[Chem. Pharm. Bull. 14(9)1010~1016(1966)] UDC 547.852.7.07

139. Ikutoshi Matsuura, Fumio Yoneda, and Yoshihiro Nitta: Pyridazines. XI.*1 Pyrido[2,3-*d*]pyridazines. II.*2

(*Research Laboratories, Chugai Pharmaceutical Co., Ltd.**3)

Interest in pyrido[2,3-*d*]pyridazine system designed as pharmacodynamic agents was increased by our finding that hydrazinochloropyrido[2,3-*d*]pyridazines reported in the previous paper*2 possessed outstanding hypotensive properties and that dialkoxypyrido[2,3-*d*]pyridazines showed strong anticonvulsant activities. Thus our efforts have been directed to the additional synthetic work in this field in expectation of another pharmacological effects. The present paper describes the preparation and properties of pyrido[2,3-*d*]pyridazine-5-carboxylic acid derivatives and N-substituted pyrido[2,3-*d*]pyridazines.

Pyrido[2,3-*d*]pyridazine-5-carboxylic Acid and Its derivatives

2-Carboxy-3-pyridineglyoxylic acid[1] (I) was used as the starting material of this series.

Reaction of I with hydrazine in water at room temperature afforded yellowish powder (II), m.p. 302° (decomp.), of the hydrazone of I as has been reported,[2] but treatment of I at 100° yielded colorless needles of a cyclized hydrazone, 8-oxo-7,8-dihydropyrido-[2,3-*d*]pyridazine-5-carboxylic acid (III), m.p. 300~301° (decomp.). These compounds, II and III, were, however, convertible to each other in hot water and prolonged heating in water often caused contamination of II and III.

Either II or III was refluxed in methanol with sulfuric acid to give the methyl ester (IV) of III. Hydrolysis of IV in dilute hydrochloric acid or in aqueous sodium hydroxide gave the acid (III). The ester could be converted to the amide (Va) with concentrated ammonia at reflux, and to the alkylamides, Vb and Vc, with alkylamines such as methylamine and ethylamine in refluxing ethanol. Arylamine, *e.g.*, aniline did not react with III at the refluxing temperature of aniline. Warm hydrazine hydrate reacted easily with III to give the hydrazide (Vd).

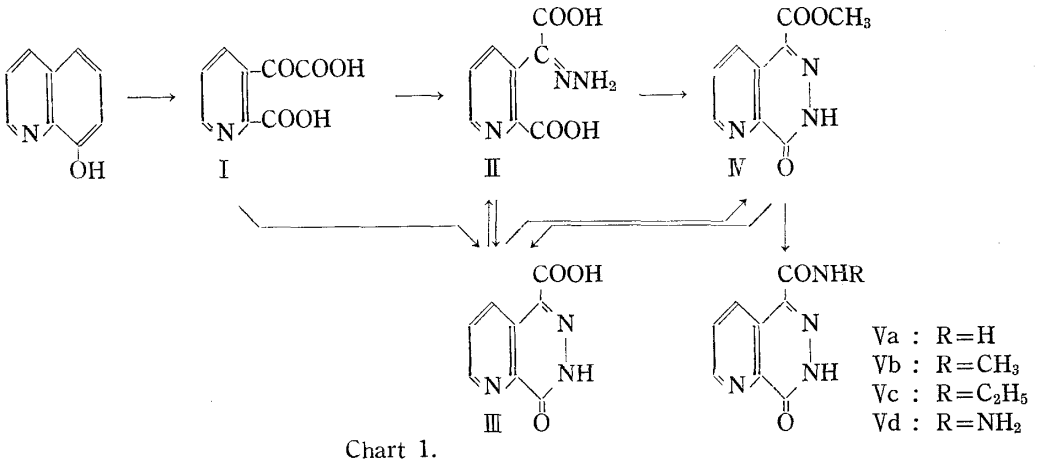


Chart 1.

*1 Part X: F. Yoneda, T. Ohtaka, Y. Nitta: This Bulletin, **14**, 698 (1966).
*2 Part I: Y. Nitta, I. Matsuura, F. Yoneda: *Ibid.*, **13**, 586 (1965).
*3 Takataminami-cho, Toshima-ku, Tokyo (松浦育敏, 米田文郎, 新田義博).
1) F. Bottari, S. Carboni: Gazz. chim. ital., **86**, 990 (1956).
2) S. Carboni: Gazz. chim. ital., **85**, 1194 (1955).

In order to prepare the N-phenyl derivative of compound (Ⅲ), compound (I) was treated with phenylhydrazine hydrochloride in water at room temperature. The reaction afforded uncyclized phenylhydrazone (Ⅵ) of I. Compound (Ⅵ) was insoluble in ordinary solvents and could not be recrystallized. Attempted recrystallization of this product from dimethylformamide, however, yielded the cyclized phenylhydrazone, 7-phenyl-8-oxo-7,8-dihydropyrido[2,3-*d*]pyridazine-5-carboxylic acid (Ⅶ). Compound (Ⅶ) could also be obtained by reaction of I with phenylhydrazine hydrochloride in hot water. Esterification of Ⅵ or Ⅶ in 20% ethanolic sulfuric acid gave rise to the cyclized ester, ethyl 7-phenyl-8-oxo-7,8-dihydropyrido[2,3-*d*]pyridazine-5-carboxylate (Ⅷb). The ester (Ⅷa) could also be prepared in a similar way. Hydrogen chloride in alcohols was not effective in this reaction.

Hydrolysis of Ⅷa or Ⅷb did not give the free acid. Treatment of Ⅷb in warm aqueous sodium hydroxide gave a yellowish solid (Ⅸ), m.p. 200° (decomp.), and colorless prisms (Xb), m.p. 223° (decomp.). Compound (Ⅸ) was soluble in alkali and reflux of Ⅸ in ethanolic hydrochloric acid afforded known 7-phenylpyrido[2,3-*d*]pyridazin-8(7*H*)-one (Ⅺ), m.p. 200°. Thus, identity of Ⅸ with known phenylhydrazone of 3-formylpicolinic acid was confirmed by alternative preparation of an authentic sample by the method of Bottari and Carboni.[1] Compound (Xb) was obtained as the sole product when Ⅷb was treated in cold aqueous sodium hydroxide. Compound (Xa), m.p. 227~229° (decomp.), the methyl analogue of Xb, could also be obtained in an excellent yield if Ⅷa was treated in cold aqueous sodium hydroxide. Compounds, Xa and Xb, were insoluble in cold alkali and had chemical formulae, $C_9H_8O_4N_2$ and $C_{10}H_{10}O_4N_2$, respectively, which indicated the elimination of the phenyl group, and retention of the ester group in Xa and Xb. The infrared spectra of these compounds in potassium bromide exhibited strong and broad absorption at 3370 cm^{-1}, which must be NH-stretching vibration of carbamoyl group since the presence of OH-group of carboxylic acid and NH< group of lactam structure of pyridazone could be denied concerning their insolubility in strong alkali. Thus, the structure of Xa and Xb were estimated to be methyl and ethyl 2-carbamoyl-3-pyridineglyoxylate, respectively. The infrared

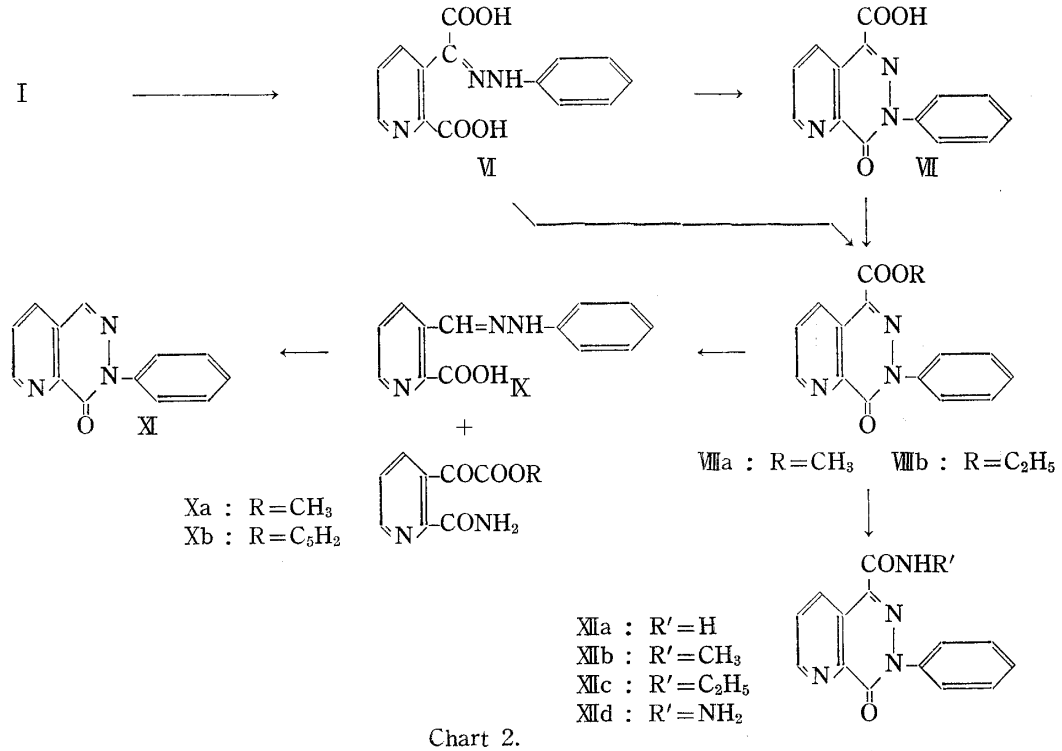


Chart 2.

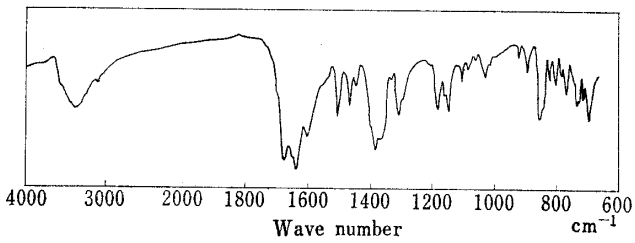


Fig. 1. Infrared Absorption Spectrum of Compound (Xb) in Potassium Bromide

spectrum of Xb is shown in Fig. 1, since the identity of this product with the estimated structure was not synthetically confirmed. The authors observed complete dissolution of the starting material before the crystals of Xa or Xb began to precipitate. Some ionized intermediate may therefore be considered on the mechanism of this new reaction. Further research will be made on this problem.

Amination of the esters (Ⅷa and Ⅷb) with aqueous ammonia, ethanolic methyl- and ethylamines and hydrazine hydrate to yield Ⅻa~d was carried out in a similar way as that of Va~d.

N-Substituted pyrido[2,3-*d*]pyridazines

Attempts to prepare 5-hydroxy-7-phenylpyrido[2,3-*d*]pyridazin-8(7*H*)-one and isomeric 6-phenyl-8-hydroxypyrido[2,3-*d*]pyridazin-5(6*H*)-one have been unsuccessful in the literatures: Gupta and Sircar[3] reported that condensation of quinolinic anhydride with phenylhydrazine yielded quinolinic acid (2 or 3) monophenylhydrazide

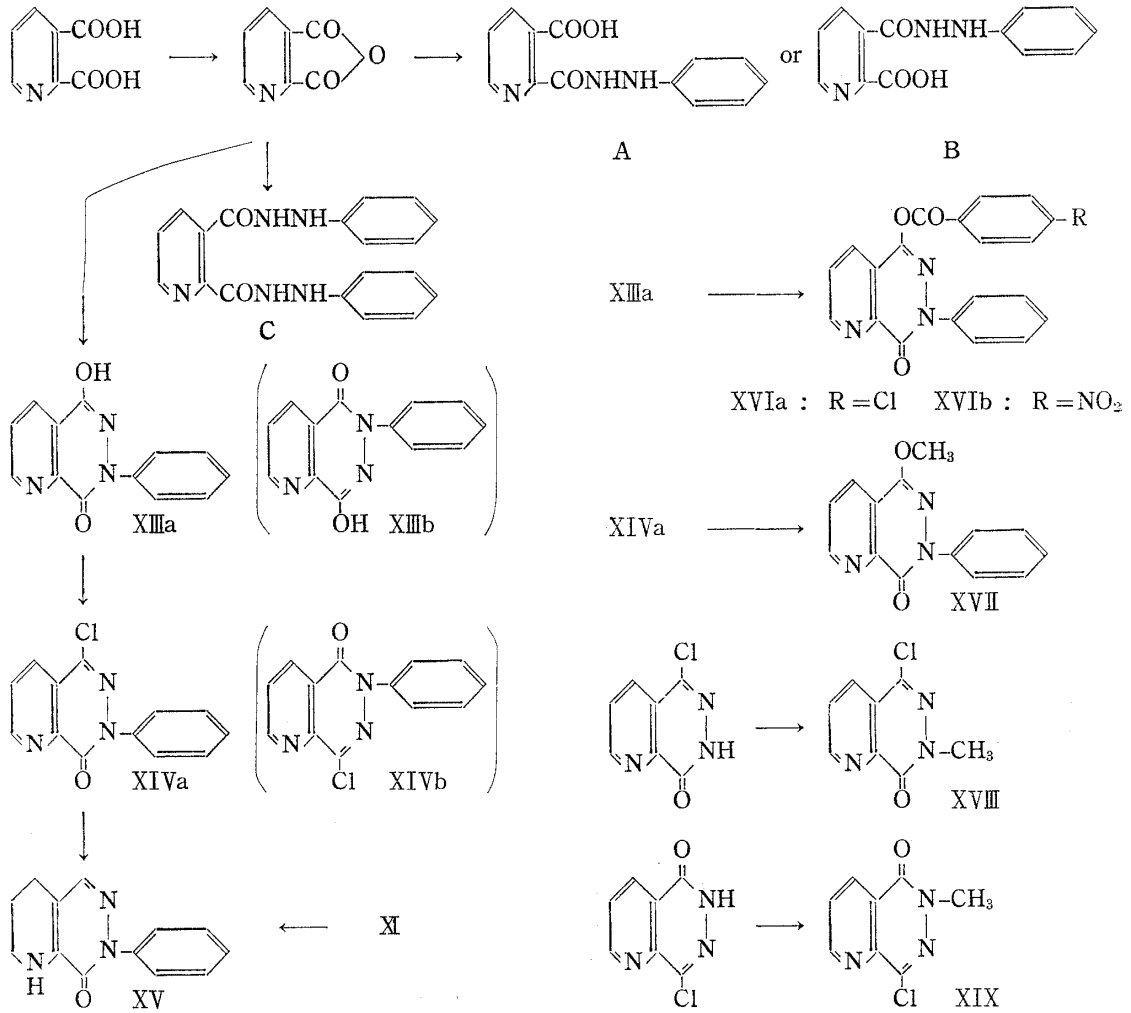


Chart 3.

3) P. R. S. Gupta, A. C. Sircar: J. Indian Chem. Soc., **9**, 145 (1932).

(A or B) and quinolinic acid bisphenylhydrazide (C), which on heating failed to give a cyclized phenylhydrazide.

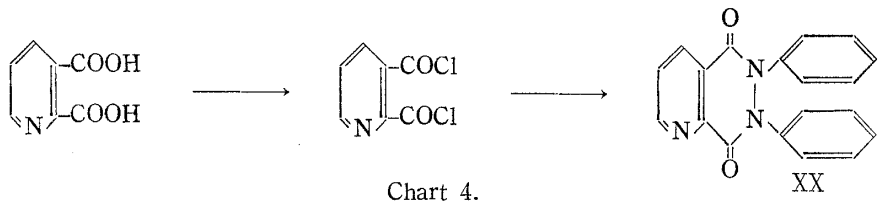
In the present attempt, reaction of quinolinic anhydride with phenylhydrazine to yield a cyclized phenylhydrazide was successful when quinolinic anhydride was treated with two moles of phenylhydrazine in acetic acid under reflux. Only one isomer, m.p. 265°, of the two expected isomeric products (XIIIa and XIIIb) was obtained by this reaction. In order to determine the structure, this product (XIIIa) was chlorinated by phosphoryl chloride to give the chloro compound (XIVa), followed by catalytic dechlorinating hydrogenation of compound (XI) to give 7-phenyl-1,2,3,4-tetrahydropyrido[2,3-*d*]pyridazin-8(7*H*)-one (XV), which was also obtained by a similar hydrogenation of the compound (XI), the structure of which has already been established.[1] Thus, the structure of XIIIa and XIVa was determined to be 5-hydroxy-7-phenylpyrido[2,3-*d*]pyridazin-8(7*H*)-one and 5-chloro-7-phenylpyrido[2,3-*d*]pyridazin-8(7*H*)-one, respectively. The acidic property of XIIIa was fairly strong. Compound (XIIIa) was soluble in aqueous sodium bicarbonate as well as sodium hydroxide, gave a stable sodium salt with sodium hydroxide and yielded brown color with aqueous ferric chloride. Action of benzoyl chlorides upon XIIIa in pyridine gave the benzoic esters (XVIa, XVIb). These facts may show the phenolic propetries of XIIIa at 5-position.

5-Methoxy-7-phenylpyrido[2,3-*d*]pyridazin-8(7*H*)-one (XVII) was obtained by reaction of XIVa with sodium methoxide in refluxing methanol. Amination of XIVa failed under ordinary conditions.

The N-methylated compounds were prepared by methylation. 5-Chloro-7-methylpyrido[2,3-*d*]pyridazin-8(7*H*)-one (XVIII) and 6-methyl-8-chloropyrido[2,3-*d*]pyridazin-5(6*H*)-one(XIX) were obtained by methylating 5-chloropyrido[2,3-*d*]pyridazin-8-ol*2 (5-chloropyrido[2,3-*d*]pyridazin-8(7*H*)-one) and 8-chloropyrido[2,3-*d*]pyridazin-5-ol*2 (8-chloropyrido[2,3-*d*]-pyridazin-5(6*H*)-one) with methyl iodide in methanolic sodium or potassium hydroxide. The O-methylated products were not isolated.

N,N′-Disubstituted pyrido[2,3-*d*]pyridazine

6,7-Diphenylpyrido[2,3-*d*]pyridazine-5,8(6*H*,7*H*)-dione (XX) was prepared by reaction of quinolinic acid dichloride with hydrazobenzene in the presence of dimethylaniline in benzene. The compound (XX), which has some structural resemblance with an analgesic agent, phenylbutazone, showed anticonvulsive and some other related effects.



XX

Chart 4.

Experimental*4

Hydrazone of I (II)——A solution of $NH_2NH_2 \cdot H_2SO_4$ (3.33 g.), AcONa (4.2 g.) and I (5.0 g.) in H_2O (100 ml.) was allowed to stand overnight at room temperature. The granular precipitate of II (4.0 g., 74%), m.p. 298°(decomp.) was collected. Recrystallization from a large amount of H_2O produced colorless granules, m.p. 302°(decomp.). IR ν_{max}^{KBr} cm^{-1}: 3540 (OH), 3490 (NH_2), 2845, 1695 (CO). *Anal.* Calcd. for $C_8H_7O_4N_3$: C, 45.94; H, 3.37; N, 20.09. Found: C, 46.38; H, 3.41; N, 20.52.

8-Oxo-7,8-dihydropyrido[2,3-*d*]pyridazine-5-carboxylic Acid (III)——Compound (I) (5.0 g.) in H_2O (50 ml.) was neutralized with 10% NaOH to pH 8 (phenolphthalein). $NH_2NH_2 \cdot H_2SO_4$ (3.35 g.) was added. The solution was heated at 100° for 1 hr. to give needles. After cooling the crystals of III (3.9 g., 80%), m.p.

*4 All melting points are uncorrected. Infrared spectra of all the compounds prepared were obtained on a Hitachi infrared spectrophotometer model EPI-2.

300～301° (decomp.), were collected. Recrystallization from H_2O gave colorless needles, m.p. 300～301° (decomp.). IR ν_{max}^{KBr} cm^{-1}: 3170 (OH), 3010 (NH), 2865, 1677 (CO). *Anal.* Calcd. for $C_8H_5O_3N_3$: C, 50.26; H, 2.64; N, 21.99. Found: C, 50.72; H, 2.80; N, 22.51.

Methyl 8-Oxo-7,8-dihydropyrido[2,3-*d*]pyridazine-5-carboxylate (IV)——Compound (II) (5.2 g.) was added to a mixture of MeOH (50 ml.) and conc. H_2SO_4 (5 ml.). After refluxing for 1 hr., a clear solution was obtained. It was treated with charcoal, filtered hot, concentrated at 100°, cooled, poured into ice, made alkaline with NH_4OH, and made acidic with AcOH to afford a solid, which was collected, washed with H_2O and recrystallized from MeOH to give needles of IV (3.2 g.), m.p. 227～229° (decomp.). *Anal.* Calcd. for $C_9H_7O_3N_3$: C, 52.68; H, 3.44; N, 20.48. Found: C, 52.91; H, 3.88; N, 20.53.

Hydrolysis of IV——Compound (IV) (0.5 g.) was refluxed in 3% HCl (10 ml.) for 1 hr. The precipitate was collected and recrystallized from H_2O to give III (0.3 g.), m.p. 298°(decomp.). This was identified by IR spectra.

8-Oxo-7,8-dihydropyrido[2,3-*d*]pyridazine-5-carboxamide (Va)——Compound (IV) (1.0 g.) was dissolved in an excess of conc. NH_4OH and heated on a water bath at 90° for 1 hr. The precipitate was washed with dil. HCl and recrystallized from H_2O to give needles of V (R=H) (0.6 g.), m.p. 352～357°(decomp.). *Anal.* Calcd. for $C_8H_6O_2N_4$: C, 50.53; H, 3.18; N, 29.47. Found: C, 50.87; H, 3.13; N, 29.29.

Methylamide of III (Vb)——Compound (IV) (1.0 g.) was added to 20% CH_3NH_2 in MeOH (10 ml.) and refluxed until precipitation was complete. After cooling, the precipitate was collected, washed with H_2O and recrystallized from MeOH to give granules of V (R=CH_3) (0.8 g.), m.p. 300～303° (decomp.). *Anal.* Calcd. for $C_9H_8O_2N_4$: C, 52.94; H, 3.95; N, 27.44. Found: C, 52.86; H, 3.88; N, 27.63.

Ethylamide of III (Vc)——Compound (IV) (1.0 g.) was added to 15% $C_2H_5NH_2$ in EtOH (10 ml.) and refluxed for 0.5 hr. The reaction mixture was concentrated and the residue was recrystallized from EtOH to give prisms of V (R=C_2H_5) (0.8 g.), m.p. 270～271°. *Anal.* Calcd. for $C_{10}H_{10}O_2N_4$: C, 55.04; H, 4.62; N, 25.68. Found: C, 55.09; H, 4.36; N, 26.28.

Hydrazide of III (Vd)——Compound (IV) (1.0 g.) and 80% $NH_2NH_2 \cdot H_2O$ (1.0 ml.) in MeOH were refluxed for 1 hr. The precipitate was collected, washed with dil. HCl and recrystallized from MeOH to give crystals (0.5 g.) of V (R=NH_2) (0.5 g.), m.p. 296°(decomp.). *Anal.* Calcd. for $C_8H_7O_2N_5$: C, 46.83; H, 3.44; N, 34.12. Found: C, 46.56; H, 3.31; N, 34.46.

Phenylhydrazone of I (VI)——Compound (I) (5.0 g.) was added to a solution of phenylhydrazine hydrochloride (7.2 g.) in H_2O (50 ml.) and allowed to stand at room temperature overnight. The yellowish solid was collected and washed with H_2O to give VI (6.2 g.), m.p. 218～220°(decomp.). IR ν_{max}^{KBr} cm^{-1}: 3400 (OH), 2860, 1665 (CO).

7-Phenyl-8-oxo-7,8-dihydropyrido[2,3-*d*]pyridazine-5-carboxylic Acid (VII). A——Compound VI (5.0 g.) was recrystallized from dimethylformamide to afford colorless granules (3.0 g.) of VII, m.p. 257°(decomp.). IR ν_{max}^{KBr} cm^{-1}: 3055～2320, 1691 (CO). *Anal.* Calcd. for $C_{14}H_9O_3N_3$: C, 62.92; H, 3.39; N, 15.73. Found: C, 62.65; H, 3.52; N, 16.04.

B——Compound (I) (5.0 g.) was added to a solution of phenylhydrazine hydrochloride (7.2 g.) in H_2O (50 ml.) at 80° and allowed to stand at 70～90° for 1 hr. The yellowish powder was collected and washed with H_2O to give VII (6.2 g.), m.p. 255～256°(decomp.). Recrystallization from dimethylformamide gave colorless granules of VII, m.p. 258°(decomp.). It was identified by comparing its IR spectrum with that of VII described at A.

Ethyl 7-Phenyl-8-oxo-7,8-dihydropyrido[2,3-*d*]pyridazine-5-carboxylate (VIIIb)——A mixture of VII (2.0 g.), EtOH (20 ml.) and conc. H_2SO_4 (4 ml.) was refluxed for 4 hr. The solution was concentrated at 100°, cooled and poured into ice water to separate precipitate (1.9 g.), which was collected, washed with H_2O and recrystallized from dil. EtOH to give colorless long needles of VIIIb (1.2 g.), m.p. 138～139°. *Anal.* Calcd. for $C_{16}H_{13}O_3N_3$: C, 65.08; H, 4.44; N, 14.23. Found: C, 65.05; H, 4.17; N, 14.33.

Methyl 7-Phenyl-8-oxo-7,8-dihydropyrido[2,3-*d*]pyridazine-5-carboxylate (VIIIa)——A mixture of VI (2.0 g.), MeOH (20 ml.) and conc. H_2SO_4 (4 ml.) was refluxed for 1 hr. The solution was concentrated at 100°, cooled and poured into ice water to give precipitate, which on recrystallization from dil. MeOH gave colorless needles of VIIIa (1.8 g.), m.p. 178～179°. *Anal.* Calcd. for $C_{15}H_{11}O_3N_3$: C, 64.05; H, 3.94; N, 14.94. Found: C, 63.99; H, 4.09; N, 15.10.

Hydrolysis of VIIIb in Warm aq. NaOH——To 5% aq. NaOH (5 ml.) VIIIb (1.0 g.) was added and heated on a water bath until a clear solution was obtained. This was made acidic with AcOH to precipitate a yellow solid of IX, m.p. 200°(decomp.). This compound proved to be phenylhydrazone of 3-formylpicolinic acid by a mixed melting point test and comparison of its IR spectrum with an authentic sample prepared by the method of Bottari and Carboni.[1] The filtrate of the acidified reaction mixture was concentrated on a water bath and cooled to separate colorless plates (0.2 g.), which were collected, washed with H_2O and recrystallized from H_2O to yield Xb, decomp. p. 227°, m.p. ca. 250°. *Anal.* Calcd. for $C_{10}H_{10}O_4N_2$: C, 54.05; H, 4.54; N, 12.61. Found: C, 54.08; H, 4.60; N, 13.24. IR ν_{max}^{KBr} cm^{-1}: 3370 (broad, NH_2), 1667 (CO), 1628 (CO), 1587, 1491, 1454, 1367.

Hydrolysis of VIIIb in Cold aq. NaOH——Compound (VIIIb) (0.75 g., 0.0025 mole) was added to 1% aq. NaOH (15 ml., 0.0037 mole) with shaking at room temperature. After a few minutes a yellowish solution

was obtained. It was allowed to stand overnight. The crystalline precipitates, decomp. p. 227°, m.p. ca. 250°(0.35 g., 62%) were collected and washed with H_2O. Recrystallization from EtOH gave colorless needles of Xb, decomp. p. 229°, m.p. ca. 250°. It was identified by comparing its IR spectrum with that of Xb described above.

Hydrolysis of VIIIa in Cold aq. NaOH——Compound (VIIIa) (1.4 g. 0.005 mole) was added to NaOH (0.20 g., 0.005 mole) in H_2O (15 ml.) with shaking at room temperature and allowed to stand at room temperature for 1 hr. to complete precipitation. The crystalline precipitate was collected, washed with H_2O and recrystallized from MeOH to give colorless crystals of Xa (0.9 g., 86%), decomp. p. 227~229°, m.p. ca. 250°. *Anal.* Calcd. for $C_9H_8O_4N_2$: C, 51.92; H, 3.87; N, 13.46. Found: C, 51.84; H, 3.88; N, 12.97.

7-Phenyl-8-oxo-7,8-dihydropyrido[2,3-*d*]pyridazine-5-carboxamide (XIIa)——Compound (VIIIb) (0.5 g.) was heated at 100° in conc. NH_4OH for 1 hr. to give a solid, which on recrystallization from dioxan gave colorless granules of XIIa (0.3 g.), m.p. 333°(decomp.). *Anal.* Calcd. for $C_{14}H_{10}O_2N_4$: C, 63.15; H, 3.79; N, 21.04. Found: C, 63.01; H, 3.82; N, 21.23.

Methylamide of VII, XIIb——Compound (VIIIb) (1.0 g.) was refluxed in a solution of CH_3NH_2 (1.0 g.) in EtOH (10 ml.) for 30 min. The reaction mixture was evaporated to approximately 1/3 volume, added with H_2O and cooled. The needles were collected and recrystallized from dil. MeOH to give colorless needles of XIIb (0.5 g.), m.p. 199~200°. *Anal.* Calcd. for $C_{15}H_{12}O_2N_4$: C, 64.27; H, 4.32; N, 19.99. Found: C, 64.01; H, 4.24; N, 19.80.

Ethylamide of VII, XIIc——Compound (VIIIb) (1.0 g.) was treated with a solution of $C_2H_5NH_2$ (1.0 g.) in EtOH (10 ml.) just as described above to give colorless needles of XIIc (0.5 g.), m.p. 169~171° from dil. MeOH. *Anal.* Calcd. for $C_{16}H_{14}O_2N_4$: C, 65.29; H, 4.80; N, 19.04. Found: C, 65.71; H, 4.79; N, 19.08.

Hydrazide of VII, XIId——Compound (VIIIa) (2.85 g.) was refluxed in a mixture of 80% $NH_2NH_2 \cdot H_2O$ (0.7 ml.) and MeOH (25 ml.) for 30 min. The solution was evaporated *in vacuo* to give a yellow solid, which on recrystallization from MeOH gave yellowish needles of XIIb (2.2 g.), m.p. 198°. *Anal.* Calcd. for $C_{14}H_{11}O_2N_5$: C, 59.78; H, 3.94; N, 24.90. Found: C, 59.71; H, 3.99; N, 24.93.

5-Hydroxy-7-phenylpyrido[2,3-*d*]pyridazin-8(7*H*)-one (XIIIa)——A mixture of quinolinic acid (100 g.) and Ac_2O (500 g.) was heated at 130~140° for a few hr. until a clear solution was obtained and cooled. Phenylhydrazine (117 ml.) was added dropwise with stirring over a period of 15 min. During this time the temperature of the solution rose to 120°. Then the solution was heated at 120~130° on an oil bath for 5 hr., cooled and the solvent was completely evaporated on a water bath at 100° under reduced pressure (20 mm. Hg). The residual oil was dissolved in MeOH (500 ml.) and allowed to stand for 3 days or more. The precipitate was collected, washed with MeOH and recrystallized from MeOH (2 L.) to give colorless needles of XIIIa (65 g., 45%), m.p. 265°. IR ν_{max}^{KBr} cm^{-1}: 3060~2480, 1668 (CO), 1590 (C_6H_5), 1486, 1256, 1168, 1086, 762, 730, 683. *Anal.* Calcd. for $C_{13}H_9O_2N_3$: C, 65.26; H, 3.79; N, 17.57. Found: C, 65.17; H, 3.43; N, 17.66.

5-Chloro-7-phenylpyrido[2,3-*d*]pyridazin-8(7*H*)-one (XIVa)——Compound (XIIIa) (4.8 g.), $POCl_3$ (10 ml.) and PCl_5 (4.2 g.) were refluxed for 4~5 hr. and then cooled. The solution was poured on ice to decompose excess $POCl_3$ and neutralized with aq. NaOH. The precipitate was collected, washed with H_2O and recrystallized from MeOH (charcoal) to give colorless needles of XIVa (2.0 g., 39%), m.p. 184°. *Anal.* Calcd. for $C_{13}H_8ON_3Cl$: C, 60.59; H, 3.13; N, 16.31. Found: C, 60.92; H, 3.35; N, 16.17. IR ν_{max}^{KBr} cm^{-1}: 3070 (CH), 1688 (CO), 1574, 1491, 1427, 1339, 1298, 984 (CCl), 814 (CCl), 723.

7-Phenyl-1,2,3,4-tetrahydropyrido[2,3-*d*]pyridazin-8(7*H*)-one (XV). From XIVa——Compound (XIVa) (0.65 g.) was hydrogenated in MeOH (20 ml.) over 10% Pd-C (0.5 g.) at room temperature at atmospheric pressure until about 200 ml. of H_2 was absorbed. The reaction mixture was filtered while hot and concentrated. The solid was extracted with H_2O and the H_2O solution was neutrallized with NaOH to give a solid which on recrystallization from dil. MeOH gave needles of XV (0.3 g.), m.p. 128°. *Anal.* Calcd. for $C_{13}H_{13}ON_3$: C, 68.70; H, 5.77; N, 18.49. Found: C, 68.71; H, 6.04; N, 18.31.

From XI——Compound (XI) (0.7 g.) was hydrogenated in MeOH (20 ml.) and conc. NH_4OH (0.5 ml.) over 10% Pd-C (1.0 g.) at room temperature at atmospheric pressure until absorption of H_2 ceased. The reaction mixture was filtered and the solvent was evaporated to give an oil, which on recrystallization from dil. aq. MeOH gave needles of XV (0.5 g.), m.p. 130~131°. This was identified by a mixed melting point test (129~130°) and comparison of IR spectra with the sample of XV obtained above.

5-*p*-Chlorobenzoyloxy-7-phenylpyrido[2,3-*d*]pyridazin-8(7*H*)-one (XVIa)——Compound (XIIIa) (1.2 g.) was added to a solution of *p*-chlorobenzoyl chloride (0.65 ml.) in pyridine (10 ml.). It was warmed on a water bath for a few min. and cooled. Cold H_2O was added to the reaction mixture to give colorless crystals. Recrystallization from MeOH gave prisms of XVIa (1.2 g.), m.p. 189~191°. *Anal.* Calcd. for $C_{20}H_{12}O_3N_3Cl$: C, 63.58; H, 3.20; N, 11.12. Found: C, 63.64; H, 3.69; N, 11.13.

5-*p*-Nitrobenzoyloxy-7-phenylpyrido[2,3-*d*]pyridazin-8(7*H*)-one (XVIb)——Compound (XIIIa) (1.2 g.) was added to a solution of *p*-nitrobenzoyl chloride (0.95 g.) in pyridine (10 ml.). After 10 min., H_2O was added to the solution. The precipitate was collected, washed with H_2O, dried and recrystallized from dioxan to give colorless crystals of XVIb (1.23 g.), m.p. 227~230°. *Anal.* Calcd. for $C_{20}H_{12}O_5N_4$: C, 61.87; H, 3.11; N, 14.43. Found: C, 62.07; H, 2.99; N, 14.26.

5-Methoxy-7-phenylpyrido[2,3-*d*]pyridazin-8(7*H*)-one (XVII)——Compound (XIVa) (1.0 g.) was added to a solution of Na (0.2 g.) in MeOH (15 ml.) and refluxed for 1.5 hr. To the hot solution, H_2O was added

until the solution became turbid. Then it was cooled to precipitate needles, which were collected, washed with H_2O and recrystallized from dil. MeOH to give colorless needles of XVII (0.7 g.), m.p. 162~163°. *Anal.* Calcd. for $C_{14}H_{11}O_2N_3$: C, 66.39; H, 4.38; N, 16.59. Found: C, 66.25; H, 4.37; N, 16.35.

5-Chloro-7-methylpyrido[2,3-*d*]pyridazin-8(7*H*)-one (XVIII)——To the Na salt of 5-chloropyrido[2,3-*d*]-pyridazin-8-ol (0.55 g.) in H_2O (5 ml.) and MeOH (10 ml.) was added CH_3I (0.3 ml.) and the mixture was refluxed 1 hr. and the solvent was evaporated to approximately 1/3 volume and cooled. Colorless needles (0.5 g.) were collected and recrystallized from MeOH to give crystals of XVIII, m.p. 194~195°. *Anal.* Calcd. for $C_8H_6ON_3Cl$: C, 49.10; H, 3.09; N, 21.49. Found: C, 48.61; H, 3.35; N, 21.01. IR ν_{max}^{KBr} cm^{-1}: 1664 (CO), 1571, 1418 (CH), 1335, 1302, 984 (CCl), 814 (CCl), 725.

6-Methyl-8-chloropyrido[2,3-*d*]pyridazin-5(6*H*)-one (XIX)——8-Chloropyrido[2,3-*d*]pyridazin-5-ol (0.9 g.) and KOH (0.5 g.) were refluxed in MeOH (20 ml.) for a few min., then CH_3I was added and the whole was heated in a sealed tube at 100° for 1 hr. The solution was concentrated to dryness to give a residue, which was washed with H_2O and recrystallized from MeOH to give prisms of XIX (0.9 g.), m.p. 159~160°. IR ν_{max}^{KBr} cm^{-1}: 1658 (CO), 1590, 1431, 1344, 1308, 1009 (CCl), 788 (CCl), 712. *Anal.* Calcd. for $C_8H_6ON_3Cl$: C, 49.10; H, 3.09; N, 21.49. Found: C, 49.36; H, 3.31; N, 21.51.

6,7-Diphenylpyrido[2,3-*d*]pyridazine-5,8(6*H*,7*H*)-dione (XX)——Quinolinic acid dichloride (2.04 g.) was added dropwise with stirring to a solution of hydrazobenzene (1.84 g.) in dimethylaniline (4 ml.) and benzene (10 ml.). The mixture was refluxed for 2 hr. and cooled. The solid was collected, washed with dil. HCl [conc. HCl (5 ml.) and H_2O (30 ml.)] followed by H_2O and recrystallized from 70% aq. MeOH to give needles of XX (1.6 g.), m.p. 217~218°. *Anal.* Calcd. for $C_{19}H_{13}O_2N_3$: C, 68.46; H, 4.54; N, 13.33 Found: C, 68.93; H, 4.38; N, 13.18.

The authors express their deep gratitude to Dr. T. Akiba, Director of these Laboratories. Thanks are also due to the members of the Analysis Room for the elemental analysis and to the members of the Section of Physical Chemistry for the spectral data.

Summary

8-Oxo-7,8-dihydropyrido[2,3-*d*]pyridazine-5-carboxylic acid, 7-phenyl-8-oxo-7,8-dihydropyrido[2,3-*d*]pyridazine-5-carboxylic acid, and their esters, amides and hydrazides were prepared. Alkaline hydrolysis of 7-phenyl-8-oxo-7,8-dihydroprido[2,3-*d*]pyridazine-5-carboxylates gave phenylhydrazone of 3-formylpicolinic acid and good yields of 3-(2-carbamoyl)pyridylglyoxylates. Reaction of quinolinic anhydride with 2 molar equivalents of phenylhydrazine in acetic acid gave the cyclized phenylhydrazide, and its structure, 5-hydroxy-7-phenylpyrido[2,3-*d*]pyridazin-8(7*H*)-one, was determined by its chlorination followed by catalytic hydrogenation to give 7-phenyl-1,2,3,4-tetrahydropyrido[2,3-*d*]pyridazin-8(7*H*)-one. 6,7-Diphenylpyrido[2,3-*d*]pyridazine-5,8(6*H*,7*H*)-dione was also prepared.

(Received January 27, 1966)