Isoo Ito and Noriichi Oda: Synthesis of Pyrazolone Derivatives. XI.\(^\text{a}\)
Synthesis of 6-Substituted 1,2,6,7-Tetrahydro-3H-pyrazolo[4,3-c]pyridine.

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In order to examine their antipyretic actions together with analgesic actions, a series of pyrazolopyridines have been reported in the previous papers.\(^1\) The present paper concerns with the synthesis of diethyl 3-oxo-1,4-dimethyl-2-phenyl-1,2,6,7-tetrahydro-3H-pyrazolo[4,3-c]pyridine-6,6-dicarboxylate (V).

Starting compound, 4-bromo-3-bromomethyl-2-methyl-1-phenyl-3-pyrazolin-5-one (II) was obtained by the method of Graef, et al.\(^4\) from 4-bromo-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one (I). This dibromo compound (II) was condensed with diethyl acetamidomalonate under the presence of sodium ethoxide to give diethyl 2-acetamido-2-\([\text{4-bromo-2-methyl-5-oxo-1-phenyl-3-pyrazolin-3-yl}][\text{methyl}]\text{malonate (III). Catalytic reduction of III using Raney nickel gave diethyl 2-acetamido-2-\([\text{2-methyl-5-oxo-1-phenyl-3-pyrazolin-3-yl}][\text{methyl}]\text{malonate (IV).}}\]

It is known that the 4-position of pyrazoline is cationoid active.\(^5\) Thus, the dehalogenated compound (IV) should cyclize to pyrazolopyridin derivative. A Bischler-Napieralski type of cyclization was carried out using phosphorus pentachloride as a cyclizing reagent, and diethyl 3-oxo-1,4-dimethyl-2-phenyl-1,2,6,7-tetrahydro-3H-pyra-

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\(^{a}\) Part X. I. Ito, T. Ueda, E. Kurokawa: This Bulletin, 14, 207 (1966).
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5) S. Sugawara, N. Yoneda: This Bulletin, 4, 360 (1956).
zolo[4,3-c]pyridine-6,6-dicarboxylate (V) was obtained in fairly good yield. The cyclization was also achieved by polyphosphoric ester (PPE).<sup>6</sup>

The cyclized compound (V) was reacted with ammonia to give corresponding amide (VII).

**Experimental**<sup>83</sup>

4-Bromo-3-bromomethyl-2-methyl-1-phenyl-3-pyrazolin-5-one (II)<sup>4</sup>—To a stirred solution of 100 g. of 4-bromomethylpyrine (I) in 700 ml. of CCl<sub>4</sub>, 70 g. of powder NBS was added in small portions over a period of 3 hr. under refluxing. Stirring and refluxing were continued for other 4 hr. The reaction mixture was filtered, and the solid was washed with 1000 ml. of hot CCl<sub>4</sub>. The filtrate and the extract were evaporated, and the residue was crystallized from EtOH to colorless prisms, m.p. 135–136<sup>°</sup>. Yield, 80.5 g. (62.1%).

Diethyl 2-Acetamido-2-[(4-bromo-2-methyl-5-oxo-1-phenyl-3-pyrazolin-5-yl)methyl]malonate (III)—To a solution of 47.4 g. of diethyl acetamidomalonate in 400 ml. of abs. EtOH containing 4.6 g. of Na, 69.2 g. of the above dibromo compound (I) was added. The mixture was heated at 60–80<sup>°</sup> for 12 hr. After evaporation of the solvent, residue was extracted with benzene. The extract was dried over Na$_2$SO$_4$ and evaporated to dryness. The remainder was crystallized from acetone-EtOH to colorless prisms, m.p. 140–141. Yield, 64 g. (66.4%). <sup>4</sup> Anal. Calcd. for C$_{25}$H$_{25}$O$_7$N$_3$Br: C, 49.80; H, 5.03; N, 8.71. Found: C, 49.70; H, 5.08; N, 8.49. IR cm$^{-1}$: $\nu_{\text{N-H}}$ 3230 (KBr); $\nu_{\text{C=O}}$ 1756 (KBr).

Diethyl 2-Acetamido-2-[(2-methyl-5-oxo-1-phenyl-3-pyrazolin-3-yl)methyl]malonate (IV)—Ten grams of the above ester (II) was reduced in a mixture of 250 ml. of EtOH, 50 ml. of water and 2.2 g. of NaHCO$_3$ at atmospheric pressure in the presence of 1.5 g. of Raney nickel catalyst. Catalyst was removed by filtration. After evaporation of the filtrate, the residue was extracted with benzene. The extract was dried over Na$_2$SO$_4$ and evaporated to a viscous oil, which was crystallized from AcOEt to colorless prisms, m.p. 134–135<sup>°</sup>. Yield, 6.4 g. (76.8%). <sup>4</sup> Anal. Calcd. for C$_{20}$H$_{18}$O$_4$N$_3$: C, 59.54; H, 6.25; N, 10.43. Found: C, 59.14; H, 6.31; N, 9.97. IR cm$^{-1}$: $\nu_{\text{N-H}}$ 3290 (KBr); $\nu_{\text{C=O}}$ 1754 (KBr).

Diethyl 3-Oxo-1,4-dimethyl-2-phenyl-1,2,6,7-tetrahydro-3H-pyrazolo[4,3-c]pyridine-6,6-dicarboxylate (V)—To a stirred solution of 3.4 g. of the above compound (IV) in 20 ml. of chloroform, 6 g. of PCl$_3$ was added in small portions with stirring. After stirring for other 2 hr., the reaction mixture was poured into 10 g. of ice water. Water layer was separated, and organic layer was extracted with dil. HCl. The water layer and the extracts were saturated with K$_2$CO$_3$, and extracted with benzene. The extracts were dried over Na$_2$SO$_4$ and evaporated to dryness. The residue, on crystallization from ether, gave colorless needles, m.p. 169–170<sup>°</sup>. Yield, 1.9 g. (58.5%). <sup>4</sup> Anal. Calcd. for C$_{25}$H$_{23}$O$_7$N$_3$: C, 62.23; H, 6.02; N, 10.90. Found: C, 62.53; H, 6.43; N, 11.26. IR cm$^{-1}$: $\nu_{\text{C=O}}$ 1736 (KBr).

2) A mixture of 1 g. of the above compound (V) and 4 g. of PPE was heated at 130–140<sup>°</sup> under mechanical stirring for 1 hr. After cooling, 10 g. of ice and 10 ml. of water were added to the reaction mixture to decompose excess PPE. The mixture was then saturated with K$_2$CO$_3$, and extracted with benzene. The extract was dried over Na$_2$SO$_4$ and evaporated to dryness. The residue, on crystallization from ether, gave colorless needles, m.p. 169–170<sup>°</sup>. Yield, 0.4 g. (41.9%). IR spectrum and mixed melting point comparison showed that this is identical with the compound (V) obtained above method 1.

3-Oxo-1,4-dimethyl-2-phenyl-1,2,6,7-tetrahydro-3H-pyrazolo[4,3-c]pyridine-6,6-dicarboxamide (VI)—One gram of the pyrazolopyridine (V) was dissolved in 5 ml. of 25% of ammonia and kept overnight. The crystals which appeared were filtered and recrystallized from EtOH to colorless prisms, m.p. 228–229<sup>°</sup>(decomp.). Yield, 0.6 g. (70.6%). <sup>4</sup> Anal. Calcd. for C$_{25}$H$_{23}$ON$_3$: C, 58.70; H, 5.23; N, 21.40. Found: C, 58.69; H, 5.03; N, 21.82. IR cm$^{-1}$: $\nu_{\text{N-H}}$ 3425, 3306 (KBr); $\nu_{\text{C=O}}$ 1690 (KBr).

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**Summary**

For pharmacological evaluation, diethyl 3-oxo-1,4-dimethyl-2-phenyl-1,2,6,7-tetrahydro-3H-pyrazolo[4,3-c]pyridine-6,6-dicarboxylate was synthesized by the Bischler-Napieralski type of reaction, from diethyl 2-acetamido-2-[(2-methyl-5-oxo-1-phenyl-3-pyrazolin-3-yl)methyl]malonate.

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83 All melting points are uncorrected.
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