

Antituberculous Compounds. XXVIII. Synthesis of Pyrazolopyridines.

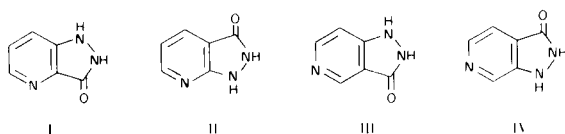
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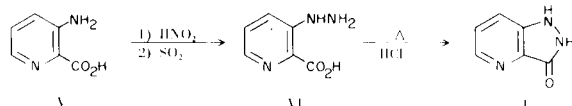
In a previous paper (1) it was reported that *N'*-alkyl derivative of isonicotinic acid hydrazide (INH) was more active against tubercle bacilli than the acyl derivative containing the same number of carbon atoms. The authors subsequently reported (2) that the pyrido[2,3-*d*]-pyridazine was closely related to the acyl derivative of INH except that the terminal carbonyl group was cyclized to the pyridine nucleus, therefore these derivatives were not effective against tubercle bacilli; however, pyridopyridazine, which is similar to the alkyl derivatives of INH, will be more effective against tubercle bacilli. According to the similar expectation, some pyrazolopyridines were prepared.

The antitubercular activity of these compounds against the human tubercle bacillus, strain H37Rv, was about one thirtieth that of INH in the same microbiological *in vitro* test. However, in the comparison with these new compounds, compound IV, having a carbonyl group in the γ -position of pyridine nucleus had the best activity (50 γ /ml.); compound I having the carbonyl group in the α -position was the next highest in activity (100 γ /ml.) and compounds II and III were not effective. These observations coincided with the fact that in three isomers of pyridine monocarboxylic acid hydrazide, isonicotinic acid hydrazide, with a γ -carbonyl group had the highest activity (2 γ /ml.), and picolinic acid hydrazide, with an α -carbonyl was the next most active (60 γ /ml.). Nicotinic acid hydrazide had no activity.



Compound I, pyrazolo[4,3-*b*]pyridin-3(2*H*)one was prepared as shown in Scheme I. 3-Aminopicolinic acid (V) was diazotized and reduced with sulphur dioxide to

Scheme I



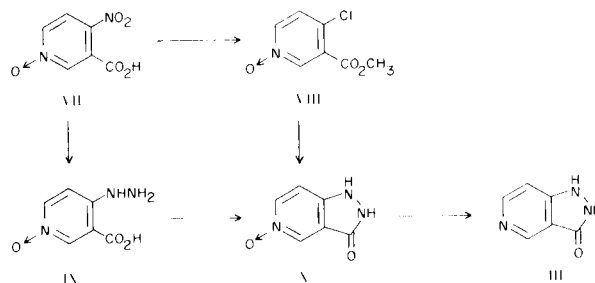
give compound VI, which was converted by cyclization with hydrochloric acid to compound I. Compound IV, 3-hydroxy-III-pyrazolo[3,4-*c*]pyridine was prepared by the same method from 3-aminoisonicotinic acid and

isolated as the hydrochloride for the measurement of physical constants and antibacterial tests.

Compound II, pyrazolo[3,4-*b*]pyridin-3(2*H*)one was prepared from methyl 2-chloronicotinate (3) by heating with hydrazine hydrate in methanol.

Compound III, 3-hydroxy-III-pyrazolo[4,3-*c*]pyridine (4) was prepared as shown in Scheme II.

Scheme II



Compound X was obtained from compound VII (5) through the hydrazine derivative (IX) by heating with hydrazine hydrate.

EXPERIMENTAL

Ir spectra as Nujol mulls were recorded on a Shimadzu Ir-27G spectrophotometer. Nmr spectra were determined on a Hitachi R-20B spectrometer with TMS as internal reference. The *in vitro* test against the human tubercle bacillus, strain H37Rv, using Kirchner's medium was conducted according to the method described in a previous paper (6).

Pyrazolo[4,3-*b*]pyridin-3(2*H*)one (I).

3-Aminopicolinic acid (2.8 g.) dissolved in 20 ml. of water and 22 ml. of concentrated hydrochloric acid was diazotized with 1.6 g. of sodium nitrite and the diazotized solution was added

to 150 ml. of a saturated solution of sulphur dioxide. More sulphur dioxide was introduced into the mixture (about 20 minutes). 3-Hydrazinopicolinic acid (3.5 g.) was obtained as the crystalline dihydrochloride, m.p. 194-195° dec. The solution of the salt in dilute hydrochloric acid was refluxed to give 1.3 g. of compound I as the hydrochloride, m.p. 256-260° dec. The salt (1.0 g.) was dissolved in water (50 ml.) and the solution was basified with dilute sodium hydroxide solution and then neutralized with dilute hydrochloric acid to give the crude product. Recrystallization from water gave 0.4 g., m.p. 247-248° dec.; ir: 1640 (amide C=O); nmr (trifluoroacetic acid): δ 8.91 (d, 1, 5-H, J = 4.5 Hz), 8.87 (d, 1, 6-H, J = 9.0 Hz), and 8.17 (dd, 7-H, J = 9.0, 4.5 Hz).

Anal. Calcd. for $C_6H_5ON_3$: C, 53.33; H, 3.73; Found: C, 53.22; H, 3.93.

Pyrazolo[4,3-c]pyridin-3(2H)one (II).

To a solution of 5 g. of methyl 2-chloronicotinate in 10 ml. of methanol, 5 g. of 85% hydrazine hydrate was added and the mixture was refluxed for 6 hours on a steam bath. The reaction mixture was evaporated to dryness under reduced pressure and the residue was recrystallized from methanol, yield 1.2 g., m.p. 248-250° dec.; ir: 1610 (amide C=O); nmr (pyridine- d_5): δ 11.0 (br, 2, -NH-NH-), 8.65 (dd, 1, 6-H, J = 2.0, 4.5 Hz), 8.25 (dd, 1, 4-H, J = 2.0, 8.0 Hz) and 7.05 (dd, 1, 5-H, J = 4.5, 8.0 Hz).

Anal. Calcd. for $C_6H_5ON_3$: C, 53.33; H, 3.73; N, 31.10. Found: C, 53.47; H, 3.79; N, 31.13.

3-Hydroxy-1H-pyrazolo[4,3-c]pyridine 5-Oxide (X).

A mixture of 1 g. of 4-nitronicotinic acid 1-oxide (5), 0.9 ml. of 85% hydrazine hydrate and 30 ml. of ethanol was refluxed for 1 hour. The yellow crystals obtained were dissolved in water and the solution was acidified with 50% acetic acid to pH 5 to give 0.6 g. of yellow crystals of compound IX, m.p. 224° dec., yield 0.6 g.

Anal. Calcd. for $C_6H_7O_3N_3$: C, 42.60; H, 4.17; N, 24.85.

Found: C, 42.68; H, 4.13; N, 24.82.

Compound IX was refluxed with dilute hydrochloric acid for 2.5 hours to give the hydrochloride salt of compound X, m.p. 209-212° dec. (4).

3-Hydroxy-1H-pyrazolo[3,4-c]pyridine (IV).

3-Hydrazinoisonicotinic acid dihydrochloride (XI) was prepared from 3-aminoisonicotinic acid in the manner as described in the case of compound I. From compound XI, m.p. 160-161° dec., compound IV was obtained as the hydrochloride, m.p. above 280°; ir: 1640 (weak, amide C=O); nmr (trifluoroacetic acid): δ 9.41 (s, 1, 7-H), 8.50 (d, 1, 5-H, J = 6.0 Hz) and 8.45 (d, 1, 4-H, J = 6.0 Hz).

Anal. Calcd. for $C_6H_5ON_3 \cdot HCl$: C, 42.00; H, 3.52. Found: 42.29; H, 3.82.

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