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Antituberclous Compounds. XXVII. Synthesis of 7,8-Dihydropyrido-[2.3-*d*]pyridazin-(6*H*)-one[1]

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In a previous paper,[2] it was reported that attempts to prepare some derivatives of dihydropyrido[2.3-*d*]pyridazine in order to study relationship between chemical constitution and tuberclostatic activity were not successful. In this paper, two different synthetic methods of 7,8-dihydropyrido[2.3-*d*]pyridazin-5(6*H*)-one will be reported; the synthesis of this substance was attempted previously.

Hurst and Wibberley[3] prepared ethyl 2-bromomethylnicotinate by the bromination of ethyl 2-methylnicotinate with *N*-bromosuccinimide (NBS). By the same method, its hydrobromide (I) was obtained directly in a pure state. When the compound was treated with hydrazine hydrate, two new compounds, (II), mp 213—215°C, and (III), mp 195—197°C, were obtained in good yields. The ratio of their yields was about 4 : 1. By treatment with alkali, III was converted to II, which was also obtained by the reduction of pyrido[2.3-*d*]pyridazin-5(6*H*)-on-thiol[4] (VI) with amalgamated aluminum. The IR spectrum of II has absorption bands at 3270 cm^{-1} (amino group) and at 1660 cm^{-1} (carbonyl group). The NMR spectrum indicates that it has three protons of the pyridine ring in an AMX-type arrangement and shows a 2-proton singlet of the methylene group at τ 6.45. The compound was oxidized to pyrido[2.3-*d*]pyridazin-5(6*H*)-one[2] (IV) by chromic acid anhydride in acetic acid or by aeration in the presence of peroxide. It was, therefore, concluded that II is 7,8-dihydropyrido[2.3-*d*]-pyridazin-5(6*H*)-one.

The behavior of the pyridine ring is different from that of the benzene ring. Methyl 2-bromomethyl benzoate was treated with hydrazine hydrate in the same way. Only phthalazin-1(2*H*)-one was produced, not 3,4-dihydrophthalazin-1(2*H*)-one. It is certain that the latter is easily oxidized during preparation. Hirsch *et al.*[5] found that some 4-substituted 3,4-dihydrophthalazine derivatives were oxidized to the corresponding phthalazinone by aeration without peroxide.

The IR spectrum of compound III has two bands, at 3330 cm^{-1} and 3270 cm^{-1} indicating an amino group, and one band, at 1690 cm^{-1}, indicating a carbonyl group. The NMR spectrum shows three 1-proton doublet-doublets due to the three protons of the pyridine ring, at τ 1.25, 1.90, and 2.60; a 2-proton singlet at τ 5.40 due to a methylene group, and a 2-proton broad peak at τ 5.65 due to an amino group. The amino group was acetylated with acetic anhydride. It is clear that III is 2-amino-dihydropyrrolo[3.4-*b*]pyridin-1-one.

Experimental[6]

Ethyl 2-Bromomethylnicotinate Hydrobromide (I). Ethyl 2-methylnicotinate (5g) was brominated with NBS in carbon tetrachrolide as usual. Dried hydrobromic acid was introduced into the reaction mixture, and then hydrobromide was separated from the mixture as a yellow crystalline substance. Recrystallization from ethanol - ligroin afforded 4.4 g of I, mp 157—159°C (decomp.). NMR (D_2O) τ: 4.93 ($-CH_2Br$, singlet). Found: C, 33.17; H, 3.62%. Calcd for $C_9H_{10}O_2NBr \cdot HBr$: C, 33.26; H, 3.41%.

7,8-Dihydropyrido[2.3-*d*]pyridazin-5(6*H*)-one (II). i) To a solution of 0.95 g of I in 20 m*l* of ethanol there was added 0.7 m*l* of hydrazine hydrate, and then the mixture was refluxed for 2.5 hr. After evaporation to a small volume, it was cooled to afford 320 mg of II, mp 213—215°C.

ii) A mixture of 0.5 g of VI, 0.5 g of amalgamated aluminum, and 100 m*l* of 50% ethanol was refluxed for 10 hr. The filtrate of the reaction mixture was then evaporated to dryness. The residue was extracted with water, and the aqueous solution was evaporated to give a crystalline product. Recrystallization from water afforded 0.1 g of II, mp 213—215°C, as needles with one mole of the water of crystallization.

IR: ν_{max} 3270, 3210 (NH), 1660 cm^{-1} (CO). NMR

1) Presented at the 21th Annual Meeting of the Chemical Society of Japan, Osaka, April, 1968.

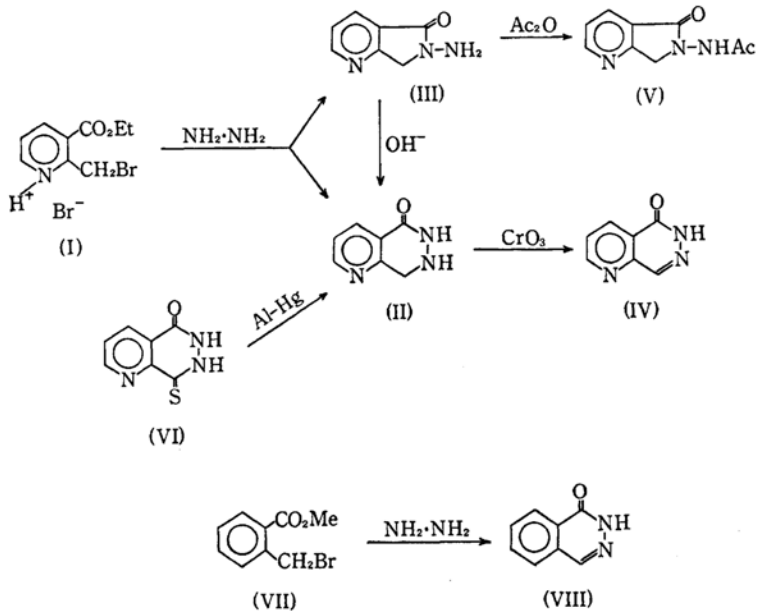
2) S. Kakimoto and S. Tonooka, This Bulletin, **40** 153 (1967).

3) J. Hurst and D. G. Wibberley, *J. Chem. Soc.*, **1962**, 120.

4) S. Kakimoto, H. Shintani and K. Yamamoto, Annual Report of Research Institute for Tuberculosis, Hokkaido University, **27**, 1 (1966).

5) A. Hirsch and D. G. Orphanos, *J. Heterocyclic Chem.*, **3**, 38 (1966).

6) All the melting points are uncorrected; the IR spectra were measured in Nujol, while the NMR spectra were determined on a Japan Electron Optics 3H-60 high resolution NMR spectrometer, using TMS or DSS as the internal reference.



(D_2O) τ: 2.20 (H_α of pyridine-ring, doublet-doublet), 2.45 (H_γ of pyridine-ring, doublet-doublet), 3.40 (H_β of pyridine-ring, doublet-doublet), $J_{\alpha\beta}=5.0$, $J_{\beta\gamma}=8.0$, $J_{\alpha\gamma}=2.0$ cps. 6.45 (-CH_2-, singlet) Found: C, 50.29; H, 5.38; H_2O, 10.88%. Calcd for $C_7H_7ON_3\cdot H_2O$: C, 50.29; H, 5.43; H_2O, 10.77%.

Oxidation of II to IV. i) To a mixture of 0.1 g of II and 2 m*l* of acetic acid these were added 10 m*l* of a 1/5 N chromic oxide solution in acetic acid; the mixture was then allowed to stand for 1 hr. After the evaporation of the acetic acid under reduced pressure, the residue was recrystallized from water to give 0.1 g of white needles. Its identity as IV was established by a study of the IR spectra and melting points.

ii) A solution of 0.1 g of II in 5 m*l* of ethanol, along with several mg of benzoyl peroxide, was aerated at 50—60°C for 24 hr. During aeration the total volume was kept at about 5 m*l* by the addition of ethanol from time to time. After the ethanol had then been removed, the residue was recrystallized from ethanol-ligroin to give 35 mg of white needles. Its identity as IV was confirmed by a study of the IR spectra and melting points.

2-Aminodihydropyrrolo[3.4-*b*]pyridin-1-one (III). The mother liquor of II was evaporated to dryness and the residue was recrystallized from ethanol-ligroin to give 85 mg of III as white crystalline plates, mp 195—197°C. IR: ν_{max} 3330, 3270 (NH), 1690 cm^{-1} (CO). NMR ($CDCl_3$) τ: 1.25 (H_α of pyridine-ring, doublet-doublet), 1.90 (H_γ of pyridine-ring, doublet-doublet), 2.60 (H_β of pyridine-ring, doublet-doublet), $J_{\alpha\beta}=4.5$, $J_{\beta\gamma}=8.0$, $J_{\alpha\gamma}=1.5$ cps. 5.40 (methylene-group, singlet), 5.65 (amino-group, broad peak). Found: C, 56.37; H, 4.75%. Calcd for $C_7H_7ON_3$: C, 56.37; H, 4.73%.

2-Acetamidodihydropyrrolo[3.4-*b*]pyridin-1-one (V). III (60 mg) was dissolved in 5 m*l* of acetic anhydride, and the mixture was warmed on a steam bath for 4 hr. After the removal of the excess acetic anhydride under reduced pressure, the residue was recrystallized from ethanol-ligroin to give 25 mg of an acetyl compound, V, mp 173—175°C. IR: ν_{max} 3230 (NH), 1720 ($COCH_3$), 1690 cm^{-1} (CO). Found: C, 51.65; H, 5.35; H_2O, 8.99%. Calcd for $C_9H_9O_2N_3\cdot H_2O$: C, 51.67; H, 5.30; H_2O, 9.23%.

III to II. III (53 mg) was heated in a dilute potassium hydroxide solution on a steam bath for 1 hr. After neutralization with dilute hydrochloric acid, the solution was evaporated to dryness under reduced pressure, and the residue was extracted with ethanol. After the ethanol had then been removed under reduced pressure, the residue was recrystallized from ethanol-ligroin to give 20 mg of white needles. Its identity as II was established by a study of the IR spectra and melting points.

Phthalazin-1(2*H*)-one (VIII). Methyl 2-methyl benzoate was treated with NBS in carbon tetrachloride in the manner used to cause I to afford VII. Its NMR spectrum showed four protons of benzene at τ 2.0—2.6, a 2-proton singlet at τ 5.05, and a 3-proton singlet at τ 6.10. VII (2 g) was treated with hydrazine hydrate in the same manner as has been described for II to give 0.35 g of VIII, mp 181—183°C. Its identity with an authentic sample[7] was confirmed by a study of the IR spectra and a mixed-melting-point determination.

7) Paul, *Ber.*, **32**, 2020 (1899).