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Metalation of Alkylpyridazines. III.[1] Nucleophilic Addition of Lithiated Methylpyridazines and Properties of the Adducts under Basic and Neutral Conditions

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The reaction of pyridazinylmethyllithiums with ketones in tetrahydrofuran afforded hitherto unaccessible tertiary alcohols in satisfactory yields. The alcohols reverted to methylpyridazines and ketones in a basic medium whereas the alcohols yielded the corresponding dehydrated products (*i.e.*, pyridazinylethylenes) on heating in neutral media.

Keywords——metalation of alkylpyridazines; nucleophilic addition; retro-aldol; reaction; heteroaromatics; pyridazines; 1,1-disubstituted 2-pyridazinylethanols; 1,1-disubstituted 2-pyridazinylethylenes

In connection with a study of side-chain modification of alkylpyridazines, we have reported the alkylation[3] and acylation[1] of metalated methylpyridazines. For an extention of utilization of the metalated methylpyridazines, we have investigated the nucleophilic reaction of them with ketones and some properties of the reaction products, on which we now describe.

Concerning the aldol reaction of the methylpyridazine series, only some aldehydes have been known to react with methylpyridazines in basic media.[4] In fact, so long as we have investigated, the reaction of methylpyridazines (II—IV) with some ketones (Ia—e), which are less favourable substrates for the aldol addition than aldehydes, gave no isolable amount of product under the conditions described in earlier literatures.[4]

Use of a stronger base such as phenyllithium or butyllithium, which is simultaneously strong nucleophile, causes formation of nucleophilic addition products of the methylpyridazines[5] in preference to the formation of pyridazinylmethyl anions.

The reaction of pyridazinylmethyllithiums (V—VII) (*in situ*) generated from methylpyridazines (II—IV) with lithium diisopropylamide (LDA), with appropriate ketones (Ia—f)

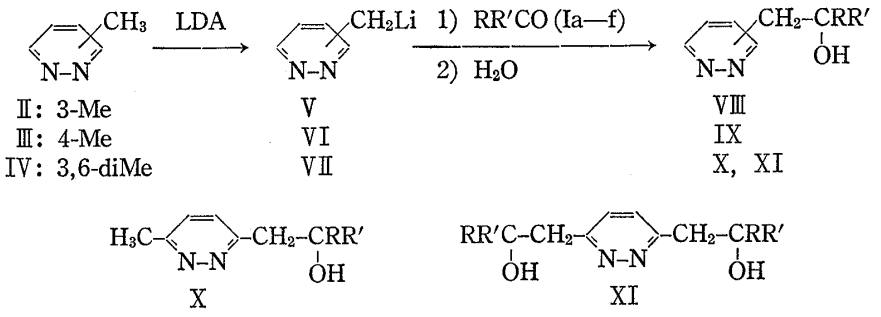

Chart 1

1) Part II: A. Ohsawa, T. Uezu, and H. Igeta, *Chem. Pharm. Bull.* (Tokyo), **26**, 3633 (1978).
2) Location: *Hatanodai, Shinagawa-ku, Tokyo 142, Japan.*
3) A. Ohsawa, T. Uezu, and H. Igeta, *Chem. Pharm. Bull.* (Tokyo), **26**, 2428 (1978).
4) *a*) R.G. Jones, E.C. Kornfeld, and K.C. McLaughlin, *J. Amer. Chem. Soc.*, **72**, 3539 (1950); *b*) R.H. Mizzoni and P.E. Spoerri, *J. Amer. Chem. Soc.*, **76**, 2201 (1954); *c*) T. Itai, S. Sako, and G. Okusa, *Chem. Pharm. Bull.* (Tokyo), **11**, 1146 (1963).
5) Ref. 3 and references cited therein.

in tetrahydrofuran (THF) gave the corresponding tertiary alcohols (VIII—XI) of nucleophilic addition products in moderate yields (isolated) as shown in Chart 1 and Table I.

Table I. Nucleophilic Addition of Pyridazinylmethyllithiums to Ketones

Run	Pyridazine	Ketone	Condition	Product	Yield (%)
1	II	Me_2CO(Ia)	A[a]	VIIIa	48
2	II	MeCOPh(Ib)	A	VIIIb	58
3	II	Ph_2CO(Ic)	A	VIIIc	80
4	III	Ia	A	IXa	92
5	III	Ib	A	IXb	91
6	III	Ic	B[b]	IXc	98
7	IV	Ia	B	Xa	27
8	IV	Ic	B	Xc	31
				XIc	17
9	IV	Bu_2CO(Id)	A	Xd	28
				XId	9
10	IV	$(CH_2)_5CO$(Ie)	B	Xe	28
				XIe	1
11	II	MeCOCH=CHPh(If)	A	VIIIf	86

a) Condition A: the reaction was carried out with cooling on dry ice-acetone bath, for 10 min.
b) Condition B: the reaction was carried out at room temperature, for 3 hr.

The reaction of VII (generated from 3,6-dimethylpyridazine (IV)) with Ic—e afforded Xc—e and bis-alcohols (XIc—e), the latter being the second products[1,3] of the former.

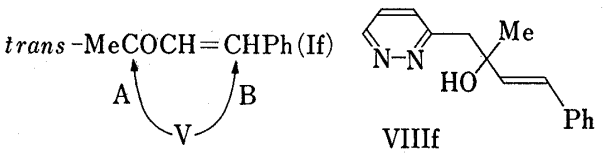

Chart 2

The reaction of V with trans-benzalacetone (If) showed higher reactivity of the anion in the addition to the carbonyl group (A in Chart 2) than in Michael addition (B); run 11.

Additionally, the reaction of V—VII with a ketone which has highly active methylene group, *e.g.*, dibenzylketone and acetylacetone, did not yield any product, the starting materials being recovered. This could be explained by assuming that the formation of enolate ions might take place by means of removal of the active protons of the ketones by V—VII, in preference to the addition of V—VII to the ketones.

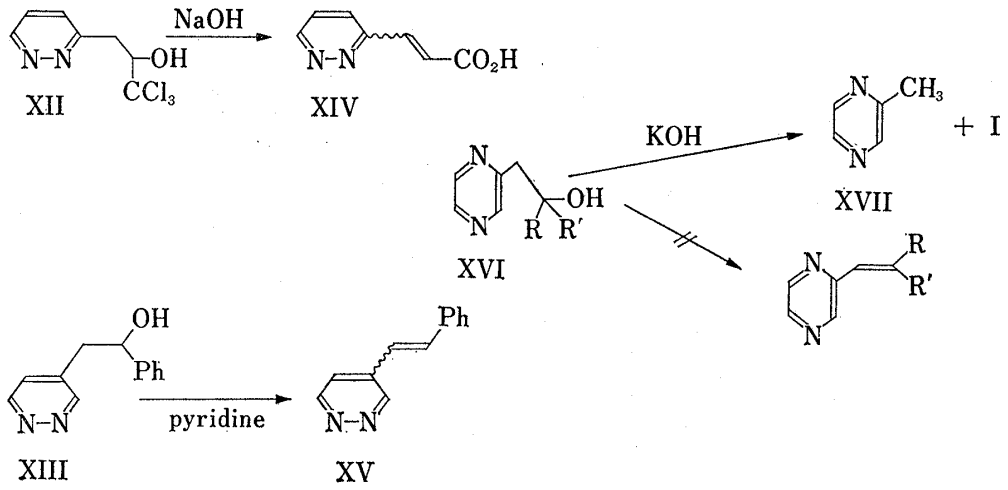

Chart 3

It has been known that 1-substituted 2-pyridazinylethanols (XII and XIII) give products of 1,2-dehydration (XIV and XV, respectively),[4] while 1,1-disubstituted 2-pyrazinylethanols (XVI) give products of retro-aldol reaction (XVII and I),[6] under basic conditions (Chart 3).

Thus, the reactions of two types, A and B (Chart 4), are expected for the behaviour of the alcohols (VIII—IX) in a basic medium. And the behaviour of VIIIa—c and IXa—c in a basic medium has been investigated as shown in Table II (condition a).

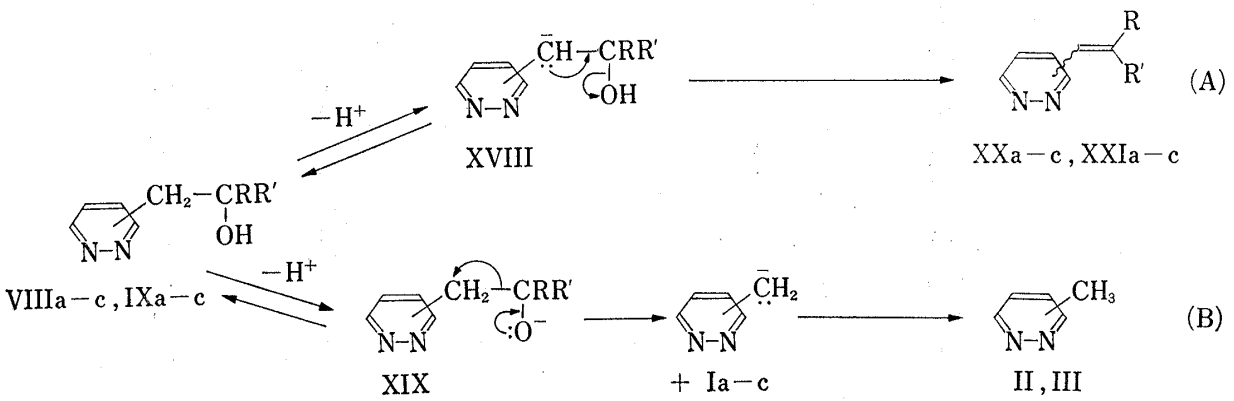

Chart 4

Table II. Decomposition of 1,1-Disubstituted 2-(3- and 4-Pyridazinyl) ethanols (VIIIa—c and IXa—c)

Compound	Condition	Product (%) Type A(1)	Product (%) Type B(2)	Starting material (%) (3)	(1)+(2)+(3)
VIIIa	a[a]	XXa 0[d]	Trace[e]	99[d]	>99
	b[b]	75[d]	18[f]	0[d]	93
	c[c]	Trace[d]	64[f]	36[d]	100
VIIIb	a	XXb 0[d]	20[e]	80[d]	100
	b	0[d]	100[f]	0[d]	100
	c	7[d]	90[f]	0[d]	97
VIIIc	a	XXc <10[g]	40[e]	50[d]	>90
	b	0[d]	100[f]	0[d]	100
	c	<10[g]	90[f]	0[d]	>90
IXa	a	XXIa 0[d]	5[e]	95[d]	100
	b	66[d]	12[f]	0[d]	78
	c	40[d]	25[f]	32[d]	97
IXb	a	XXIb <4[g]	96[e]	<4[g]	>96
	b	28[d]	72[f]	0[d]	100
	c	Trace[d]	90[f]	0[d]	>90
IXc	a	XXIc <1[g]	99[e]	<1[g]	>99
	b	88[d]	12[f]	0[d]	100
	c	<20[g]	80[f]	0[d]	>80

a) Condition a: in 5 mol% CD_3ONa-CD_3OD, 60°, 3 hr.
b) Condition b: in DMSO, 180°, 3 hr.
c) Condition c: in DCB, 180°, 3 hr.
d) Estimation by ^{1}H-NMR.
e) Estimation by VPC.
f) Estimation by ^{1}H-NMR and VPC.
g) Estimation has not been established.

6) J.D. Behun and R. Levine, *J. Amer. Chem. Soc.*, **81**, 5666 (1959).

The reaction of type B (retro-aldol) occurred preferentially, while that of type A (dehydration) was very minor one in the decomposition of VIII and IX under the described condition. Less reactive character in type B reaction of VIIIa—c compared with that of corresponding IXa—c, under the described condition, could be explained by the assumption that a participation of the hydrogen-bonded structure (XXII) of VIII retards the deprotonation from the hydroxy group to give the anion XIX (Chart 5).

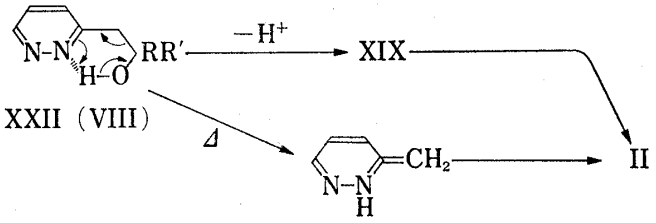

Chart 5

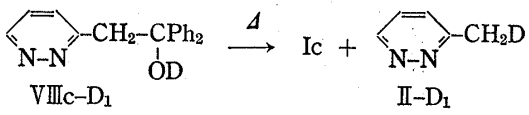

Chart 6

Additionally, the lower reactivity in type B reaction of VIIIa and IXa, compared with the other alcohols, could be explained by assuming that the methyl groups lower the acidity of the hydroxy groups of them and this effect may retard the type B reaction.

Next, the alcohols (VIIIa—c and IXa—c) have been heated under neutral conditions as shown in Table II (conditions b and c). The type B reaction again occurred in dimethylsulfoxide (DMSO) as well as in *o*-dichlorobenzene (DCB) at elevated temperature, and simultaneously, the type A reaction occurred with two exceptions (VIIIb and VIIIc in DMSO).

The difference of the solvent effect between DMSO and DCB has been unclear. Although the mechanisms of the reactions under these conditions have not been revealed, it is recognized that the ratios (type B)/(type A) for VIIIa—c are larger than those for the corresponding IXa—c, and this could be explained by assuming that an effect of the ring nitrogen atom, as shown in Chart 5, accelerates the type B reaction in the neutral conditions at the elevated temperature.

Finally, the reaction of type B was applied to the preparation of 3-CH_2D-pyridazine(II-D_1).[3] When deuterated VIIIc (VIIIc-D_1) was heated at 190°, II-D_1 was obtained in 89% yield (Chart 6).

Experimental

The nuclear magnetic resonance (^{1}H-NMR) spectra were run on Hitachi R-20 (60 MHz) and Hitachi R-22 (90 MHz) spectrometers. A Shimadzu GC-4B instrument (with a ϕ2.5 mm×2 m column packed with SE 30 on Chromosolv W) was employed for the vapour phase chromatographic (VPC) analyses. The mass spectra were recorded on a Hitachi RMS-4 spectrometer.

Preparation of Pyridazinylmethyllithium (V—VII) Solutions[3]——A solution containing 12.7 mmol of BuLi (15% in hexane) was added dropwise to a solution of isoPr$_2$NH (1.94 ml in 90 ml THF) under nitrogenic atmosphere with stirring and cooling in a dry ice-acetone bath. The mixture was allowed to stand at ambient temperature for 30 min and then cooled in a dry ice-acetone bath and a solution of a methylpyridazine (II, III or IV, 10.6 mmol, in 10 ml of THF) was added dropwise with stirring. The mixture was allowed to stand at room temperature for 1 hr and again cooled on a dry ice-acetone bath prior to the next procedure.

Reaction of V—VII with Ketones (Ia—f): General Procedures——(1) Condition A: A solution containing 12.7 mmol of a ketone in 20 ml of THF was added dropwise to the above mentioned solution with stirring and cooling on a dry ice-acetone bath under N_2 atmosphere and the mixture was allowed to stand at the temperature for 10 min, and then quenched by *ca.* 3 ml of H_2O (in 10 ml of THF). The mixture was allowed to warm to ambient temperature prior to the work-up described below.

(2) Condition B: A solution of a ketone (12.7 mmol, in 20 ml of THF) was added dropwise to the solution of V, VI or VII with stirring and cooling (under N_2 atmosphere) and the mixture was allowed to stand at room temperature for 3 hr before the treatment with H_2O.

(3) Work-up and Isolation of the Products: When the product was soluble in THF and organic precipitate was absent in the reaction mixture, the solution was dried directly over $MgSO_4$ and evaporated

Table III. 1,1-Disubstituted 2-(3- and 4-Pyridazinyl)ethanols

Compound	Analysis (%) Found (Calcd.) C	H	N	^{1}H-NMR (δ)[a]	mp (°C)[b]	Remark
VIIIa	62.94 (63.13	8.06 7.95	18.34 18.41)	1.28 (6H, s, $CH_3\times2$), 3.21 (2H, s, CH_2), 3.41 (1H, bs, OH), 7.34—7.40 (2H, m, 4- and 5-H), 8.95—9.05 (1H, m, 6-H)	65— 66	Needless ($(C_2H_5)_2O$–C_6H_{14})
VIIIb	72.68 (72.87	6.66 6.59	13.26 13.08)	1.64 (3H, s, CH_3), 3.44 (2H, s, CH_2), 5.19 (1H, bs, OH), 7.01—7.52 (7H, m, Ar-H×5,4- and 5-H), 8.98 (1H, dd, J=5.0 and 2.0 Hz, 6-H)	123—124	Granules ($isoPr_2O$–CH_2Cl_2)
VIIIc	77.89 (78.24	5.76 5.83	10.20 10.14)	3.93 (2H, s, CH_2), 6.21 (1H, bs, OH), 7.02—7.56 (12H, Ar–H×10,4- and 5-H), 8.95 (1H, dd, J=4.0 and 2.0 Hz, 6-H)	152—153	Needles ($isoPr_2O$–CH_2Cl_2)
VIIIf[c]	75.52 (75.00	6.43 6.67	11.49 11.67)	1.49 (3H, s, CH_3), 3.20 and 3.36 (1H+1H, d, J=14.0 Hz, CHH′), 4.70 (1H, bs, OH), 6.26 and 6.63 (1H+1H, d, J=17.2 Hz, CH=CH), 7.10—7.35 (5H, m, Ar–H×5), 7.40 (2H, d, J=3.7 Hz, 4- and 5-H), 9.08 (1H, t, J=3.7Hz, 6-H)	Glassy solid	
IXa	63.35 (63.13	8.10 7.95	18.21 18.41)	1.28 (6H, s, $CH_3\times2$), 2.78 (2H, s, CH_2), 3.25 (1H, bs, OH), 7.36 (1H, dd, J=4.5 and 2.2 Hz, 5-H), 8.87—9.03 (2H, m, 3- and 6-H)	93.5—94.5	Needles ($isoPr_2O$–CH_2Cl_2)
IXb·H_2O[d]	67.47 (67.22	6.97 6.94	12.07 12.06)	1.56 (3H, s, CH_3), 3.02 (2H, s, CH_2), 3.28 (2H, s, H_2O), 5.20 (1H, bs, OH), 7.08—7.44 (6H, m, Ar–H×5 and 5-H), 8.76—8.96 (2H, m, 3- and 6-H)[f]	84— 86	Plates (AcOEt)
IXc·H_2O[e]	73.67 (73.45	6.50 6.16	9.57 9.52)	3.27 (2H, s, H_2O), 3.62 (2H, s, CH_2), 6.01 (1H, s, OH), 6.85—7.55 (11H, m, Ar–H×10 and 5-H), 8.66—8.97 (2H, m, 3- and 6-H)[g]	163—165	Plates (AcOEt)
Xa[c]	64.49 (65.06	8.22 8.43	16.40 16.87)	1.26 (6H, s, $CH_3\times2$), 2.68 (3H, s, 6-CH_3), 3.08 (2H, s, CH_2), 4.45 (1H, bs, OH), 7.35 (1H, s, 4- and 5-H)	Oil	
Xc	78.92 (78.59	6.22 6.25	9.83 9.65)	2.60 (3H, s, 6-CH_3), 3.84 (2H, s, CH_2), 6.42 (1H, bs, OH), 6.83—7.55 (12H, m, Ar–H×10, 4- and 5-H)	151—152	Needles ($isoPr_2O$–CH_2Cl_2)
XIc	80.97 (81.33	5.99 5.97	6.01 5.93)	3.83 (4H, s, $CH_2\times2$), 6.24 (2H, bs, OH×2), 7.08—7.53 (22H, m, Ar–H×20, 4- and 5-H)[g]	215—216	Needles (THF)
Xd	71.72 (71.95	10.56 10.47	11.31 11.19)	0.61—1.71 (18H, m, Bu×2), 2.70 (3H, s, 6-CH_3), 3.05 (2H, s, CH_2), 4.10 (1H, bs, OH), 7.25 (2H, s, 4- and 5-H)	71— 72	Needles (C_6H_{14})
XId	73.62 (73.42	11.43 11.30	7.04 7.14)	0.55—1.65 (36H, m, Bu×4), 3.06 (4H, s, $CH_2\times2$), 3.75 (2H, bs, OH×2), 7.32 (2H, s, 4- and 5-H)	99—100	Needles (C_6H_{14})
Xe	69.92 (69.87	8.88 8.80	13.81 13.58)	1.12—1.85 (10H, m, $CH_2\times5$), 2.69 (3H, s, CH_3), 3.06 (2H, s, CH_2), 3.85 (1H, bs, OH), 7.25—7.34 (2H, m, 4- and 5-H)	95— 96	Plates (CCl_4–C_6H_{14})
XIe	70.97 (71.01	9.60 9.12	9.10 9.20)	1.15—1.75 (20H, m, $CH_2\times5$), 3.08 (4H, s, $CH_2\times2$), 3.56 (2H, bs, OH×2), 7.36 (2H, s, 4- and 5-H)	176—178	Needles (AcOEt)

a) $CDCl_3$ was used as the solvent, unless otherwise noted.
b) All melting points are uncorrected.
c) Some attempts to convert into simple crystalline derivatives (*e.g.* acetates or benzoates) of VIIIf and Xa have been unsuccessfull. For the compound VIIIf, see the last part in this section.
d) This hydrate afforded an heavy oil when it was stored *in vacuo* at room temperature. The signal due to the molecular H_2O(δ 3.28) was not observed in ^{1}H-NMR spectrum of the oil. On exposure to moisture, the oil changed into the crystalline hydrate.
e) This hydrate afforded a gummy compound when it was stored *in vacuo*, whose ^{1}H-NMR spectrum showed only a weak signal of the H_2O molecule (δ 3.27). On exposure to moisture, the compound changed into the hydrate, and on exposure to MeOH, the compound afforded crystalline IXc·CH_3OH (mp 143—144°).
f) In $CDCl_3$-5%DMSO(d_6).
g) In DMSO(d_6).

in vacuo to dryness. The residue was subjected to purification by recrystallization or aluminum oxide column chromatography (CH_2Cl_2-$(C_2H_5)_2O$ or CH_2Cl_2) to give the product (see footnotes *d* and *e* in Table III). In the case where the product separated out as crystals from the reaction mixture (runs 3, 6 and 8), the mixture was filtered and the crystals were washed with small amounts of water and THF. and recrystallized. Additional products were obtained from the filtrate after the work-up and the purification described above. The elemental analyses and the ^{1}H-NMR spectral data of the products are collected in Table III.

Decomposition of VIIIa—c and IXa—c——Most of the data in Table II were obtained from ^{1}H-NMR analyses. Appropriate amount of a VIIIa—c or IXa—c (10—20 mg) was placed in an NMR tube with 0.4 ml of 5 mol % CD_3ONa–CD_3OD, DMSO or DCB, each of which contained *ca.* 0.2% of cyclohexane (as an internal standard for estimation). The tube was sealed, and the sample was heated at the temperature described in Table II for the period of 3 hr.[7,8] The sample was subjected to ^{1}H-NMR analysis. The signals were assigned being compared with those of the authentic samples in each solvent and the amounts of the products were determined using the signal of cyclohexane as a standard. Some data were rectified or supplemented by VPC estimation. Nominal temperatures of the injection port and the column were 100—130°, in which, decomposition of each VIIIa—c and IXa—c in the VPC instrument was negligible.

Preparation of the Authentic Samples of 1,1-Disubstituted Pyridazinylethylenes (XXa—c and XXIa—c)——Compounds XXa and XXIa were obtained on heating VIIIa and IXa, respectively, in DMSO. The alcohol VIIIa (180 mg) was dissolved in DMSO (3 ml) and heated at 200° for 1 hr. DMSO was distilled off *in vacuo* and the residue was taken up in CH_2Cl_2 and chromatographed over basic aluminum oxide (CH_2Cl_2). A colourless oil (XXa, 58 mg, 37%) was obtained. ^{1}H-NMR (δ): 2.09 (3H, d, J=1.2 Hz, CH_3), 2.20 (3H, d, J=1.2 Hz, CH_3), 6.47 (1H, m, CH=), 7.24—7.50 (2H, m, 4- and 5-H), 9.02 (1H, dd, J=4.2 and 2.2 Hz, 6-H). Picrate: needles from EtOH, mp 150—151°. Compounds XXb, XXc, XXIb and XXIc were obtained by the dehydration of the corresponding alcohols with trifluoroacetic acid (TFA) in $CHCl_3$. The alcohol VIIIb (180 mg) was dissolved in 5 ml of TFA–$CHCl_3$ (1 : 1) and heated at 60° for 3 hr. The solvent was evaporated off *in vacuo*, and 5 ml of 15% NaOH was added to the residue. The mixture was extracted with CH_2Cl_2 and the extract was dried over $MgSO_4$. The crude material obtained after evaporation of CH_2Cl_2 was purified by a silica gel thick layer plate ($(C_2H_5)_2O$–CH_2Cl_2, Rf=*ca.* 0.6) to give colourless needles ($(C_2H_5)_2O$–C_6H_{14}) of mp 57—58° (XXb, 130 mg, 78%). ^{1}H-NMR (δ): 2.55 (3H, d, J=1.2 Hz, CH_3), 6.85—6.95 (1H, m, CH=), 7.25—7.82 (7H, m, Ar-H×5, 4- and 5-H), 8.96—9.14 (1H, m, 6-H). Picrate: needles from EtOH, mp 161—162°.

Table IV. Preparation of 1,1-Disubstituted 2-(3- and 4-Pyridazinyl)ethylenes (XXa—c and XXIa—c)

Compound	From	Condition	Yield (%)	Analysis (%) Found (Calcd.) C	H	N	mp (°C)[c]	Remark
XXa	VIIIa	A[a]	37		—		—	Oil
XXa picrate				45.91 (46.28	3.28 3.61	19.68 19.28)	150—151	Needles (EtOH)
XXb	VIIIb	B[b]	78	79.39 (79.59	6.11 6.12	14.25 14.29)	57— 58	Needles ($(C_2H_5)_2O$–C_6H_{14})
XXc	VIIIc	B	95	83.47 (83.69	5.50 5.46	10.83 10.85)	83— 86	Prisms ($(C_2H_5)_2O$–C_6H_{14})
XXIa	IXa	A	50		—		38— 40	Needles ($(C_2H_5)_2O$–C_6H_{14})
XXIa picrate				46.00 (46.28	3.40 3.61	19.78 19.28)	153—154	Needles (EtOH)
XXIb	IXb	B	73		—		—	Oil
XXIb picrate				53.81 (53.65	3.49 3.53	16.21 16.47)	139—141	Prisms (EtOH)
XXIc	IXc	B	93	83.65 (83.69	5.57 5.46	10.78 10.85)	90— 91	Granules (PhH–C_6H_{14})

a) Condition A: 200° in DMSO, for 1 hr.
b) Condition B: 60° in 50%TFA–$CHCl_3$, for 3 hr.
c) Uncorrected.

7) Intermediate estimations of the alcohol in each sample showed that the reaction was not necessarily a simple first-order one.
8) Controllable error of the temperature of the used oil bath was ±2°.

Preparation of Mono Deuterated 3-Methylpyridazine (II-D_1)——The alcohol (VIIIc, 0.65 g) was suspended in a mixture of D_2O–CD_3OD–CH_2Cl_2 (1: 1: 2, 2 ml) and then the solvent was evaporated *in vacuo*. After the described operations have been repeated further two times, the residue (neat) was heated at 190° for 15 min. After cooling to ambient temperature, CH_2Cl_2 (30 ml) was added to the residue and the mixture was extracted with 10% HCl (10 ml). The aqueous layer was made to alkaline (10% NaOH) and extracted with CH_2Cl_2. The extract was dried over $MgSO_4$, and CH_2Cl_2 was evaporated. An oil (II-D_1, 0.20 g, 89%) was obtained whose mass spectrum and ^{1}H-NMR spectrum were identical with those of deuterated 3-methylpyridazine obtained from a reaction of V with D_2O.[3] Mass Spectrum (*m/e*); 96 (M^++1, 10%), 95 (M^+, Base), 94 (M^+−1, 20%), 93 (M^+−2, 18%). ^{1}H-NMR (δ): 2.74 (2.11H, bs∼m, CH_2D), 7.40—7.50 (2H, m, 4- and 5-H), 8.98—9.12 (1H, m, 6-H).

Reaction of VIIIf with Ac_2O and with PhCOCl——The reaction of VIIIf with Ac_2O at room temperature for 2 days and afterwards at 80° for 0.5 hr formed the acetate (undistillable oil). ^{1}H-NMR (δ): 1.70 (3H, s, CH_3), 2.01 (3H, s, CH_3CO_2), 3.63 (2H, s, CH_2), 6.49 (2H, s, CH=×2), 7.20—7.50 (7H, m, Ar–H×5, 4- and 5-H), 9.10 (1H, t, J=4.0 Hz, 6-H). The reaction of VIIIf with PhCOCl (at room temperature for 2 days) gave the dehydrated product (mp 121—122°, flakes from $(C_2H_5)_2O$–C_6H_{14}), instead of the benzoate. ^{1}H-NMR (δ) of the dehydrate: 2.49 (3H, m, CH_3), 6.77—7.33 (3H, m, CH=C(Me)–CH=CHPh), 7.40—7.70 (7H, m, Ar×5, 4- and 5-H), 9.03 (1H, t, J=4.0 Hz, 6-H).