Isamu Maeba

Faculty of Pharmacy, Meijo University, Tenpaku-cho, Tenpaku-ku, Nagoya, Japan

Raymond N. Castle

Department of Chemistry, Brigham Young University, Provo, Utah 84602

Received July 21, 1978

The synthesis of some pyrido[2,3-*c*]pyridazines from 5,8-dichloro-3-methyl-2-oxo-2*H*-pyrano-[2,3-*d*]pyridazine (I) is described. Attempted oxidation of 8-amino-3-chloro-1,6-dimethyl-4,7-dioxo-1,4,7,8-tetrahydropyrido[2,3-*c*]pyridazine (VI) with LTA led only to the deaminated compound VII. Treatment of VI with LTA in the presence of cyclohexene gave the nitrene adduct XI.

J. Heterocyclic Chem., 16, 249 (1979).

In the preceding paper it was shown that 4,7-dichloro-2-methylfuro[2,3-*d*]pyridazine undergoes ring expansion with potassium cyanide in dimethylsulfoxide to give 5,8-dichloro-3-methyl-2-oxo-2*H*-pyrano[2,3-*d*]pyridazine (I) (1). The fact that compound I was available prompted us to attempt to use this compound as a convenient starting material for the synthesis of pyrido[2,3-*c*]pyridazines. Although, many of the isomeric pyridopyridazines have been extensively investigated in order to obtain useful pharmacologic agents (2), it has been difficult to synthesize the pyrido[2,3-*c*]pyridazine ring system, because pyridazines tend to cyclize with one of the ring nitrogen atoms at a bridgehead position (3). The synthesis of the pyrido[2,3-*c*]pyridazine ring system has only been reported in one paper when Tisler, *et al.* (4), reported that cyclization of 3-aminopyridazine 1-oxide gave the oxide of pyrido[2,3-*c*]pyridazine and deoxygenation of the oxide failed.

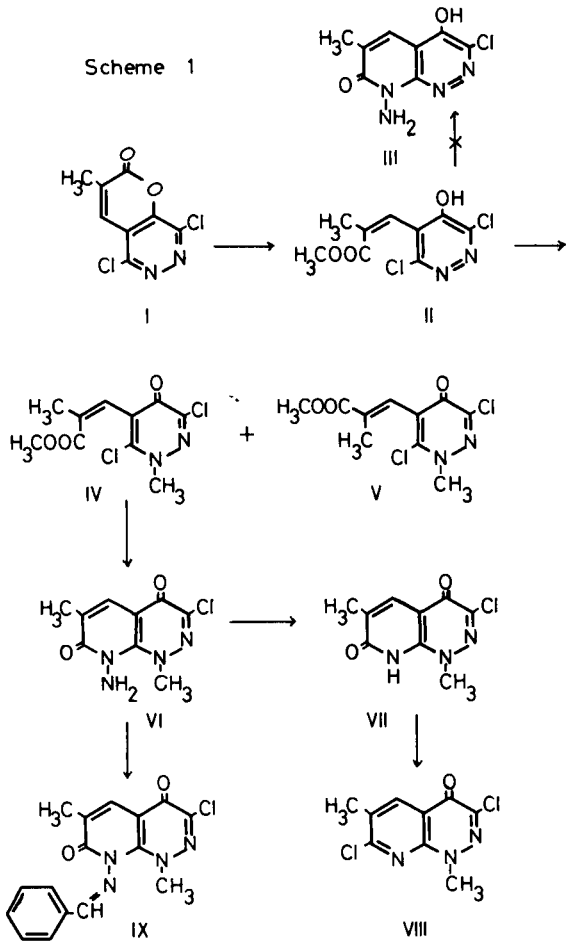
We report herein a new synthesis of the pyrido[2,3-*c*]-pyridazine ring system by an entirely different route, employing a different starting material.

Synthesis of Pyrido[2,3-*c*]pyridazines.

Treatment of I with potassium carbonate in methanol at room temperature afforded the desired ester, methyl 3-(3,6-dichloro-5-hydroxypyridazin-4-yl)-2-methylacrylate (II) in 95% yield. Attempted purification of II failed due to thermal instability, however, the formation of II was established by ir and nmr spectral data. Compound II was reconverted into I by heating with 80% hydrazine hydrate, rather than into the desired compound III. When II was treated with methyl iodide in the presence of potassium carbonate in hexamethylphosphoric triamide (HMPT), two products were obtained. Compound IV was obtained as colorless needles, m.p. 131-132°, yield 76% and compound V was obtained as light yellow prisms, m.p. 183° dec., yield 5%. The ir spectra of IV and V showed the presence of an amidocarbonyl group by absorption bands at 1605 and 1595 cm^{-1}. These data clearly indicate that compound III reacts with methyl iodide to afford the *N*-methylated compounds IV and V, and that none of the *O*-methylated compound was obtained. A comparison of the nmr spectra of IV with V indicate the signal of the vinyl proton of IV appeared at higher field (δ 6.26) than that of V (δ 6.40), thus compound IV can be assigned as (*Z*) and V can be assigned the (*E*)-structure.

Intramolecular cyclization of IV with 80% hydrazine hydrate in methanol afforded 8-amino-3-chloro-1,6-dimethyl-4,7-dioxo-1,4,7,8-tetrahydropyrido[2,3-*c*]pyridazine (VI) in 92% yield. The structure of VI is based on the

Scheme 1



0022-152X/79/020249-03$02.25

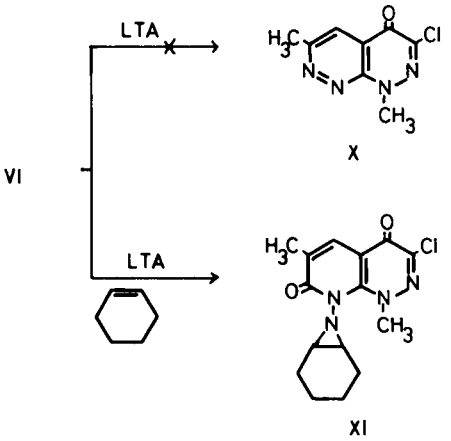
© HeteroCorporation

following evidence: The nmr (ppm in deuteriodimethylsulfoxide) assignment of the protons of compound VI were in agreement with this structure with the following signals; 2.13 (3H, doublet, J = 1.0 Hz, 6-methyl), 4.32 (3H, singlet, 1-methyl), 7.83 (1H, quartet, J = 1 Hz, ring proton 5 position) and 5.73 (2H, singlet, $-NH_2$). The signal of the last protons disappeared on the addition of deuterium oxide. The ir spectrum showed absorption bands at 3170 and 3280 cm^{-1} attributable to an amino group. Deamination of the *N*-amino compound VI with *N*-nitrosodiphenylamine in benzene afforded VII in 74% yield. Chlorination of VII with phosphorus oxychloride afforded VIII in 18% yield. Further, VI was characterized as its benzylidene derivative IX (Scheme 1).

Oxidation of VI with Lead Tetraacetate (LTA).

The pyridazino[3,4-*c*]pyridazine ring system is still unknown in the literature in spite of a number of attempts to prepare this ring system (5). It was reported that oxidation of 1-amino-3,4,5,6-tetraphenylpyrid-2-one with LTA results in the loss of carbon monoxide to give tetraphenylpyridazine (6). In the present paper the results of the attempted synthesis of the pyridazino[3,4-*c*]pyridazine ring system (X), by the method previously described, are reported.

Attempts to oxidize VI with LTA in benzene and methylene chloride were unsuccessful. In addition to a number of other products (tlc), a small amount of VII was obtained. Evidence that the nitrene was an intermediate was provided by repeating the oxidation in the presence of cyclohexene; the expected nitrene adduct 7-(3-chloro-1,6-dimethyl-4,7-dioxo-1,4,7,8-tetrahydropyrido-[2,3-*c*]pyridazin-8-yl)-7-azabicyclo[4.1.0]heptane (XI), m.p. 228-229°, was formed (Scheme 2).



Scheme 2

EXPERIMENTAL

Melting points are uncorrected. The ir spectra were measured with a Jasco IRA-1 spectrometer and the nmr spectra were recorded on a JEOL-PS-100 spectrometer using tetramethylsilane as an internal standard. Mass spectra were taken with a Hitachi M-52 spectrophotometer.

Methyl 3-(3,6-Dichloro-5-hydroxypyridazin-4-yl)-2-methylacrylate (II).

A mixture of 4.6 g. (0.02 mole) of I, 3.0 g. of anhydrous potassium carbonate and 50 ml. of methanol was stirred for 2 hours at room temperature. The solvent was removed under reduced pressure and the residue was added to water. The solution was acidified with dilute hydrochloric acid and the crystals were filtered, washed with water, and dried in air, giving a crude product II 5.0 g. (95%), m.p. 177° dec., suitable for use in the next stage; ir (potassium bromide): 3170-2880 cm^{-1} (OH), 1680 cm^{-1} (C=O); nmr (deuteriodimethylsulfoxide): δ 2.00 (d, 3H, J = 1.5 Hz, CH_3), 3.43 (s, 3H, $COOCH_3$), 6.33 (q, 1H, J = 1.5 Hz, vinyl).

(*Z*)-Methyl 3-(3,6-dichloro-1-methyl-4-oxo-1,4-dihydropyridazin-5-yl)-2-methylacrylate (IV) and (*E*)-Methyl 3-(3,6-dichloro-1-methyl-4-oxo-1,4-dihydropyridazin-5-yl)-2-methylacrylate (V).

A mixture of 3.9 g. (0.015 mole) of II, 2.0 g. of anhydrous potassium carbonate, 7.0 g. of methyl iodide and 40 ml. of hexamethylphosphoric triamide was stirred for 1 hour at room temperature. The excess methyl iodide was removed under reduced pressure and the residue was added to water. The solution was extracted with three 100 ml. portions of ethyl acetate and dried with anhydrous magnesium sulfate and evaporated. The mixture of compounds IV and V was separated by fractional crystallization from methanol, colorless needles of IV, 3.4 g. (76%), m.p. 131-132°; light yellow prisms of V, 0.2 g. (5%), m.p. 183° dec. Compound IV had ms: *m/e* 276 (M^+); ir (potassium bromide): 1710, 1605 cm^{-1} (C=O); nmr (deuteriochloroform): δ 2.13 (d, 3H, J = 1.5 Hz, CH_3), 3.65 (s, 3H, N-CH_3 or O-CH_3), 4.01 (s, 3H, N-CH_3 or O-CH_3), 6.27 (q, 1H, J = 1.5 Hz, vinyl).

Anal. Calcd. for $C_{10}H_{10}Cl_2N_2O_3$: C, 43.34; H, 3.64; N, 10.11. Found: C, 43.44; H, 3.58; N, 10.03.

Compound V had ms: *m/e* 276 (M^+); ir (potassium bromide): 1710, 1595 cm^{-1} (C=O); nmr (deuteriochloroform): δ 2.13 (d, 3H, J = 1.5 Hz, CH_3), 3.66 (s, 3H, N-CH_3 or O-CH_3), 4.30 (s, 3H, N-CH_3 or O-CH_3), 6.40 (q, 1H, J = 1.5 Hz, vinyl).

Anal. Calcd. for $C_{10}H_{10}Cl_2N_2O_3$: C, 43.34; H, 3.64; N, 10.11. Found: C, 43.38; H, 3.60; N, 9.93.

8-Amino-3-chloro-1,6-dimethyl-4,7-dioxo-1,4,7,8-tetrahydropyrido-[2,3-*c*]pyridazine (VI).

A mixture of 280 mg. (0.001 mole) of IV, 100 mg. of 80% hydrazine hydrate and 5 ml. of methanol was refluxed for 1 hour. The solvent was removed under reduced pressure and the solid was recrystallized from methanol to give light yellow needles of VI, 220 mg. (92%), m.p. 230-231°; ir (potassium bromide): 3170, 3280 cm^{-1} (NH_2), 1665 cm^{-1} (C=O).

Anal. Calcd. for $C_9H_9ClN_4O_2$: C, 44.92; H, 3.77; N, 23.28. Found: C, 45.03; H, 3.69; N, 22.97.

3-Chloro-1,6-dimethyl-4,7-dioxo-1,4,7,8-tetrahydropyrido[2,3-*c*]-pyridazine (VII).

A mixture of 100 mg. (0.0004 mole) of VI, 200 mg. of *N*-nitrosodiphenylamine and 10 ml. of benzene was refluxed for 6 hours. Benzene was removed under reduced pressure and the residue was recrystallized from methanol to give colorless prisms of VII, 70 mg. (74%), m.p. >310°; ms: *m/e* 225 (M^+); ir (potassium bromide): 3200-2800 cm^{-1} (OH), 1660, 1600 cm^{-1} (C=O); nmr (deuteriodimethylsulfoxide): δ 2.19 (d, 3H, J = 1.0 Hz, CH_3), 3.99 (s, 3H, CH_3), 7.99 (q, 1H, J = 1.0 Hz, ring proton 5 position).

Anal. Calcd. for $C_9H_8ClN_3O_2$: C, 47.91; H, 3.57; N, 18.62.

Found: C, 48.16; H, 3.47; N, 18.68.

3,7-Dichloro-1,6-dimethyl-1,4-dihydropyrido[2,3-*c*]pyridazine (VIII).

A mixture of 50 mg. (0.00022 mole) of VII and 1 ml. of phosphorus oxychloride was heated for 1 hour at 90°. The reaction mixture was poured into ice water. The solution was extracted with three 10 ml. portions of chloroform and dried with anhydrous magnesium sulfate and evaporated under reduced pressure. Purification of the residue by preparative tlc (developing with chloroform) and by crystallization from methanol gave colorless needles 10 mg. (18%), m.p. 189-190°; ms: *m/e* 243 (M^+); ir (potassium bromide): 1635 cm^{-1} (C=O); nmr (deuteriochloroform): δ 2.48 (d, 3H, J = 1.0 Hz, CH_3), 4.13 (s, 3H, CH_3), 8.40 (q, 1H, J = 1.0 Hz, ring proton 5 position).

Anal. Calcd. for $C_9H_7Cl_2N_3O$: C, 44.29; H, 2.89; N, 17.22. Found: C, 44.48; H, 2.87; N, 17.09.

Benzylidene Derivative (IX) of VI.

A mixture of 120 mg. (0.0005 mole) of VI, 100 mg. of benzaldehyde and 5 ml. of glacial acetic acid was heated for 3 hours at 100°. The solvent was removed under reduced pressure and the residue was purified from methanol to give colorless needles of IX, 100 mg. (30%), m.p. 186-187°; ir (potassium bromide): 1660, 1620 cm^{-1} (C=O); nmr (deuteriodimethylsulfoxide): δ 2.18 (d, 3H, J = 1.0 Hz, CH_3), 4.07 (s, 3H, CH_3), 8.0-7.55 (m, 6H, aromatic protons), 8.90 (s, 1H, -CH=N-).

Anal. Calcd. for $C_{16}H_{13}ClN_4O_2$: C, 58.46; H, 3.99; N, 17.04. Found: C, 58.98; H, 3.96; N, 16.86.

Oxidation of VI with LTA.

Compound VI (200 mg.) was suspended in benzene (40 ml.), methylene chloride (40 ml.), and LTA (400 mg.) added in small solid portions during 30 minutes with vigorous stirring at room temperature. After stirring for a further 1.5 hours, the lead salts were removed and the solution evaporated and triturated with chloroform to give VII, 30 mg. (16%), m.p. >310°. Identity was confirmed by comparing ir spectra and mixed melting point.

7-(3-Chloro-1,6-dimethyl-4,7-dioxo-1,4,7,8-tetrahydropyrido[2,3-*c*]pyridazin-8-yl)-7-arabicyclo[4.1.0]heptane (XI).

Compound VI (100 mg.) was suspended in cyclohexene (5 ml.) and benzene (70 ml.), and LTA (200 mg.) added in small solid portions during 10 minutes with vigorous magnetic stirring at room temperature. After stirring for further 50 minutes, the lead salts were removed, and the solution evaporated. Recrystallization from methanol gave the aziridine XI, 120 mg. (90%), m.p. 228-229°; ms: *m/e* 320 (M^+); ir (potassium bromide): 1655, 1605 cm^{-1} (C=O); nmr (deuteriochloroform): δ 1.48 (m, 4H), 2.20 (m, 7H), 2.55 (m, 2H), 4.21 (s, 3H), 7.70 (q, 1H, J = 1.0 Hz).

Anal. Calcd. for $C_{15}H_{17}ClN_4O_2$: C, 56.17; H, 5.34; N, 17.47. Found: C, 56.20; H, 5.35; N, 17.38.

REFERENCES AND NOTES

(1) I. Maeba, M. Ando, S. Yoshina and R. N. Castle, *J. Heterocyclic Chem.*, **16**, (1979).

(2) H. A. Offe, W. Siekfen and G. Domagk, *Z. Naturforsch.*, **76**, 462 (1952); Japanese Patent, 192 (1967); *Chem. Abstr.*, **66**, 76026 (1967); German Patent 948,976 (1956); *Chem. Abstr.*, **53**, 2263 (1959).

(3) B. Stanovnik, M. Tišler, M. Ceglar and V. Bah, *J. Org. Chem.*, **35**, 1138 (1970).

(4) P. Kregar-Čadež, A. Pollak, B. Stanovnik, M. Tišler and B. Wechtersbach-Lažetić, *J. Heterocyclic Chem.*, **9**, 351 (1972).

(5) T. La Noce, E. Bellasio, A. Vigevani and E. Testa, *Ann. Chim. (Rome)*, **59**, 552 (1969); B. Stanovnik and M. Tišler, *Synthesis*, 180 (1970).

(6) C. W. Rees and M. Yelland, *Chem. Commun.*, 337 (1969).