Studies on Pyridazines. XXIII.¹⁾ Synthesis of N-Substituted
1,4-Dihydropyridazines

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1-Methylpyridazinium salts, derived from pyridazines (Ia—f), were reduced with sodium borohydride to give the corresponding 1-methyl-1,6-dihydropyridazines (IIa—f) in 40—60% yields. Then, pyridazines (I) were reduced with sodium borohydride in the presence of methyl chloroformate to afford 1-methoxycarbonyl-1,6-dihydropyridazines (IV) and their 1,4-isomers (V), in total 35—65% yields, ratio of which depended on the kinds of the substituents.

Recent studies^{1,3)} on the reaction of pyridazines which proceeds *via* dihydropyridazines as intermediates have shown that 1,4- and 1,6-dihydropyridazines are valuable for further studies on pyridazine derivatives. Although a number of dihydropyridazines have been prepared,⁴⁻⁷⁾ the majority of these compounds are highly substituted or have strong electron-withdrawing groups on the pyridazine ring. Up to date, simple dihydropyridazines have not been obtained because of their instability and the lack of convenient methods for their preparation except in a case⁸⁾ which has yielded 1-alkyl-3,6-dimethyl-1,4-dihydropyridazines by cyclization reaction of acetonyl acetone with alkyl hydrazines. Therefore, we have ex-

amined the general synthetic route and have succeeded in the preparation of simple N-substituted dihydropyridazines by reduction of the parent pyridazines.

Pyridazines (Ia—f) were methylated with dimethyl sulfate,⁹⁾ followed by removal of excess of the reagent by extraction with ether. The quaternary salts thus obtained were reduced with sodium borohydride in water at 0—5°. Each case afforded the corresponding 1-methyl-1,6-dihydropyridazines (IIa—f) in 40—60% yield. In cases of Ic, Ie, and If, 1,4,5,6-tetrahydropyridazines

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(IIIc, e, and f) were obtained besides II. In every case, the formation of any 1,4-dihydropyridazines was not observed.

The phenyl-substituted compounds (IIe and f) were so stable that they were separated by column chromatography on alumina, but 1-methyl-dihydropyridazine (IIa) and methyl- and methoxyl-substituted compounds (IIb—d) were relatively unstable and decomposed during separation by column chromatography on alumina or silica gel. Therefore, they were separated by distillation under a reduced pressure at low temperature. The dihydropyridazines (II) thus obtained gradually decomposed in the air at room temperature for prolonged periods, but could be stored under nitrogen in a refrigerator for several days.

TABLE I. NMR Spectral Data of Dihydropyridazines, II, IV, and V (δ , J =cps)

IIa	2.77 (s, N-CH ₃), 3.35 (broad d, 6-H ₂), 5.90 (d, mc, 5-H), 5.72 (mc, 4-H), 6.66 (t, 3-H), $J_{5,6}=J_{5,6}'=3.6$ $J_{4,5}=9.5$, $J_{6,6}'=2.0$
IIb	1.83 (s, 3-CH ₃), 2.68 (s, N-CH ₃), 3.17 (broad d, 6-H ₂), 5.95 (d, t, 5-H), 5.64 (d, mc, 4-H), $J_{6,6}'=J_{5,6}'=4.0$, $J_{4,5}=9.5$, $J_{6,6}'=2.0$
IIc	0.85 (d, 6-CH ₃), 1.80 (s, 3-CH ₃), 2.78 (s, N-CH ₃), 3.32 (mc, 6-H), 5.48 (broad, 4-H and 5-H), $J_{6,CH_3}=6.0$
IId	2.58 (s, N-CH ₃), 3.58 (s, OCH ₃), 3.10 (d, d, 6-H ₂), 5.77 (d, mc, 4-H), 6.14 (d, t, 5-H), $J_{4,5}=9.5$, $J_{5,6}=J_{5,6}'=4.0$, $J_{6,6}'=2.4$
IIe	2.92 (s, N-CH ₃), 3.41 (d, d, 6-H ₂), 5.98 (d, t, 5-H), 6.35 (d, t, 4-H), 7.12—7.30 (3H) and 7.50—7.70 (2H) (mc, Ph) $J_{4,5}=10.0$, $J_{5,6}=J_{5,6}'=4.0$, $J_{6,6}'=2.0$, $J_{4,6}=J_{4,6}'=0.9$
IIf	1.14 (d, 6-CH ₃), 3.12 (s, N-CH ₃), 3.75 (mc, 6-H), 5.88 (d, d, 5-H), 6.33 (broad d, 4-H), 7.16—7.40 (3H) and 7.50—7.70 (2H) (mc, Ph), $J_{4,5}=9.5$, $J_{5,6}=J_{5,6}'=4.5$, $J_{6,CH_3}=6.0$
IVa	3.73 (s, CO ₂ CH ₃), 4.40 (d, d, 6-H ₂), 5.60—5.90 (mc, 4-H), 5.92—6.41 (mc, 5-H), 6.70—6.95 (mc, 3-H), $J_{3,4}=3.5$, $J_{3,5}=1.6$, $J_{4,5}=10.0$, $J_{5,6}=J_{5,6}'=4.0$, $J_{6,6}'=2.5$
IVb	1.95 (s, 3-CH ₃), 3.72 (s, CO ₂ CH ₃), 4.21 (d, d, 6-H ₂), 5.74 (d, t, 4-H), 6.18 (d, t, 5-H), $J_{4,5}=10.0$, $J_{5,6}=J_{5,6}'=4.0$, $J_{6,6}'=2.0$, $J_{4,6}=J_{4,6}'=1.5$
IVd	3.79 (6H, s, OCH ₃ and CO ₂ CH ₃), 4.31 (d, broad d, 6-H ₂), 5.82 (d, t, 4-H), 6.38 (d, t, 5-H), $J_{4,5}=10.0$, $J_{5,6}=J_{5,6}'=4.0$, $J_{6,6}'=2.0$, $J_{4,6}=J_{4,6}'=1.5$
IVe	3.73 (s, CO ₂ CH ₃), 4.28 (broad d, 6-H ₂), 5.85—6.35 (mc, 4-H and 5-H), 7.0—7.4 (3H) and 7.45—7.80 (2H) (mc, Ph), $J_{6,6}'=2.0$
Vb	1.99 (broad s, 3-CH ₃), 3.87 (s, CO ₂ CH ₃), 2.78 (broad d, 4-H ₂), 4.91 (d, t, 5-H), 7.01 (d, t, 6-H), $J_{4,4}'=2.0$, $J_{4,5}=J_{4,5}'=4.0$, $J_{4,6}=J_{4,6}'=1.2$, $J_{5,6}=9.0$
Vc	2.05 (s, 6-CH ₃), 2.14 (broad s, 3-CH ₃), 3.81 (s, CO ₂ CH ₃), 2.65 (broad d, 4-H ₂), 4.75 (broad t, 5-H), $J_{4,4}'=2.0$, $J_{4,5}=J_{4,5}'=3.6$
Vd	3.72 (s, OCH ₃), 3.78 (s, CO ₂ CH ₃), 2.81 (d, d, 4-H ₂), 4.91 (d, t, 5-H), 6.98 (d, t, 6-H), $J_{4,4}'=2.0$, $J_{4,5}=J_{4,5}'=4.0$, $J_{4,6}=J_{4,6}'=1.5$, $J_{5,6}=8.0$
Ve	3.74 (s, CO ₂ CH ₃), 3.02 (d, d, 4-H ₂), 4.90 (d, t, 5-H), 6.98 (d, t, 6-H), 7.1—7.45 (3H) and 7.5—7.85 (2H) (mc, Ph), $J_{4,4}'=2.0$, $J_{4,5}=J_{4,5}'=4.0$, $J_{4,6}=J_{4,6}'=1.2$, $J_{5,6}=8.5$

Ph=phenyl

The synthetic method to obtain N-methoxycarbonyl-1,6- and -1,4-dihydropyridines from pyridine described by Fowler¹⁰⁾ was applied to the pyridazines. Pyridazines (I) were reduced with sodium borohydride in tetrahydrofuran in the presence of methyl chloroformate, affording 1-methoxycarbonyl-1,6-dihydropyridazines (IV) in 30—50% yield and 1-methoxycarbonyl-1,4-dihydropyridazines (V) in a small amount. The N-methoxycarbonyl compounds (IV and V) were relatively more resistant to air oxidation and more stable than N-methyl compounds (II), and were isolated by column chromatography on alumina. The compound Ia hardly gave the 1,4-dihydro compound (V), while Ie hardly afforded the 1,6-dihydro compound (IV).

The nuclear magnetic resonance (NMR) spectral data of the above-mentioned dihydropyridazines, summarized in Table I, are consistent with their proposed structure. Further evidence was obtained from chemical studies described below.

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Chart 2

The compound IIa was also obtained in a low yield by lithium aluminum hydride reduction of 1-methyl-6-pyridazinone. It has been well known¹⁰⁾ that the N-methoxycarbonyl substituent is a versatile group and can be converted to a hydrogen-substituted derivative or can be reduced to an N-methyl group. In the present work, we also observed that treatment of the N-methoxycarbonyl compound (IVa) with lithium aluminum hydride gave the N-methyl derivative (IIa). The heating of 1,6-

dihydropyridazine (IVb) at 140–150° in a sealed tube caused a rearrangement⁷⁾ to give 1,4-dihydro compound (Vb). This fact suggested the initial formation of 1,6-dihydropyridazine, a part of which was thermally isomerized to 1,4-dihydropyridazine. The reason why N-methyl-1,4-dihydropyridazine was not formed might be due to the instability of 1,6-dihydro compound, which was decomposed before rearrangement to the 1,4-isomer.

Experimental

NMR spectra were recorded on Hitachi R-20 and R-22 spectrometers in CCl_4 or CDCl_3 solution using tetramethylsilane as internal standard. Infrared (IR) spectra were determined with a JASCO IRA-1 spectrometer and mass spectra were recorded on a Hitachi RMS-4 instrument. Melting points (mp) were measured on a Yamato MP-1 apparatus and are uncorrected. Microanalyses were performed in the analytical laboratory of this school by Miss T. Kihara and Mrs. K. Shiobara.

Reaction of Pyridazine (Ia–f) with Me_2SO_4 and NaBH_4 ; General Procedure—To pyridazine (I, 3–5 g) excess of dimethyl sulfate (10–20 ml) was added at 60–80° [in the case of phenyl-substituted pyridazines (Ie and If), at 110–120°] for 2–3 hr. After removal of unreacted dimethyl sulfate by extraction with ether, 1-methylpyridazinium methosulfate thus obtained was dissolved in water (150–200 ml) and NaBH_4 (2–3 g) was added at 0–5° over 20 min and the solution was stirred for 5 hr at the same temperature. The reaction mixture was extracted with CH_2Cl_2 and the organic layer was dried over MgSO_4 and evaporated. In cases of Ia–Id, the residues were distilled *in vacuo* below 60° under N_2 to give 1-methyl-1,6-dihydropyridazine (IIa–d) and 1,3,6-trimethyl-1,4,5,6-tetrahydropyridazine (IIIc). In cases of Ie and If, the residues were chromatographed on alumina with degassed benzene to give IIe,f and IIIe,f successively.

1-Methyl-1,6-dihydropyridazine (IIa): Yield 46%, colorless oil, bp_{15} 50–55°. Mass Spectrum m/e : 96 (M^+). *Anal.* Calcd. for $\text{C}_5\text{H}_8\text{N}_2$: C, 62.47; H, 8.39; N, 29.14. Found: C, 62.31; H, 8.50; N, 29.11.

1,3-Dimethyl-1,6-dihydropyridazine (IIb): Yield 63%, colorless oil, bp_{28} 52–55°. Mass Spectrum m/e : 110 (M^+). *Anal.* Calcd. for $\text{C}_6\text{H}_{10}\text{N}_2$: C, 65.42; H, 9.15; N, 25.43. Found: C, 65.46; H, 8.87; N, 25.23.

1,3,6-Trimethyl-1,6-dihydropyridazine (IIc): Yield 47%, colorless oil, bp_{30} 58–60°. Mass Spectrum m/e : 124 (M^+). *Anal.* Calcd. for $\text{C}_7\text{H}_{12}\text{N}_2$: C, 67.70; H, 9.74; N, 22.56. Found: C, 67.91; H, 9.73; N, 22.43.

1-Methyl-3-methoxy-1,6-dihydropyridazine (IId): Yield 58%, colorless oil, bp_{20} 48°. Mass Spectrum m/e : 126 (M^+). *Anal.* Calcd. for $\text{C}_6\text{H}_{10}\text{ON}_2$: C, 57.11; H, 7.99; N, 22.21. Found: C, 57.14; H, 8.18; N, 22.08.

1-Methyl-3-phenyl-1,6-dihydropyridazine (IIe): Yield 45–50%, pale yellow viscous oil. Mass Spectrum m/e : 172 (M^+). *Anal.* Calcd. for $\text{C}_{11}\text{H}_{12}\text{N}_2$: C, 76.71; H, 7.02; N, 16.27. Found: C, 76.92; H, 7.13; N, 16.22.

1,6-Dimethyl-3-phenyl-1,6-dihydropyridazine (IIIf): Yield 38%, colorless viscous oil. Mass Spectrum m/e : 186 (M^+). *Anal.* Calcd. for $\text{C}_{12}\text{H}_{14}\text{N}_2$: C, 77.38; H, 7.58; N, 15.04. Found: C, 77.25; H, 7.51; N, 14.73.

1,3,6-Trimethyl-1,4,5,6-tetrahydropyridazine (IIIc): Yield ca. 5%, colorless oil, bp_{30} 60–62°. Mass Spectrum m/e : 126 (M^+). *Anal.* Calcd. for $\text{C}_7\text{H}_{14}\text{N}_2$: C, 66.62; H, 11.18; N, 22.20. Found: C, 66.54; H, 11.00; N, 22.30. NMR δ : 1.05 (d, $J=6.0$ cps, 6- CH_3), 1.75 (s, 3- CH_3), 2.67 (s, N- CH_3), 1.5–2.6 (5H, unassigned mc).

1-Methyl-3-phenyl-1,4,5,6-tetrahydropyridazine (IIIe): Yield 6–7%, colorless viscous oil, Mass Spectrum m/e : 174 (M^+). *Anal.* Calcd. for $\text{C}_{11}\text{H}_{14}\text{N}_2$: C, 75.82; H, 8.10; N, 16.08. Found: C, 75.51; H,

7.83; N, 15.98. NMR δ : 2.92 (s, N-CH₃), 2.10 (mc, 5-H₂), 2.48 (mc, 4-H₂), 2.78 (mc, 6-H₂), 7.18—7.40 and 7.55—7.75 (3H and 2H, mc, C₆H₅).

1,6-Dimethyl-3-phenyl-1,4,5,6-tetrahydropyridazine (III_f): Yield *ca.* 4%, colorless solid, mp below 20°. Mass Spectrum m/e : 188 (M⁺). *Anal.* Calcd. for C₁₂H₁₆N₂: C, 76.55; H, 8.57; N, 14.88. Found: C, 76.53; H, 8.32; N, 14.79. NMR δ : 1.14 (d, 6-CH₃, J =6.0 cps), 2.93 (s, N-CH₃), 1.89 (mc, 5-H₂), 2.43 (mc, 4-H₂), 2.79 (mc, 6-H₂), 7.10—7.35 and 7.50—7.61 (3H and 2H, mc, C₆H₅).

Reaction of Pyridazine (Ia—e) with Methyl Chloroformate and NaBH₄; General Procedure—To a solution of pyridazine (I, 3—5 g) and NaBH₄ (*ca.* 2 g) dissolved in dried tetrahydrofuran (THF) (200 ml), slightly excess of methyl chloroformate was added in portions to keep the reaction temperature below 5° in an ice bath. The reaction mixture was then stirred for an additional 3 hr and water (100—150 ml) was added. The mixture was extracted with CH₂Cl₂ and the organic layer was washed with water, dried over MgSO₄, and evaporated *in vacuo*. The residue was chromatographed on alumina with degassed benzene to give 1,6-dihydropyridazine (IV) and 1,4-dihydropyridazine (V) successively, which were again purified by distillation *in vacuo* or recrystallization. IR spectra of all compounds (IV and V) showed absorptions at around 1715 cm⁻¹ due to methoxycarbonyl groups.

1-Methoxycarbonyl-1,6-dihydropyridazine (IVa): Yield 35%, colorless oil, bp₄ 110°. Mass Spectrum m/e : 140 (M⁺). *Anal.* Calcd. for C₆H₈O₂N₂: C, 51.42; H, 5.75; N, 19.99. Found: C, 51.56; H, 5.74; N, 19.80.

3-Methyl-1-methoxycarbonyl-1,6-dihydropyridazine (IVb): Yield 43%, colorless oil, bp₃ 110—120°. Mass Spectrum m/e : 154 (M⁺). *Anal.* Calcd. for C₇H₁₀O₂N₂: C, 54.53; H, 6.54; N, 18.17. Found: C, 54.71; H, 6.41; N, 17.99.

3-Methoxy-1-methoxycarbonyl-1,6-dihydropyridazine (IVd): Yield 38%, colorless oil, bp₁ 97—100°. Mass Spectrum m/e : 170 (M⁺). *Anal.* Calcd. for C₇H₁₀O₃N₂: C, 49.40; H, 5.92; N, 16.46. Found: C, 49.48; H, 6.03; N, 16.22.

3-Phenyl-1-methoxycarbonyl-1,6-dihydropyridazine (IVe): Yield 50%, colorless needles, mp 69—70° (from isopropylether (IPE)—ether). Mass Spectrum m/e : 216 (M⁺). *Anal.* Calcd. for C₁₂H₁₂O₂N₂: C, 66.65; H, 5.59; N, 12.96. Found: C, 66.90; H, 5.51; N, 13.23.

3-Methyl-1-methoxycarbonyl-1,4-dihydropyridazine (Vb): Yield 8%, colorless oil, bp₃ 110—115°. Mass Spectrum m/e : 154 (M⁺). *Anal.* Calcd. for C₇H₁₀O₂N₂: C, 54.53; H, 6.54; N, 18.17. Found: C, 54.86; H, 6.43; N, 18.16.

1,3,6-Trimethyl-1-methoxycarbonyl-1,4-dihydropyridazine (Vc): Yield 35%, colorless oil, bp₁ 80°. Mass Spectrum m/e : 168 (M⁺). *Anal.* Calcd. for C₈H₁₂O₂N₂: C, 57.13; H, 7.19; N, 16.16. Found: C, 57.25; H, 7.12; N, 16.48.

3-Methoxy-1-methoxycarbonyl-1,4-dihydropyridazine (Vd): Yield 3%, colorless oil, bp₁ *ca.* 100°. Mass Spectrum m/e : 170 (M⁺). *Anal.* Calcd. for C₇H₁₀O₃N₂: C, 49.40; H, 5.92; N, 16.46. Found: C, 49.73; H, 5.82; N, 16.18.

3-Phenyl-1-methoxycarbonyl-1,4-dihydropyridazine (Ve): Yield 15%, colorless prisms, mp 77—78° (from IPE). Mass Spectrum m/e : 216 (M⁺). *Anal.* Calcd. for C₁₂H₁₂O₂N₂: C, 66.65; H, 5.59; N, 12.96. Found: C, 66.60; H, 5.74; N, 13.04.

LiAlH₄ Reduction of 2-Methyl-3(2H)-pyridazinone (VI) to 1-Methyl-1,6-dihydropyridazine (IIa)—To a solution of LiAlH₄ (2 g) dissolved in THF (50 ml) cooled in an ice bath, VI (3 g) was added slowly over 10 min. The reaction mixture was cooled in an ice bath and the excess of reagent was decomposed with water (20 ml), and extracted with CH₂Cl₂. The organic layer was washed with water, dried, and evaporated. The residue was distilled *in vacuo* to give IIa in 8% yield, which was identified in comparison of NMR spectral data with those of authentic sample.

LiAlH₄ Reduction of 1-Methoxycarbonyl-1,6-dihydropyridazine (IVa) to 1-Methyl-1,6-dihydropyridazine (IIa)—To a solution of LiAlH₄ (1.5 g) dissolved in THF (30 ml) cooled in an ice bath, IVa (2.0 g) was added over 10 min. The reaction mixture was kept at room temperature, stirring for 3 hr under N₂. The mixture was then cooled in an ice bath and the excess of LiAlH₄ was decomposed with 10% aq. NaOH (20 ml), and extracted with CH₂Cl₂. The organic layer was washed with water, dried, and evaporated *in vacuo* to give IIa in *ca.* 10% yield.

Rearrangement of 3-Methyl-1-methoxycarbonyl-1,6-dihydropyridazine (IVb) to Its 1,4-Dihydro Isomer (Vb)—The compound (IVb, 0.5 g) was heated at 140—150° in a sealed tube for 1 hr and the oil thus obtained was distilled *in vacuo* to give Vb in 15—20% yield as a mixture containing the starting material. The yield was determined by NMR integration and the identification was confirmed in comparison of the common peaks of the NMR spectra with those of authentic sample.