

Studies on Seven-Membered Heterocycles. XXXIII.¹⁾ Synthesis of Fully Unsaturated 1,2,5-Triazepines by Photochemical Ring Expansion of 4-Azidopyridazines

Hiroyuki SAWANISHI, Shuichi SAITO, and Takashi TSUCHIYA*

Faculty of Pharmaceutical Sciences, Hokuriku University, Kanagawa-machi, Kanazawa 920-11, Japan. Received May 7, 1990

Photolysis of the 3-methoxy-4-azidopyridazines (11) in the presence of a base such as methoxide ion and diethylamine resulted in ring-expansion to produce the 1*H*-1,2,5-triazepines (12 and 27), which were too unstable to be isolated, but tautomerized to the stable 4*H*-isomers (13 and 28) on further treatment with sodium methoxide and were converted to the stable 1-acetyl-1*H*-1,2,5-triazepines (14 and 29) by acetylation with acetyl chloride. The products 12—14 and 27—29 are the first examples of fully unsaturated 1,2,5-triazepines and were characterized by means of spectral analyses and some chemical reactions.

Keywords 4-azidopyridazine; 1*H*-1,2,5-triazepine; 4*H*-1,2,5-triazepine; photolysis; ring-expansion; pyridazinyl nitrene; azirine intermediate

Syntheses of new fully unsaturated seven-membered heterocyclic rings with two or more heteroatoms have recently been widely studied.²⁾ With regard to monocyclic triazepines,³⁾ 1,2,4-triazepines have been prepared by the cycloaddition of 1-azirines to 1,2,4,5-tetrazines⁴⁾ or by a photochemical walk-rearrangement of 3,4,7-triaza-2,4-norcaradienes.⁵⁾ However, the other three possible isomers due to the isomeric positions of the three nitrogen atoms, 1,2,3-, 1,2,5-, and 1,3,5-triazepines, have remained unknown, although some reactions^{3,6)} involving such triazepines as unisolable intermediates and the syntheses^{2,3)} of di- and per-hydrotriazepines have been reported. Therefore, we were interested in the synthesis of new triazepines and report here the synthesis of the first examples of fully unsaturated 1,2,5-triazepines.⁷⁾

The singlet arylnitrenes generated from arylazides either by photolysis or by thermolysis are known to undergo ring-expansion.⁸⁾ We have already reported⁹⁾ that the photolysis of the 4-azidopyridines (1) in the presence of methoxide ion resulted in ring-expansion to give the 6*H*-1,4-diazepines (3) via the azirine intermediates 2 formed

from the initially generated 4-pyridylnitrenes. In the case of 3-azidopyridines (4),¹⁰⁾ 2-unsubstituted compounds give the 5*H*-1,3-diazepines (6) via the azirines (5), while 2-substituted compounds afford the 2*H*-1,4-diazepines (8) via the different azirines (7). These results prompted us to examine the photolysis of 4-azidopyridazines.

The synthetic route to the starting 4-azidopyridazines (11a—f) used in the present work is shown in Chart 2. The known 4-nitropyridazine 1-oxides (9a—f) were treated with sodium azide to give the 4-azidopyridazine 1-oxides (10: 80—90% yields), which were deoxygenated by treatment with phosphorus trichloride to afford the 4-azidopyridazines (11) in 50—70% yields.

Irradiation (400 W, high-pressure Hg lamp; Pyrex filter) of the 3-methoxy-4-azidopyridazines (11a—c: ca. 0.5 g) in methanol-dioxane (1:1; 150 ml) containing a large excess of sodium methoxide (ca. 10 mol eq) until almost all of the starting azides had been consumed (for 60—90 min) gave the desired 4*H*-1,2,5-triazepines (13a—c) in 50—60% yields via the 1*H*-isomers 12, as the sole ring-expansion products. In order to confirm the initial formation of the 1*H*-isomers 12, the azides (11a, b) were irradiated in the presence of equimolecular amounts of sodium methoxide under ice-cooling for 50—60 min to form the expected 1*H*-1,2,5-triazepines (12) together with the 4*H*-isomers 13. The product mixtures containing 12 and 13 in the ratios of 3—4:1 (based on proton nuclear magnetic resonance (¹H-NMR) spectral analysis) were chromatographed to give

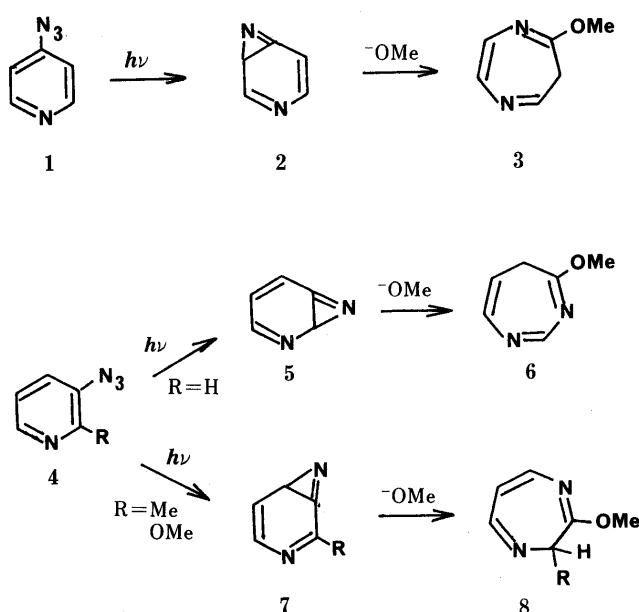
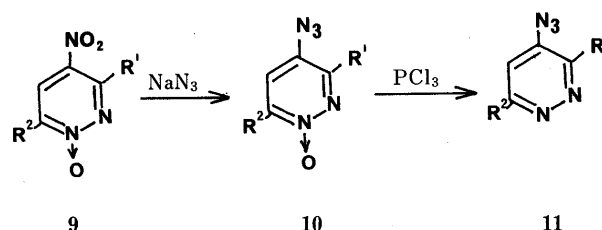


Chart 1



	R ¹	R ²
a	OMe	H
b	OMe	Me
c	OMe	OMe
d	H	H
e	H	Me
f	Me	Me

Chart 2

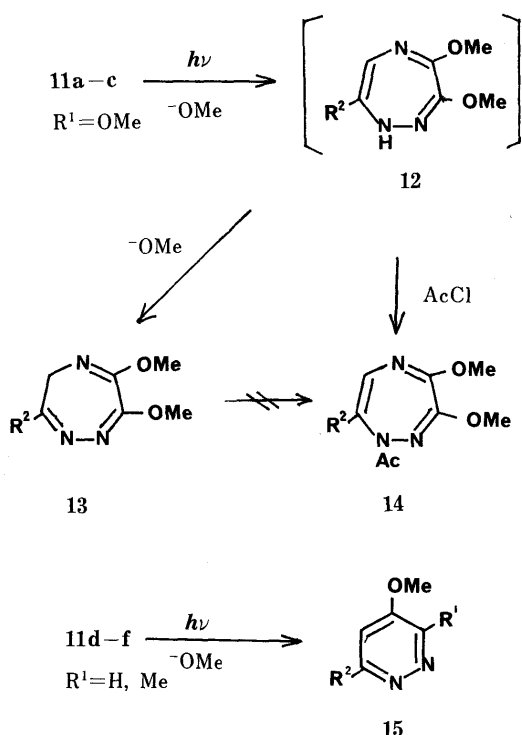


Chart 3

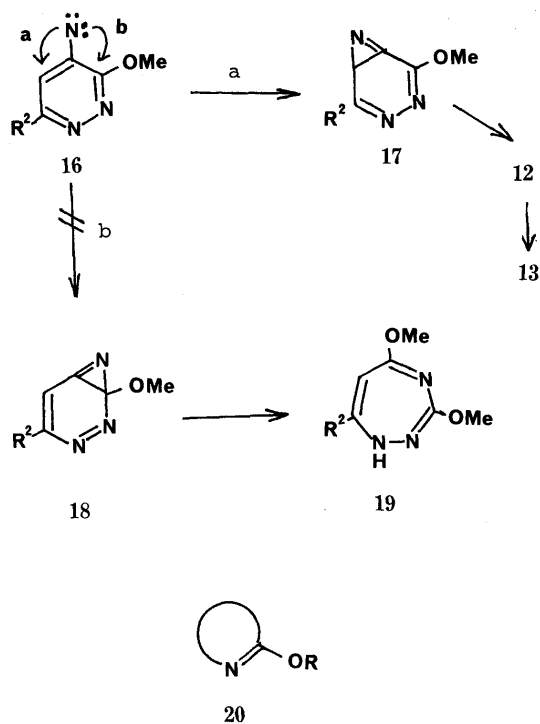


Chart 4

only the 4H-isomers 13 in low yields (13a: 15%; 13b: 27%), but were further treated with a large excess of sodium methoxide in methanol for 3–5 h at room temperature to give 13 in higher yields (13a: 45%; 13b: 51%). These results clearly indicate that the 1H-isomers 12 initially formed are unstable and readily decomposed when passed through a silica gel or alumina column, but tautomerize to the more stable 4H-isomers 13 on treatment with sodium methoxide, by analogy with the case of 1H-1,4-benzodiazepines.¹¹ Therefore, the structures of 12 were confirmed by means of ¹H-NMR spectral analysis of the product mixtures without isolation and by the following chemical study. The photolysed product mixtures containing the 1H-isomers 12 obtained from 11a,b were treated with acetyl chloride in pyridine to give the desired 1-acetyl-1H-1,2,5-triazepines (14a: 26%; 14b: 46%) as stable crystals. It is known that the CH-forms of diazepines such as 4H-1,2,¹² and 6H-1,4-diazepines⁹ and 3H-1,4,¹¹ and 5H-2,3-benzodiazepines¹³ undergo acetylation with tautomerization, giving rise to the corresponding N-acetyl derivatives. However, attempts to convert the 4H-isomers 13 into the 1-acetyl-1H-triazepines (14) have been unsuccessful, resulting only in decomposition. These results show that the acetyl compounds 14 are directly formed from the 1H-isomers 12.

It should be noted that, on the contrary, the 4-azido-pyridazines (11d–f) having no methoxy group, upon irradiation under similar conditions, gave only the substitution products 15, 4-methoxypyridazines, in low yields (10–20%) and no ring-expansion products.

The formation of the 1,2,5-triazepines (12) from the azides (11) may proceed via the azirine intermediates 16, but that of 1,2,4-triazepines such as 19 expected from the other possible azirine intermediates 18 was not observed in the present photolysis. This direction of azirine formation is analogous to that of 2-substituted phenylnitrenes¹⁴ and

3-pyridylnitrenes,¹⁰ which are known to cyclize preferentially at the vacant α-position. Although the effect of the methoxy group is not clear, we assume that the strong electron-donating methoxy group may provide assistance for the cyclization of the initially formed pyridazinylnitrenes (16) to the azirines (17), and for stabilization of the triazepine ring obtained. It has been observed that azepine and diazepine rings are stabilized by an iminoether structure 20.^{9,10}

The ¹H-NMR spectra of the a-series of the 1H-triazepines showed AB pairs of doublets (12a: δ 5.80 and 5.97, J = 6 Hz; 14a: δ 6.20 and 6.34, J = 6 Hz) assignable to 7-H and 6-H and, in the case of 12a, a broad NH signal at δ 5.15, in addition to methoxy and acetyl proton signals, while that of the 4H-isomer 13a showed a methylene proton signal at δ 3.72 (2H, d, J = 5 Hz) due to 4-H₂ and a triplet signal at δ 7.50 (J = 5 Hz) due to 3-H. The ¹³C-NMR spectra of 13a–c exhibited signals due to sp³ ring carbon atoms at around δ 45 (t), whereas those of 14 showed no sp³ ring carbon signals. These spectral data and the results of the following chemical studies are consistent with the proposed 1,2,5-triazepine structures for 12–14.

LiAlH₄ reduction of the 4H-triazepines (13a, b) afforded the dihydro compounds 21 in moderate yields (21a: 87%; 21b: 51%). Treatment of 21a with acetyl chloride in pyridine gave 1-acetyl-3,4-dimethoxy-6,7-dihydro-1H-1,2,5-triazepine (22: 41% yield), which was also obtained from the 1-acetyl-1H-triazepine (14a) by hydrogenation over Pd–C in 73% yield. Heating 14a in o-dichlorobenzene at 190–200 °C for 65 h in a sealed tube resulted in isomerization to give the 6-acetylaminopyrazine (24) in 76% yield, presumably via the diaziridine intermediate 23. This thermal behavior, including the mode of the diaziridine ring fission and the substituent effect, is similar to that observed in the thermolysis of 1,2- and 1,3-triaze-

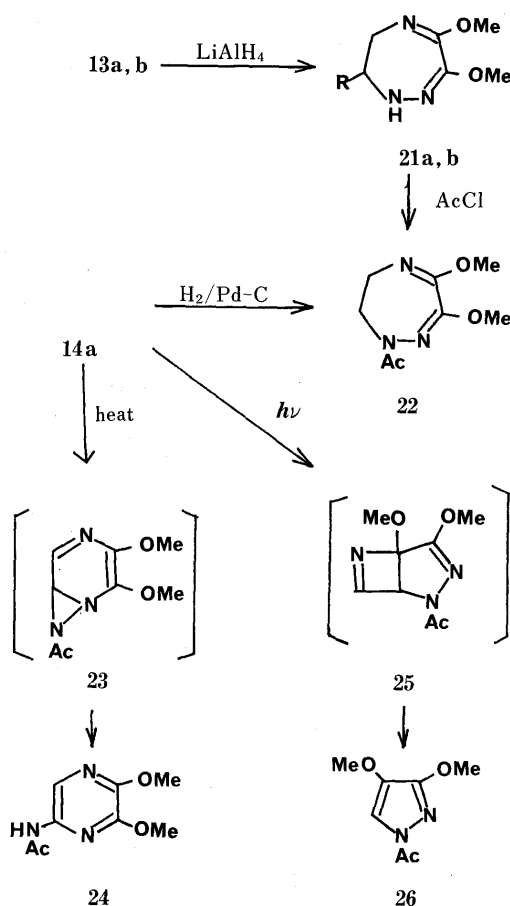


Chart 5

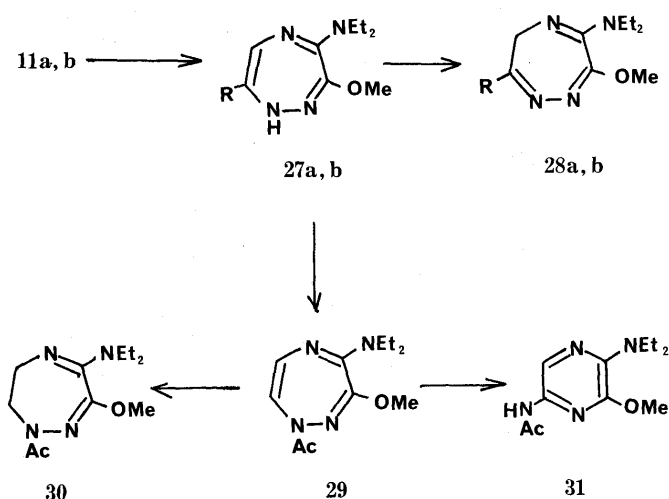


Chart 6

pinines.^{9,10,15} Irradiation of 14a in benzene for 4.5 h gave 1-acetyl-3,4-dimethoxypyrazole (26) in 71% yield, probably *via* the bicyclic intermediate 25. This photochemical behavior is also analogous to those observed for a variety of fully unsaturated seven-membered heterocyclic rings.^{2,16}

Next, when an amine was used as a base instead of sodium methoxide in the present photolysis, similar results were obtained. Irradiation of the azides (11a, b) in diethylamine-dioxane (1:1) for 70–80 min formed the unstable 1*H*-triazepines (27) and the stable 4*H*-isomers (28) in the ra-

tios of 3–5:1. These product mixtures were treated with sodium methoxide in methanol, and then chromatographed on alumina to give the 4*H*-1,2,5-triazepines (28) in *ca.* 40% yields. The photolysed mixture obtained from 11a was acetylated with acetyl chloride in pyridine to give the 1-acetyl compound 29 in 46% yield. Hydrogenation of 29 over Pd-C afforded the 6,7-dihydro compound 30 in 79% yield and the thermolysis of 29 at 190–200 °C gave the pyrazole derivative 31 in 62% yield.

In conclusion, the products 12–14 and 27–29 are the first examples of fully unsaturated 1,2,5-triazepines.

Experimental

Melting points were measured on a Yanagimoto micro melting point hot stage apparatus and are uncorrected. Infrared (IR) spectra were determined with a Hitachi 270–30 spectrometer and mass spectra (MS) were measured with a JEOL DX-300 instrument. $^1\text{H-NMR}$ spectra were recorded on a JEOL JNM-MH100 spectrometer in CDCl_3 using tetramethylsilane as an internal standard unless otherwise stated; spectral assignments were confirmed by spin-decoupling experiments and, in the case of NH protons, by exchange with D_2O . $^{13}\text{C-NMR}$ spectra were recorded on a JEOL FX-100 spectrometer in CDCl_3 . Microanalyses were performed in the Microanalytical Center of this faculty by Mrs. R. Igarashi. Photolyses were carried out under a nitrogen atmosphere in an immersion apparatus equipped with a 400 W high-pressure Hg lamp and a Pyrex filter, which was cooled internally with running water. Kieselgel 60 (70–230 mesh, Merck) was used for silica gel column chromatography. For alumina column chromatography, Aluminiumoxid 90 standardisiert (Activitätsstufe II–III, 70–230 mesh, Merck) was used.

Starting Materials The 4-nitropyridazine 1-oxides (9a,¹⁷ 9b,¹⁸ 9c,¹⁹ 9d,²⁰ 9e,²¹ and 9f²²) were prepared by the reported methods.

4-Azidopyridazine 1-Oxides (10a–f) General Procedure: A solution of sodium azide (3–5 mol eq) in water (3–5 ml) was added to a solution of 9 (2–8 g) in EtOH (50–150 ml) with stirring at room temperature. The mixture was refluxed for 4–6 h and then evaporated *in vacuo*. The residue was extracted with CH_2Cl_2 and the extract was washed with water, dried over MgSO_4 , and evaporated *in vacuo*. The residue was chromatographed on alumina using CH_2Cl_2 as an eluent to give 10.

10a: 93% yield, mp 140–141 °C, pale yellow needles [from isopropyl ether (IPE)]. IR (KBr): 2136 (N_3) cm^{-1} . $^1\text{H-NMR}$ δ : 4.10 (3H, s, 3-OMe), 7.03 (1H, d, 5-H), 7.84 (1H, d, 6-H), $J_{5,6}$ = 6 Hz. Anal. Calcd for $\text{C}_5\text{H}_5\text{N}_5\text{O}_2$: C, 35.93; H, 3.02; N, 41.91. Found: C, 36.20; H, 2.91; N, 40.16.

10b: 78% yield, mp 103–105 °C, pale yellow needles (from hexane- CH_2Cl_2). IR (KBr): 2120 (N_3) cm^{-1} . $^1\text{H-NMR}$ δ : 2.40 (3H, s, 6-Me), 4.06 (3H, s, 3-OMe), 6.99 (1H, s, 5-H). Anal. Calcd for $\text{C}_6\text{H}_7\text{N}_5\text{O}_2$: C, 39.78; H, 3.89; N, 38.66. Found: C, 40.03; H, 3.79; N, 38.52.

10c: 90% yield, mp 93–94 °C, pale yellow needles (from IPE). IR (KBr): 2120 (N_3) cm^{-1} . $^1\text{H-NMR}$ δ : 4.05 and 4.06 (each 3H, s, 3- and 6-OMe), 7.03 (1H, s, 5-H). Anal. Calcd for $\text{C}_6\text{H}_7\text{H}_5\text{O}_3$: C, 36.55; H, 3.58; N, 35.52. Found: C, 36.72; H, 3.61; N, 35.39.

10d: 90% yield, mp 125–126 °C (lit.²³) mp 123–124 °C.

10e: 81% yield, mp 139–140 °C, pale yellow needles (from hexane- CH_2Cl_2). IR (KBr): 2132 (N_3) cm^{-1} . $^1\text{H-NMR}$ δ : 2.48 (3H, s, 6-Me), 7.20 (1H, d, 5-H), 8.04 (1H, d, 3-H), $J_{3,5}$ = 3 Hz. Anal. Calcd for $\text{C}_5\text{H}_5\text{N}_5\text{O}$: C, 39.73; H, 3.33; N, 46.34. Found: C, 39.80; H, 3.25; N, 46.59.

10f: 82% yield, mp 143–144 °C, pale yellow needles (from hexane- CH_2Cl_2). IR (KBr): 2124 (N_3) cm^{-1} . $^1\text{H-NMR}$ δ : 2.36 (3H, s, 3-Me), 2.48 (3H, s, 6-Me), 7.22 (1H, s, 5-H). Anal. Calcd for $\text{C}_6\text{H}_7\text{N}_5\text{O}$: C, 43.63; H, 4.27; N, 42.41. Found: C, 43.88; H, 4.22; N, 42.12.

4-Azidopyridazines (11a–f) General Procedure: The procedure²³ for the preparation of 11d was employed. Phosphorus trichloride (*ca.* 3 mol eq) was added dropwise with stirring to a solution of 10 (2–5 g) in CHCl_3 (50–150 ml) in an ice bath. The mixture was stirred for 4–8 h at room temperature and then poured into ice-water (50–100 ml). The aqueous mixture was made alkaline with NaHCO_3 and extracted with CH_2Cl_2 . The extract was washed with brine, dried, and evaporated *in vacuo*. The residue was chromatographed on silica gel using CH_2Cl_2 as an eluent to give 11 as colorless needles (from IPE).

11a: 73% yield, mp 70.5–71.5 °C. IR (KBr): 2136 (N_3) cm^{-1} . $^1\text{H-NMR}$ δ : 4.22 (3H, s, 3-OMe), 6.94 (1H, d, 5-H), 8.71 (1H, d, 6-H), $J_{5,6}$ = 5 Hz. Anal. Calcd for $\text{C}_5\text{H}_5\text{N}_5\text{O}$: C, 39.73; H, 3.33; N, 46.34. Found: C, 39.53;

H, 3.19; N, 46.10.

11b: 60% yield, mp ca. 20°C. MS m/z : 165 (M^+). IR (KBr): 2124 (N_3) cm^{-1} . 1H -NMR δ : 2.53 (3H, s, 6-Me), 4.14 (3H, s, 3-OMe), 6.72 (1H, s, 5-H). Anal. Calcd for $C_6H_7N_3O$: C, 43.63; H, 4.27; N, 42.41. Found: C, 43.69; H, 4.01; N, 42.16.

11c: 45% yield, mp 74–75°C. IR (KBr): 2128 (N_3) cm^{-1} . 1H -NMR δ : 3.97 (3H, s, 6-OMe), 4.07 (3H, s, 3-OMe), 6.41 (1H, s, 5-H). Anal. Calcd for $C_6H_7N_3O_2$: C, 39.78; H, 3.89; N, 38.66. Found: C, 39.91; H, 3.82; N, 38.60.

11d: 70% yield, mp 63–65°C (lit.²³) mp 62–64°C).

11e: 51% yield, mp ca. 15°C. MS m/z : 135 (M^+). IR (neat): 2120 (N_3) cm^{-1} . 1H -NMR δ : 2.70 (3H, s, 6-Me), 6.93 (1H, d, 5-H), 8.68 (1H, d, 3-H), $J_{3,5}$ = 3 Hz. Anal. Calcd for $C_5H_5N_3$: C, 44.44; H, 3.73; N, 51.83. Found: C, 44.21; H, 3.92; N, 51.56.

11f: 69% yield, mp 86–87°C. IR (KBr): 2128 (N_3) cm^{-1} . 1H -NMR δ : 2.52 (3H, s, 3-Me), 2.64 (3H, s, 6-Me), 6.98 (1H, s, 5-H). Anal. Calcd for $C_6H_7N_3$: C, 48.31; H, 4.73; N, 46.96. Found: C, 48.20; H, 4.63; N, 46.67.

Photolysis of 11a–c in the Presence of Sodium Methoxide: Formation of the 4H-1,2,5-triazepines (13) via the 1H-isomers (12). i) In the Presence of a Large Excess of Sodium Methoxide General Procedure: A solution of **11** (ca. 0.5 g) in MeOH–dioxane (1 : 1, 150 ml) containing a large excess of NaOMe (ca. 10 mol eq) was irradiated with a 400 W high-pressure Hg lamp under a nitrogen atmosphere. The photolysis was followed in terms of the disappearance of the spot of the starting azide on thin-layer chromatography, and was complete in 60–90 min. After removal of the solvent *in vacuo*, ice-water (20–30 ml) was added to the residue and the aqueous mixture was extracted with benzene. The extract was washed with brine, dried, and evaporated *in vacuo*. The residue was chromatographed on alumina using CH_2Cl_2 as an eluent to give the 6,7-dimethoxy-4H-1,2,5-triazepines (**13**).

13a: 52% yield, pale yellow viscous oil. MS m/z : 155 (M^+). IR (neat): 1666 and 1646 ($C=N$) cm^{-1} . 1H -NMR δ : 3.72 (2H, br d, 4-H₂), 3.72 and 3.92 (each 3H, s, 6- and 7-OMe), 7.50 (1H, t, 3-H), $J_{3,4}$ = 5 Hz. ^{13}C -NMR δ : 43.7 (t, 4-C), 54.0 (q), 54.3 (q), 151.3 (d, 3-C), 152.4 (s), 154.5 (s). Anal. Calcd for $C_6H_9N_3O_2$: C, 46.44; H, 5.85; N, 27.08. Found: C, 46.60; H, 5.83; N, 26.81.

13b: 60% yield, mp ca. 15°C, colorless prisms (from IPE–hexane). MS m/z : 169 (M^+). IR (neat): 1646 ($C=N$) cm^{-1} . 1H -NMR δ : 2.21 (3H, s, 3-Me), 3.72 (2H, s, 4-H₂), 3.72 and 3.90 (each 3H, s, 6- and 7-OMe). ^{13}C -NMR δ : 23.5 (q), 47.7 (t, 4-C), 53.9 (q), 54.1 (q), 152.2 (s), 155.0 (s), 160.2 (s). Anal. Calcd for $C_7H_{11}N_3O_2$: C, 49.69; H, 6.55; N, 24.84. Found: C, 49.58; H, 6.56; N, 24.66.

13c: 60% yield, mp 66–68°C, colorless prisms (from IPE–hexane). MS m/z : 185 (M^+). IR (KBr): 1654 ($C=N$) cm^{-1} . 1H -NMR δ : 3.84 (2H, s, 4-H₂), 3.76, 3.82, and 3.94 (each 3H, s, 3-, 6-, and 7-OMe). ^{13}C -NMR δ : 46.2 (t, 4-C), 54.1 (q), 54.4 (q), 55.2 (q), 153.4 (s), 155.7 (s), 160.7 (s). Anal. Calcd for $C_7H_{11}N_3O_3$: C, 45.40; H, 5.99; N, 22.69. Found: C, 45.36; H, 6.08; N, 22.50.

ii) In the Presence of Equimolecular Amounts of Sodium Methoxide The azides (**11a–c**; 0.4–0.5 g) were irradiated in the presence of NaOMe (ca. 1.1 mol eq) and worked up as described for i). In the cases of **11a** and **11b**, the 1H -NMR spectrum of the residue obtained from the extract showed that the product was a mixture of **12** and **13** (4 : 1 for **a**; 2 : 1 for **b**), but the residue obtained from **11c** contained only **13c**. The 1H-isomers (**12a**, **b**) were unstable and readily decomposed during isolation by chromatography, and therefore were characterized only by the following 1H -NMR spectral data. **12a:** δ 3.68 (3H, s, OMe), 3.80 (3H, s, OMe), 5.15 (1H, br, NH), 5.80 (1H, d, 7-H), 5.97 (1H, d, 6-H), $J_{6,7}$ = 6 Hz. **12b:** δ 1.84 (3H, s, 7-Me), 3.72 (3H, s, OMe), 3.80 (3H, s, OMe), 5.2 (1H, br, NH), 6.36 (1H, s, 6-H). The residue was chromatographed on alumina or silica gel to give only the 4H-isomer **13** in a low yield (**13a**: 15%; **13b**: 27%; **13c**: 37%). However, the residue was dissolved in MeOH containing a large excess of NaOMe and the solution was stirred for 3–5 h at room temperature, and then poured into ice-water. The aqueous mixture was extracted with benzene. The extract was washed, dried, and evaporated *in vacuo*. The residue showed no signals due to **12** in the 1H -NMR spectrum was chromatographed on alumina to give **13** in a higher yield (**13a**: 45%; **13b**: 51%; **13c**: 47%).

I-Acetyl-1H-1,2,5-triazepines (14a, b) The azides (**11a,b**; ca. 0.5 g) were photolysed in the presence of NaOMe (ca. 1 mol eq) and worked up as described for the photolysis of **11a–c** (ii). The residue, containing a mixture of **12** and **13** was dissolved in pyridine (3–4 ml). AcCl (0.4 g) was added to the ice-cold pyridine solution and the mixture was stirred for 5–6 h at room temperature, and then poured into ice-water (ca. 20 ml). The aqueous mixture was extracted with CH_2Cl_2 and the extract was successively washed

with saturated $NaHCO_3$ and water, and then dried and evaporated *in vacuo*. The residue was chromatographed on alumina using CH_2Cl_2 – Et_2O (10 : 1) as an eluent to give **14**.

14a: 26% yield, mp 112–113°C, pale yellow plates (from hexane). MS m/z : 197 (M^+). IR (KBr): 1684 ($C=O$) cm^{-1} . 1H -NMR δ : 2.21 (3H, s, 1-COMe), 3.82 and 3.89 (each 3H, s, 3- and 4-OMe), 6.20 (1H, d, 6-H), 6.34 (1H, d, 7-H), $J_{6,7}$ = 6 Hz. ^{13}C -NMR δ : 21.1 (q), 54.1 (q), 55.9 (q), 120.9 (d), 128.4 (d), 157.2 (s), 158.0 (s), 172.3 (s). Anal. Calcd for $C_8H_{11}N_3O_3$: C, 48.72; H, 5.62; N, 21.31. Found: C, 48.68; H, 5.67; N, 21.35.

14b: 46% yield, mp 101.5–103.5°C, pale yellow plates (from hexane). MS m/z : 211 (M^+). IR (KBr): 1678 ($C=O$) cm^{-1} . 1H -NMR δ : 2.06 (3H, s, 7-Me), 2.12 (3H, s, 1-COMe), 3.80 and 3.90 (each 3H, s, 3- and 4-OMe), 6.32 (1H, s, 6-H). Anal. Calcd for $C_9H_{13}N_3O_3$: C, 51.17; H, 6.20; N, 19.90. Found: C, 51.40; H, 6.05; N, 19.86.

Photolysis of 11d–f The azides (**11d–f**; 0.3–0.5 g) were photolysed in the presence of a large excess of NaOMe and worked up as described for **11a–c** to give 4-methoxypyridazines (**15**) and no triazepines.

15d: 8% yield, mp 42–44°C (lit.²⁴) mp 43–44°C).

15e: 16% yield, viscous oil. MS m/z : 124 (M^+). 1H -NMR δ : 2.64 (3H, s, 6-Me), 3.89 (3H, s, 4-OMe), 6.74 (1H, d, 5-H), 8.73 (1H, d, 3-H), $J_{3,5}$ = 3 Hz. Anal. Calcd for $C_6H_8N_2O$: C, 58.05; H, 6.50; N, 22.57. Found: C, 57.89; H, 6.54; N, 22.31.

15f: 8% yield, mp 73–75°C, colorless needles (from IPE). MS m/z : 138 (M^+). 1H -NMR δ : 2.50 and 2.60 (each 3H, s, 3- and 6-Me), 3.87 (3H, s, 4-OMe), 6.63 (1H, s, 5-H). Anal. Calcd for $C_7H_{10}N_2O$: C, 60.85; H, 7.30; N, 20.28. Found: C, 60.83; H, 7.46; N, 20.01.

LiAlH₄ Reduction of 13a, b $LiAlH_4$ (2–3 mol eq) was added in small portions to a solution of **13** (0.1–0.2 g) in dry Et_2O (10 ml) with stirring in an ice bath. The mixture was stirred for a further 1 h at room temperature. After addition of saturated NaCl (0.5 ml) to decomposed excess reagent, the reaction mixture was dried over $MgSO_4$ and filtered. The filtrate was evaporated and the residue was chromatographed on alumina using CH_2Cl_2 –benzene (1 : 1) as an eluent to give the 6,7-dihydro-1H-1,2,5-triazepines (**21**).

21a: 87% yield, mp 73–74°C, colorless needles (from hexane). MS m/z : 157 (M^+). IR (KBr): 3352 (NH), 1676 ($C=N$) cm^{-1} . 1H -NMR δ : 3.32 (2H, t, 7-H₂), 3.68 and 3.72 (each 3H, s, 3- and 4-OMe), 3.80 (2H, t, 6-H₂), 5.36 (1H, br, 1-NH), $J_{6,7}$ = 5 Hz. ^{13}C -NMR δ : 50.2 (t, 7-C), 51.7 (t, 6-C), 53.3 (q), 54.0 (q), 143.2 (s), 151.1 (s). Anal. Calcd for $C_6H_{11}N_3O_2$: C, 45.85; H, 7.05; N, 26.74. Found: C, 45.83; H, 7.11; N, 26.52.

21b: 51% yield, colorless viscous oil. MS m/z : 171 (M^+). IR (neat): 3360 (NH), 1666 ($C=N$) cm^{-1} . 1H -NMR δ : 1.20 (3H, d, 7-Me), 3.2–3.4 (1H, m, 7-H), 3.68 and 3.72 (each 3H, s, 3- and 4-OMe), 3.70 (2H, d, 6-H₂), 4.90 (1H, br, 1-NH), $J_{6,7}$ = 5, $J_{7,7-Me}$ = 6 Hz. ^{13}C -NMR δ : 18.2 (q), 53.2 (q), 54.0 (q), 55.9 (t, 6-C), 57.1 (d, 7-C), 143.9 (s), 151.3 (s). Anal. Calcd for $C_7H_{13}N_3O_2$: C, 49.11; H, 7.65; N, 24.55. Found: C, 49.01; H, 7.69; N, 24.31.

Acetylation of 21a with Acetyl Chloride AcCl (75 mg, 1.3 mol eq) was added dropwise to a solution of **21a** (100 mg) in pyridine (2 ml) with stirring in an ice bath. The mixture was stirred for a further 5 h at 0–5°C and then ice-water (ca. 20 ml) was added. The aqueous mixture was extracted with CH_2Cl_2 and the extract was successively washed with saturated $NaHCO_3$ and brine, and then dried and evaporated *in vacuo*. The residue was chromatographed on alumina using CH_2Cl_2 as an eluent to give 1-acetyl-3,4-dimethoxy-6,7-dihydro-1H-1,2,5-triazepine (**22**): 54 mg, 41% yield, mp 64–65°C, colorless needles (from IPE– CH_2Cl_2). MS m/z : 199 (M^+). IR (KBr): 1680 ($C=O$) cm^{-1} . 1H -NMR δ : 2.28 (3H, s, 1-COMe), 3.77 and 3.80 (each 3H, s, 3- and 4-OMe), 3.80 and 4.05 (each 2H, t, 6- and 7-H₂), $J_{6,7}$ = 4 Hz. Anal. Calcd for $C_8H_{13}N_3O_3$: C, 48.23; H, 6.58; N, 21.10. Found: C, 48.25; H, 6.86; N, 21.07.

Hydrogenation of 14a The 1-acetyl compound **14a** (65 mg) was hydrogenated over 5% Pd–C (100 mg) in MeOH (15 ml) under atmospheric pressure at room temperature for 3 h. The catalyst was filtered off and the filtrate was evaporated *in vacuo*. The residue was chromatographed on silica gel using CH_2Cl_2 –MeOH (10 : 1) as an eluent to give the dihydro compound (48 mg, 73% yield), which was identical with **22** obtained from **21a** by acetylation.

Thermolysis of 14a A solution of **14a** (33 mg) in *o*-dichlorobenzene (0.5 ml) was heated at 190–200°C in a sealed NMR tube until the 1H -NMR signals due to starting **14a** disappeared (for 65 h). After cooling, the solution was chromatographed on silica gel using CH_2Cl_2 – Et_2O (5 : 1) as an eluent to give 6-acetyl-2,3-dimethoxypyridazine (**24**): 25 mg, 76% yield, mp 184–185°C, colorless needles (from hexane– CH_2Cl_2). MS m/z : 197 (M^+). IR (KBr): 3260 (NH), 1652 ($C=O$) cm^{-1} . 1H -NMR δ : 2.24 (3H, s, COMe), 3.99 and 4.04 (each 3H, s, 2- and 3-OMe), 7.60 (1H, br,

NH), 8.52 (1H, s, 3-H). $^{13}\text{C-NMR}$ δ : 24.2 (q), 54.0 (q), 54.2 (q), 121.5 (d), 138.0 (s), 146.9 (s), 148.3 (s), 167.9 (s). *Anal.* Calcd for $\text{C}_8\text{H}_{11}\text{N}_3\text{O}_3$: C, 48.72; H, 5.62; N, 21.31. Found: C, 48.70; H, 5.68; N, 21.19.

Photolysis of 14a A solution of **14a** (350 mg) in benzene (130 ml) was irradiated for 4.5 h and then evaporated *in vacuo*. The residue was chromatographed on silica gel using CH_2Cl_2 as an eluent to give 1-acetyl-3,4-dimethoxypyrazole (**26**): 212 mg, 71% yield, mp 96–97°C, colorless plates (from hexane). MS m/z : 170 (M^+). IR (KBr): 1706 ($\text{C}=\text{O}$) cm^{-1} . $^1\text{H-NMR}$ δ : 2.50 (3H, s, COMe), 3.79 and 3.84 (each 3H, s, 3- and 4-OMe), 7.60 (1H, s, 5-H). $^{13}\text{C-NMR}$ δ : 20.5 (q), 56.5 (q), 59.0 (q), 110.1 (d), 138.2 (s), 156.8 (s), 168.5 (s). *Anal.* Calcd for $\text{C}_7\text{H}_{10}\text{N}_2\text{O}_3$: C, 49.40; H, 5.92; N, 16.46. Found: C, 49.48; H, 5.79; N, 16.43.

Photolysis of 11a, b in the Presence of Diethylamine A solution of **11** (ca. 0.5 g) in Et_2NH -dioxane (1:1, 150 ml) was irradiated for 70–80 min and then evaporated *in vacuo*. The $^1\text{H-NMR}$ spectrum of the residue showed that the residue contained the 1*H*-1,2,5-triazepine (**27**) and the 3*H*-isomer (**28**) in a ratio of 3–5:1. However, the residue was chromatographed on alumina using CH_2Cl_2 - Et_2O (1:1) as an eluent to give only **28** in a low yield (5–10%), indicating that the 1*H*-isomers (**27**) are too unstable to be isolated. Therefore, they were characterized only by the following $^1\text{H-NMR}$ spectral data. **27a**: δ 1.12 and 3.1–3.4 (6H, t, and 4H, m, 4- NEt_2), 3.60 (3H, s, 3-OMe), 4.88 (1H, br, 1-NH), 5.76 (1H, d, 7-H), 6.10 (1H, d, 6-H), $J_{6,7}=6\text{ Hz}$. **27b**: δ 1.08 and 3.0–3.4 (6H, t, and 4H, m, 4- NEt_2), 1.84 (3H, s, 7-Me), 4.04 (3H, s, 3-OMe), 4.9 (1H, br, NH), 6.52 (1H, s, 6-H).

The above residue was dissolved in MeOH (10 ml) containing NaOMe (ca. 0.5 g) and the solution was stirred for 10 h at room temperature, and then evaporated *in vacuo*. Ice-water (5–10 ml) was added to the residue and the aqueous mixture was extracted with CH_2Cl_2 . The extract was washed with water, dried, and evaporated *in vacuo*. The residue was chromatographed on alumina using CH_2Cl_2 - Et_2O (1:1) as an eluent to give the 4*H*-1,2,5-triazepines (**28**) as colorless viscous oils.

28a: 36% yield. MS m/z : 196 (M^+). IR (neat): 1634 ($\text{C}=\text{N}$) cm^{-1} . $^1\text{H-NMR}$ δ : 1.04 and 2.95–3.35 (6H, t, and 4H, m, 6- NEt_2), 3.80 (3H, s, 7-OMe), 3.8 (2H, br, 4- H_2), 7.40 (1H, t, 3-H), $J_{3,4}=6\text{ Hz}$. $^{13}\text{C-NMR}$ δ : 13.1 (q, $2\times\text{C}$), 42.8 (t, $2\times\text{C}$), 44.9 (t, 4-C), 53.5 (q), 152.4 (s), 154.9 (d, 3-C), 155.7 (s). *Anal.* Calcd for $\text{C}_9\text{H}_{16}\text{N}_4\text{O}$: C, 55.08; H, 8.22; N, 28.55. Found: C, 54.87; H, 8.23; N, 28.32.

28b: 41% yield. MS m/z : 210 (M^+). IR (neat): 1630 ($\text{C}=\text{N}$) cm^{-1} . $^1\text{H-NMR}$ δ : 1.08 and 3.0–3.4 (6H, t, and 4H, m, 6- NEt_2), 2.16 (3H, s, 3-Me), 3.5 (2H, br, 4- H_2), 3.98 (3H, s, 7-OMe). *Anal.* Calcd for $\text{C}_{10}\text{H}_{18}\text{N}_4\text{O}$: C, 57.11; H, 8.63; N, 26.65. Found: C, 56.98; H, 8.61; N, 26.40.

1-Acetyl-4-diethylamino-3-methoxy-1*H*-1,2,5-triazepines (29) A mixture of the residue obtained by the photolysis of **11a** (0.5 g) in the presence of Et_2NH , acetyl chloride (0.3 g), and pyridine (5 ml) was stirred for 10 h at room temperature, and then ice-water (10 ml) was added to the mixture. The aqueous mixture was extracted with CH_2Cl_2 and the extract was washed with water, dried, and evaporated *in vacuo*. The residue was chromatographed on alumina using CH_2Cl_2 - Et_2O (1:1) as an eluent to give **29**: 46% yield, mp 60–61°C, yellow plates (from hexane). MS m/z : 238 (M^+). IR (KBr): 1680 ($\text{C}=\text{O}$) cm^{-1} . $^1\text{H-NMR}$ δ : 1.16 and 3.32 (6H, t, and 4H, q, 4- NEt_2), 2.16 (3H, s, 1-COMe), 3.87 (3H, s, 3-OMe), 6.03 (1H, d, 6-H), 6.50 (1H, d, 7-H), $J_{6,7}=6\text{ Hz}$. *Anal.* Calcd for $\text{C}_{11}\text{H}_{18}\text{N}_4\text{O}_2$: C, 55.44; H, 7.61; N, 23.52. Found: C, 55.58; H, 7.41; N, 23.49.

1-Acetyl-4-diethylamino-3-methoxy-6,7-dihydro-1*H*-1,2,5-triazepine (30) Compound **29** (100 mg) was hydrogenated over 5% Pd-C and worked up as described for the hydrogenation of **14** to give **30**: 80 mg, 79% yield, mp 51.5–53°C, colorless needles (from IPE). MS m/z : 240 (M^+). IR (KBr): 1660 ($\text{C}=\text{O}$) cm^{-1} . $^1\text{H-NMR}$ δ : 1.14 (6H, t, NEt_2 -Me₂), 3.1–3.5 [6H, m, NEt_2 -(CH₂)₂ and 7- H_2], 2.08 (3H, s, 1-COMe), 3.84 (2H, t, 6- H_2), 3.96 (3H, s, 2-OMe). $^{13}\text{C-NMR}$ δ : 13.2 (q, $2\times\text{C}$), 21.8 (q), 42.1 (t, $2\times\text{C}$), 45.5 (t, 7-C), 51.1 (t, 6-C), 54.7 (q), 155.1 (s), 160.4 (s), 171.9 (s). *Anal.*

Calcd for $\text{C}_{11}\text{H}_{20}\text{N}_4\text{O}_2$: C, 54.98; H, 8.39; N, 23.32. Found: C, 55.07; H, 8.36; N, 23.37.

Thermolysis of 29 A solution of **29** (130 mg) in *o*-dichlorobenzene was heated at 190–200°C and worked up as described for the thermolysis of **14a** to give 6-acetylamino-3-diethylamino-2-methoxypyrazine (**31**): 80 mg, 62% yield, mp 121–122°C, colorless needles (from hexane). MS m/z : 238 (M^+). IR (KBr): 3152 (NH), 1706 ($\text{C}=\text{O}$) cm^{-1} . $^1\text{H-NMR}$ δ : 1.12 and 3.46 (6H, t, and 4H, q, 3- NEt_2), 2.20 (3H, s, COMe), 3.92 (3H, s, 2-OMe), 7.50 (1H, br, NH), 8.54 (1H, s, 5-H). *Anal.* Calcd for $\text{C}_{11}\text{H}_{18}\text{N}_4\text{O}_2$: C, 55.44; H, 7.61; N, 23.52. Found: C, 55.63; H, 7.54; N, 23.48.

References

- 1) Part XXXII: H. Sashida, M. Kaname, and T. Tsuchiya, *Chem. Pharm. Bull.*, **38**, 2919 (1990).
- 2) J. T. Sharp, "Comprehensive Heterocyclic Chemistry," Vol. 7, ed. by A. R. Katritzky and C. W. Rees, Pergamon Press, Oxford, 1984, p. 608.
- 3) N. P. Peet, "The Chemistry of Heterocyclic Compounds," Vol. 43 (2), ed. by A. Rosowsky, John Wiley & Sons, N. Y., 1984, p. 719.
- 4) D. J. Anderson and A. Hassner, *J. Chem. Soc., Chem. Commun.*, **1974**, 45; G. C. Johnson and R. H. Levin, *Tetrahedron Lett.*, **1974**, 2303; V. Nair, *J. Heterocycl. Chem.*, **12**, 183 (1975); M. Takahashi, N. Suzuki, and Y. Igari, *Bull. Chem. Soc., Jpn.*, **48**, 2605 (1975).
- 5) I. Saito, A. Yazaki, and T. Matsuura, *Tetrahedron Lett.*, **1974**, 2459.
- 6) O. Tsuge and K. Kamata, *Heterocycles*, **3**, 547 (1975); T. Tsuchiya, J. Kurita, and K. Takayama, *Chem. Pharm. Bull.*, **28**, 2676 (1980).
- 7) A part of this work has been published in a preliminary communication: H. Sawanishi, S. Saito, and T. Tsuchiya, *Chem. Pharm. Bull.*, **36**, 4240 (1988).
- 8) R. Purvis, R. K. Smalley, H. Suschitzky, and M. A. Alkhader, *J. Chem. Soc., Perkin Trans. 1*, **1984**, 249; Y. Ohba, S. Kudo, T. Nishiwaki, and N. Aratani, *Heterocycles*, **22**, 457 (1984); and references cited therein.
- 9) H. Sawanishi, K. Tajima, M. Osada, and T. Tsuchiya, *Chem. Pharm. Bull.*, **32**, 4694 (1984); H. Sawanishi, K. Tajima, and T. Tsuchiya, *ibid.*, **35**, 3175 (1987).
- 10) H. Sawanishi and T. Tsuchiya, *Chem. Pharm. Bull.*, **33**, 5603 (1985); H. Sawanishi, K. Tajima, and T. Tsuchiya, *ibid.*, **35**, 4101 (1987).
- 11) H. Sashida, A. Fujii, and T. Tsuchiya, *Chem. Pharm. Bull.*, **35**, 3182 4110 (1987).
- 12) D. J. Harris, G. Kan, V. Snieckus, and O. Buchardt, *Synthesis*, **1975**, 603.
- 13) J. Kurita, M. Enkaku, and T. Tsuchiya, *Chem. Pharm. Bull.*, **30**, 3764 (1982).
- 14) T. de Boer, J. I. G. Cadgan, H. M. McWilliam, and A. G. Rowley, *J. Chem. Soc., Perkin Trans. 2*, **1975**, 554.
- 15) T. Tsuchiya, J. Kurita, and H. Kojima, *J. Chem. Soc., Chem. Commun.*, **1980**, 444; J. Kurita, H. Kojima, and T. Tsuchiya, *Chem. Pharm. Bull.*, **29**, 3688, 3696 (1981); J. Kurita, K. Iwata, and T. Tsuchiya, *J. Chem. Soc., Chem. Commun.*, **1986**, 1188; *idem*, *Chem. Pharm. Bull.*, **35**, 3166 (1987).
- 16) For reviews, see T. Mukai, T. Kumagai, and Y. Yamashita, *Heterocycles*, **15**, 1569 (1981); T. Tsuchiya, *Yuki Gosei Kagaku Kyokai Shi*, **39**, 99 (1981); *idem*, *ibid.*, **41**, 641 (1983).
- 17) H. Igeta, *Chem. Pharm. Bull.*, **8**, 550 (1960).
- 18) T. Nakagome, *Yakugaku Zasshi*, **82**, 249, 253 (1961).
- 19) T. Itai and H. Igeta, *Yakugaku Zasshi*, **75**, 966 (1955).
- 20) T. Itai and S. Natsume, *Chem. Pharm. Bull.*, **11**, 83 (1963).
- 21) M. Ogata and H. Kano, *Chem. Pharm. Bull.*, **11**, 29 (1963).
- 22) T. Itai and S. Sako, *Chem. Pharm. Bull.*, **9**, 149 (1961).
- 23) T. Itai and S. Kamiya, *Chem. Pharm. Bull.*, **11**, 1059 (1963).
- 24) K. Eichenberger, R. Rometsch, and J. Druey, *Helv. Chim. Acta*, **39**, 1755 (1956).