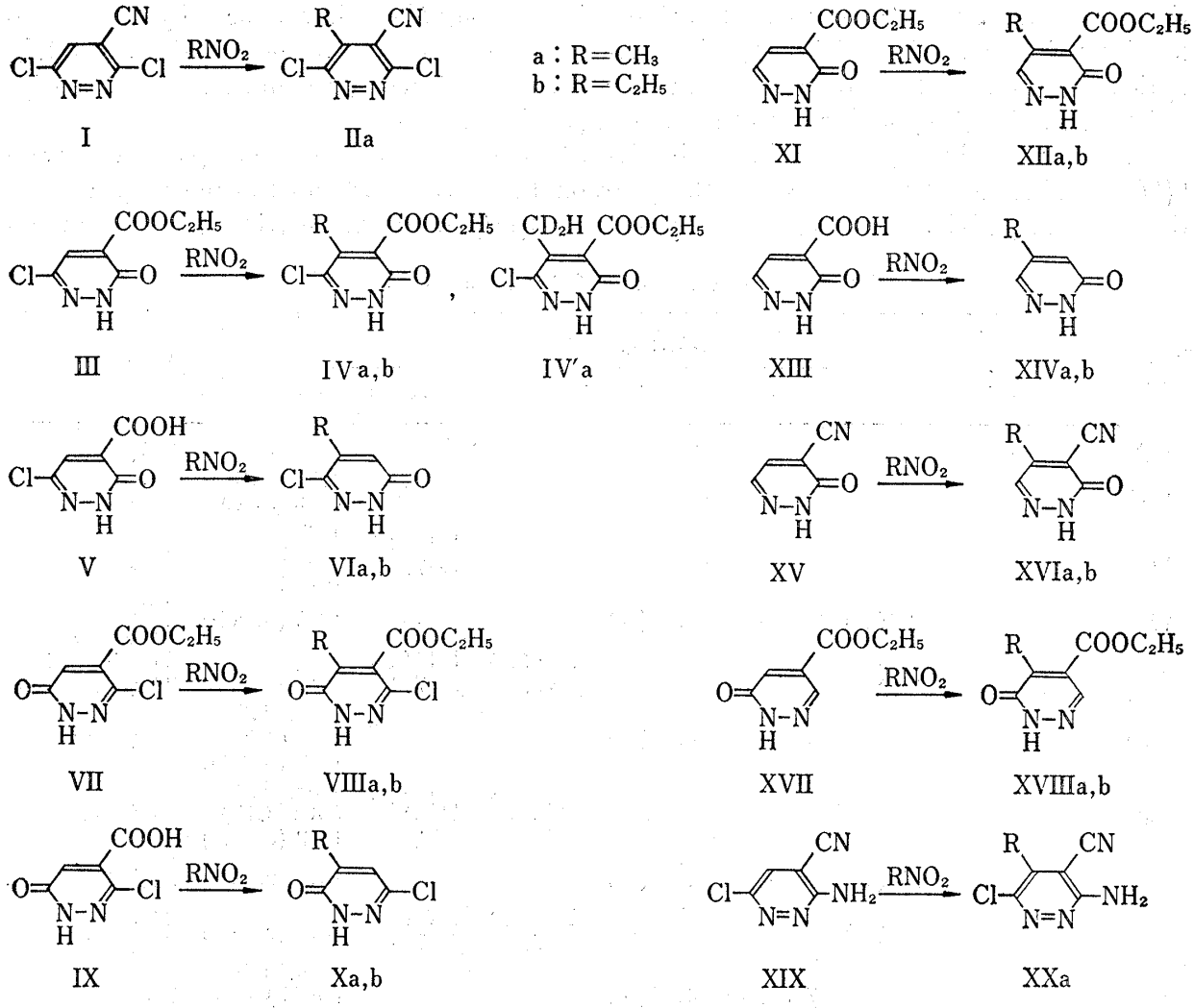

Chart 1

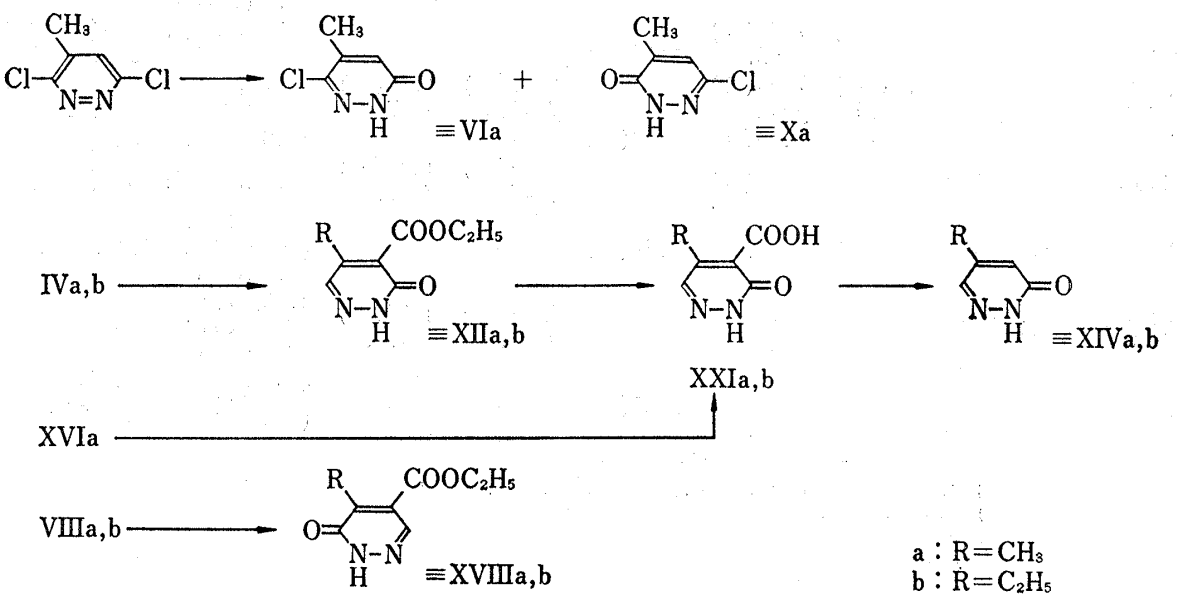

Chart 2

derivative (VIb) were obtained in 85% and 36%, respectively. The product VIa was identified with an authentic sample of 6-chloro-5-methyl-3(2*H*)-pyridazinone[4] by the mixed melting point test and the IR comparison, and VIb was proved to be 6-chloro-5-ethyl-3(2*H*)-pyridazinone on the basis of the elementary analysis, the NMR spectrum, and the similarity of its ultraviolet (UV) spectrum to that of VIa (Table I and II).

Similar reactions of pyridazine derivatives; 3-chloro-4-ethoxycarbonyl[5] (and carboxy[4])-6(1*H*)-pyridazinone(VII and IX), 4-ethoxycarbonyl-, 4-carboxy-,[6] and 4-cyano-[6] 3(2*H*)-pyridazinone (XI, XIII, and XV), 4-ethoxycarbonyl-6(1*H*)-pyridazinone (XVII), and 3-amino-

Table I. Spectral Data of Pyridazine Derivatives

Compound No.	NMR spectra[a]							UV spectra λ_{max}^{EtOH} nm (log ε)
	3–H	4–H	6–H	5–CH_3	5–CH_2CH_3	5–CH_2CH_3	Other signals	
IIa[b]	—	—	—	2.68(s)	—	—	—	295(3.32)
IVa[c]	—	—	—	2.15(s)	—	—	4.32, 1.28 (OCH_2CH_3),	307(3.38)
IVb[c]	—	—	—	—	2.45(q) J=7.5	1.15(t) J=7.5	4.30, 1.20 (OCH_2CH_3), 13.2 (b, NH)	308(3.16)
VIa[c]	—	6.90(s)	—	2.16(s)	—	—	12.6 (b, NH)	230(sh., 3.62) 298(3.32)
VIb[c]	—	6.80(s)	—	—	2.48(q) J=7.0	1.14(t) J=7.0	12.9 (b, NH)	230(sh., 3.26) 297(2.89)
VIIIa[c]	—	—	—	2.03(s)	—	—	4.38, 1.30 (OCH_2CH_3), 13.2 (b, NH)	303(3.46)
VIIIb[c]	—	—	—	—	2.42(q) J=7.5	1.10(t) J=7.5	4.38, 1.35 (OCH_2CH_3), 13.2 (b, NH)	305(3.42)
Xa[c]	—	7.43(s)	—	2.01(s)	—	—	13.3 (b, NH)	230(3.34) 296(3.19)
Xb[c]	—	7.32(s)	—	—	2.44(q) J=7.5	1.10(t) J=7.5	13.3 (b, NH)	230(3.63) 296(3.51)
XIIa[c]	—	—	7.78(s)	2.25(s)	—	—	4.40, 1.38 (OCH_2CH_3), 13.2 (b, NH)	297(3.49)
XIIb[c]	—	—	7.98(s)	—	2.43(q) J=7.5	1.14(t) J=7.5	4.29, 1.28 (OCH_2CH_3), 13.6 (b, NH)	297(3.51)
XIVa[c]	—	6.58(d) J=2.0	7.66(d) J=2.0	2.15(s)	—	—	12.6 (b, NH)	225(sh., 3.45) 286(3.36)
XIVb[c]	—	6.64(d) J=2.0	7.83(d) J=2.0	—	2.52(q) J=7.0	1.15(t) J=7.0	13.5 (b, NH)	225(sh., 3.46) 286(3.33)
XVIa[c]	—	—	8.08(s)	2.38(s)	—	—	13.5 (b, NH)	323(3.59)
XVIb[c]	—	—	8.12(s)	—	2.68(q) J=7.5	1.20(t) J=7.5	13.5 (b, NH)	323(3.60)
XVIIIa[b]	8.15(s)	—	—	2.51(s)	—	—	4.42, 1.43 (OCH_2CH_3), 12.2 (b, NH)	310(3.72)
XVIIIb[b]	8.15(s)	—	—	—	2.98(q) J=7.0	1.24(t) J=7.0	4.45, 1.44 (OCH_2CH_3), 12.0 (b, NH)	308(3.62)
XXa[c]	—	—	—	2.27(s)	—	—	7.4, 7.1 (b, NH_2)	227(4.26) 250(sh., 3.89) 356(3.48)

a) δ, ppm from tetramethylsilane; *J* in Hz; s, singlet; q, quartet; t, triplet; b, broad.
b) Solvent: $CDCl_3$.
c) Solvent: DMSO-d_6.
sh.: shoulder.

5) T. Kuraishi, *Chem. Pharm. Bull.* (Tokyo), **6**, 551 (1958).
6) P. Schmidt and J. Druey, *Helv. Chim. Acta*, **37**, 134 (1954).

6-chloro-4-cyanopyridazine[1] (XIX) with nitromethane and nitroethane afforded also the corresponding 5-methyl and 5-ethyl pyridazine derivatives, respectively, as shown in Chart 1.

The structures of products were established on the basis of the elementary analyses and spectral (IR, UV, and NMR) data (Table I and II). Several compounds were synthesized *via* another routes in the following manner. (Chart 2) That is, Xa was identified with 3-chloro-5-methyl-6(1*H*)-pyridazinone[4] by the testing of mixed melting point and by the comparison of IR spectrum, and Xb was proved to be 3-chloro-5-ethyl-6(1*H*)-pyridazinone by similarity of its UV spectrum to that of Xa; XIIa, XIIb, XVIIIa, and XVIIIb were identified with 4-ethoxycarbonyl-5-methyl (and ethyl)-3(2*H*)-pyridazinone, 4-ethoxycarbonyl-5-methyl (and ethyl)-6(1*H*)-pyridazinone obtained by dechlorination of IVa, IVb, VIIIa, and VIIIb by the testing of mixed melting point and by the comparison of IR spectra; XIVa and XIVb were identified by the mixed melting point test and the IR comparison with 5-methyl- and 5-ethyl-3(2*H*)-pyridazinone, which were obtained by the hydrolysis of XIIa and XIIb, followed by decarboxylation; XVIa was proved to be 4-cyano-5-methyl-3(2*H*)-pyridazinone, from the fact that XVIa was hydrolyzed to 4-carboxy-5-methyl-3(2*H*)-pyridazinone[7]; XVIb was proved to be 4-cyano-5-ethyl-3(2*H*)-pyridazinone by the similarity of its UV spectrum to that of XVIa.

As described above, the authors were able to obtain an interesting result that the reaction of various pyridazine derivatives with nitromethane and nitroethane in DMSO afforded the corresponding 5-methyl and 5-ethyl pyridazine derivatives, respectively.

However, the following compounds, 4-ethoxycarbonyl- and-4-carboxypyridazine,[7] 4-carboxy-6(1*H*)-pyridazinone, 4-carbamoyl-3,6-dichloropyridazine,[8] 4-cyanopyridine, and 1-chloro-2,4-dinitrobenzene, were treated with nitromethane and nitroethane in the similar manner, and resulted in recovery of starting materials.

Further, when III was treated with nitromethane-d_3 in DMSO or DMSO-d_6, IV'a of mp 172—173° could be obtained in colorless columns. The mass spectrum (MS) of IV'a showed peaks *m/e* 218 (M^+: $C_8H_7{}^{35}ClD_2N_2O_3$ =218) and *m/e* 220 (M^++2); and the NMR spectrum (in DMSO-d_6) showed singlet of one proton at 2.19 ppm. Therefore, the methyl group of IV'a was proved to be CD_2H.

This result evidently indicates that the formation of the alkylated compound resulted from nucleophilic attack by nitroalkane at the 5-position of pyridazine derivative.

Kloetzel[9] has reported that dimethyl fumarate reacts with 2-nitropropane in the presence of diethylamine to give dimethyl teraconate (XXIII) *via* dimethyl 3-methyl-3-nitro-1,2-butanedicarboxylate (XXII) which was obtained upon using of triethylamine instead of diethylamine as base.

We could not obtain the nitroalkylated pyridazine derivatives by the using of triethylamine.

Although our reaction is apparently resembles the Kloerzel's reaction, the reaction mechanism should be possibly assumed to follow a different course.

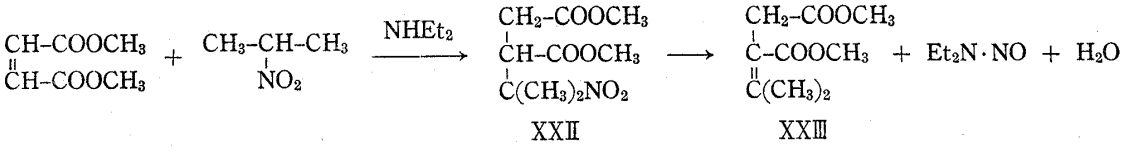

Chart 3

7) P. Schmidt and J. Druey, *Helv. Chim. Acta*, **37**, 1467 (1954).
8) M. Yanai, T. Kinoshita, H. Watanabe, and S. Iwasaki, *Chem. Pharm. Bull.* (Tokyo), **19**, 1849 (1971).
9) M. C. Kloetzel, *J. Am. Chem. Soc.*, **70**, 3571 (1948).

Experimental

Preparation of 4-Ethoxycarbonyl-3(2*H*)-pyridazinone (XI)——0.5 g of III in a mixture of 20 ml of EtOH and 0.18 ml (1.1 eq) of 28% aq. ammonia was hydrogenated over 0.2 g of 5% Pd-C. After filtration of the catalyst, the filtrate was acidified with 10% HCl and evaporated to dryness *in vacuo*. The residue was extracted with ether. The ethereal extract was concentrated to dryness; the residue was recrystallized from ether to give 0.25 g (60%) of colorless plates, mp 92—94.5°. *Anal.* Calcd. for $C_7H_8N_2O_3$: C, 50.00; H, 4.80; N, 16.66. Found: C, 49.82; H, 4.76; N, 16.70.

Preparation of 4-Ethoxycarbonyl-6(1*H*)-pyridazinone (XVII)——0.5 g of VII was hydrogenated in the same manner as III; the product was recrystallized from ether to give 0.33 g (80%) of colorless needles, mp 125—127°. *Anal.* Calcd. for $C_7H_8N_2O_3$: C, 50.00; H, 4.80; N, 16.66. Found: C, 49.93; H, 4.75; N, 16.60.

Reactions of Pyridazine Derivatives with Nitromethane and Nitroethane

4-Cyano-3,6-dichloro-5-methylpyridazine (IIa)——A mixture of 0.75 g of I, 0.75 g (3 eq) of CH_3NO_2 and 0.75 g (1.2 eq) of anhydrous K_2CO_3 in 15 ml of absolute THF was refluxed for 3 hr. After filtration of the black insoluble material, the filtrate was evaporated to dryness *in vacuo*; the residue was extracted with acetone. The acetone extract was concentrated and passed through an alumina column. The acetone elution was evaporated to dryness; the crystalline mass was recrystallized to give IIa. When the black

Table II

Compound No.	mp (°C)	Yield (%)	Appearance[a]	Recryst. solvent	Formula	Analysis (%) Calcd. (Found) C	H	N
IIa	99 — 99.5	50[b]	C.N.	Ether	$C_6H_3Cl_2N_3$	38.29 (38.51)	1.60 (1.54)	22.34 (22.48)
IVa	173 —175	63[b], 96[c]	C.Cl.	AcOEt	$C_8H_9ClN_2O_3$	44.35 (44.20)	4.19 (4.07)	12.93 (12.87)
IVb	131 —132	70[b], 84[c]	C.Cl.	Ether	$C_9H_{11}N_2O_3$	46.86 (46.65)	4.81 (4.73)	12.15 (12.05)
VIa	228 —229	67[b], 85[c]	C.Cl.	Acetone	$C_5H_5ClN_2O$	41.54 (41.69)	3.49 (3.30)	19.38 (19.42)
VIb	190 —193	38[b], 36[c]	C.Cl.	Acetone	$C_6H_7ClN_2O$	45.44 (45.59)	4.45 (4.34)	17.67 (17.44)
VIIIa	122 —123	40[b], 90[c]	C.Cl.	AcOEt	$C_8H_9ClN_2O_3$	44.35 (44.46)	4.19 (4.21)	12.93 (12.96)
VIIIb	111 —113	55[b], 80[c]	C.Cl.	Ether	$C_9H_{11}N_2O_3$	46.86 (46.56)	4.81 (4.74)	12.15 (12.13)
Xa	170 —171	25[c]	C.N.	Acetone	$C_5H_5ClN_2O$	41.54 (41.63)	3.49 (3.26)	19.38 (19.54)
Xb	138 —141	24[c]	C.N.	Acetone	$C_6H_7ClN_2O$	45.44 (45.42)	4.45 (4.38)	17.67 (17.76)
XIIa	100 —101	40[c]	C.Cl.	Ether	$C_8H_{10}N_2O_3$	52.74 (52.75)	5.53 (5.61)	15.38 (15.30)
XIIb	77 — 79	55[c]	C.N.	Ether	$C_9H_{12}N_2O_3$	55.09 (55.00)	6.17 (6.25)	14.28 (14.34)
XIVa	157 —158.5	55[c]	C.Cl.	AcOEt	$C_5H_6N_2O$	54.54 (54.47)	5.49 (5.53)	25.44 (25.25)
XIVb	100 —101	27[c]	C.Cl.	Ether	$C_6H_8N_2O$	58.05 (57.52)	6.50 (6.47)	22.57 (22.43)
XVIa	228 —230	35[b], 46[c]	C.Cl.	MeOH	$C_6H_5N_3O$	53.33 (53.13)	3.70 (3.63)	31.11 (31.26)
XVIb	155 —158	20[b], 33[c]	C.N.	MeOH	$C_7H_7N_3O$	56.37 (56.27)	4.73 (4.73)	28.18 (28.35)
XVIIIa	144.5—145.5	39[b], 60[c]	C.N.	Ether	$C_8H_{10}N_2O_3$	52.74 (52.55)	5.53 (5.36)	15.38 (15.25)
XVIIIb	112 —115	16[b]	C.N.	Ether–petr. ether	$C_9H_{12}N_2O_3$	55.09 (54.80)	6.17 (6.20)	14.28 (14.08)
XXa	220	10[b]	Y.Cl.	Benzene–*n*-hexane	$C_6H_5ClN_4$	42.73 (42.53)	2.96 (2.91)	33.23 (33.43)

a) C.: colorless, Y.: yellow, N.: needles, Cl.: columns.
b) Anhydrous potassium carbonate was used as a basic catalyst.
c) Triethylamine was used as a basic catalyst.

insoluble material (1.0 g) was dissolved in 10—15 ml of water and acidified with HCl, HNO_2 gas was generated (detection with KI-starch paper).

6-Chloro-4-ethoxycarbonyl-5-methyl-3(2*H*)-pyridazinone (IVa)——The preparation of IVa illustrates the general procedure: A mixture of 2.5 g of III, 3.8 g (5 eq) of CH_3NO_2 and 1.4 g (1.1 eq) of Et_3N in 7 ml of DMSO was stirred at room temperature for 3 days. To the reaction mixture *ca.* 10 g of water was added; separated crystals were collected by suction, washed with water, dried, and recrystallized to give IVa. Further, the mother liquor of reaction mixture was evaporated to dryness on a water bath. The residue was recrystallized to give IVa.

Dechlorinations of IVa, IVb, VIIIa, and VIIIb——The following reaction of IVb illustrates the general procedure: 0.6 g of IVb in a mixture of 10—15 ml of EtOH and 0.18—0.19 ml of 28% aq. ammonia was hydrogenated over 0.5 g of 10% Pd-C. After filtration of the catalyst, the filtrate was acidified with 10% HCl and evaporated to dryness *in vacuo*. The residue was extracted with ether. The ethereal extract was concentrated; separated crystals were collected by suction, and were recrystallized from ether to give 0.46 g (90%) of colorless needles, mp 78—79°. This compound was identified with XIIb by the mixed melting point test and by the comparison of IR spectrum of an authentic specimen.

Hydrolysis of XIIa and XIIb with 10% NaOH——To 0.4 g of XIIb, 3 ml of 10% NaOH was added. The mixture was heated on a boiling water bath for 30 min. The reaction mixture was acidified with 10% HCl and evaporated to dryness *in vacuo*. The residue was extracted with ether; the ethereal extract was concentrated to dryness; and the crystalline mass was recrystallized from ether to give 0.24 g (70%) of XXIb in colorless columns, mp 117—119°. *Anal.* Calcd. for $C_7H_8N_2O_3$: C, 50.00; H, 4.80; N, 16.66. Found: C, 49.85; H, 4.68; N, 16.77.

Decarboxylation of XXIb——0.25 g of XXIb was heated at 200—210° for 30 min. The reaction mass was extracted with acetone; the acetone extract was evaporated to dryness *in vacuo*. The residue was recrystallized from ether to give 0.06 g (33%) in colorless needles, mp 100—101°. This compound was identified with XIVb by the mixed melting point test and by the comparison of IR spectrum of an authentic specimen.

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