PYRIDO[2,3-d]PYRIMIDINES

6.* REACTIONS OF HYDROXYPYRIDO[2,3-d]PYRIMIDINES WITH THIONYL CHLORIDE IN THE PRESENCE OF DMF

O. A. Burova, N. M. Smirnova, and T. S. Safonova

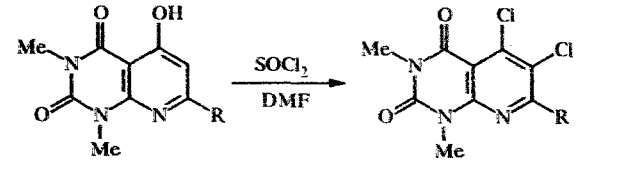
Depending on the reaction conditions, 5-hydroxy- and 5,7-dihydroxypyrido[2,3-d]pyrimidines react with thionyl chloride in the presence of DMF to give chlorination at position 6 along with replacement of the hydroxy groups at C(5) and C(7) with chlorine, while a nitro group at C(6) is ipsosubstituted by chlorine.

The conversion of 7-hydroxypyrido[2,3-d]pyrimidines into 7-chloropyrido[2,3-d]pyrimidines with thionyl chloride in the presence of DMF has been described [2, 3] and we have previously described the preparation of 1,3-dimethyl-5,7-dichloropyrido[2,3-d]pyrimidin-2,4-dione from 1,3-dimethyl-5-hydroxy-7-chloropyrido[2,3-d]pyrimidin-2,4-dione under analogous conditions [4].

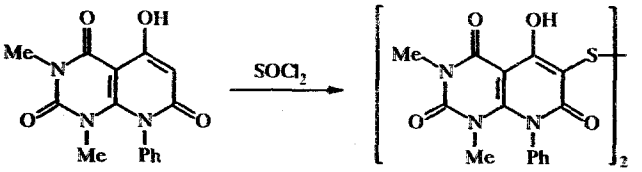
We have studied the interaction of 5-hydroxy- and 5,7-dihydroxypyridopyrimidines with $SOCl_2$-DMF with the aim of producing 5- and 7-chloropyridopyrimidines, which are the starting materials for the synthesis of various derivatives of pyrido[2,3-d]pyrimidine and potentially biologically active compounds.

Boiling compound Ia [4] with $SOCl_2$ with added DMF gave a mixture of products from which 5,6,7-trichloropyridopyrimidine IIa was isolated in 20% yield. Its mass spectrum contained the following peaks which confirmed the presence of three chlorine atoms in the molecule: ($M^{+\cdot}$) 293 (100), (M + 2) 295 (97), (M + 4) 297 (34), (M + 6) (5).

The 5,6-dichloro-7-azido derivative IIb was obtained from 5-hydroxy-7-azidopyridopyrimidine Ib in 29% yield under analogous conditions [5]. The C(6)-H signal at 6.03 ppm, present in the starting material Ib, was absent from the ^1H NMR spectrum of IIb. Elemental analysis results and the mass spectrum [($M^{+\cdot}$)300, (M + 2) 302, (M + 4) 304] confirmed the presence of two chlorine atoms in the molecule.



Ia, b IIa, b



I b III

Ia R=OH; IIa R=Cl; I, II b R=N_3

The formation of compounds IIa and IIb shows that, under the given conditions, $SOCl_2$ not only causes substitution of the 5- and 7-hydroxy groups by chlorine atoms, but it also acts as an electrophilic agent leading to chlorination at C(6) of

*For Communication 5, see [1].

Novokuznetsk Chemicopharmaceutical Research Institute, Novokuznetsk 654034. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 9, pp. 1230-1233, September, 1992. Original article submitted April 24, 1991.

 0009-3122/92/2809-1042$12.50

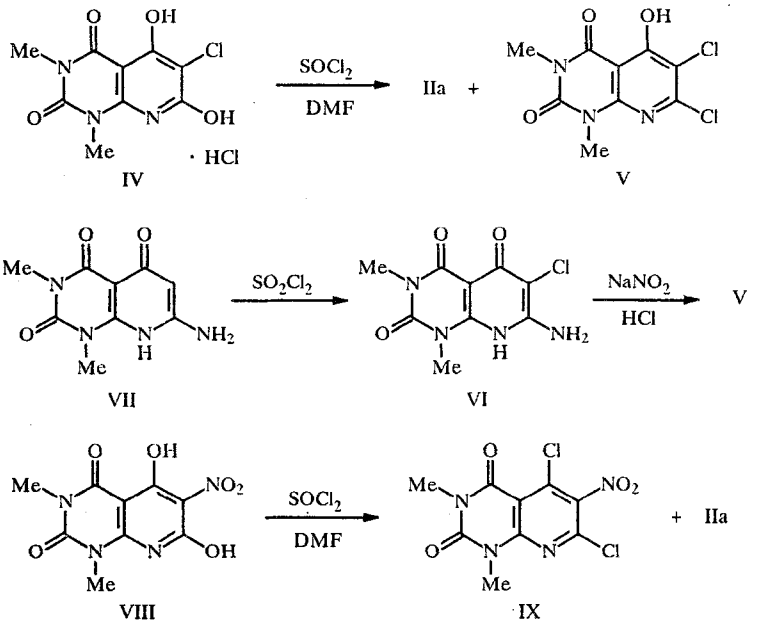
the pyridopyrimidine. Some similar cases have been described in the literature, e.g., the reaction of 6-amino(methylamino)pyrimidines with $SOCl_2$ gave the corresponding 5-chloro derivatives [6, 7]. 5-Chlorosulfinyl derivatives were considered as intermediates since a mixture of sulfides and sulfoxides was isolated from the reaction mixture [6].

It is possible that the reaction sequence leading to compounds IIa and IIb also includes electrophilic attack by the thionyl chloride molecule at position 6 to give 6-chlorosulfinyl derivatives. Some confirmation of the proposed reaction scheme is provided by the preparation of compound III from heating the pyridopyrimidine Ic [4] with $SOCl_2$ for a short time.

The ^1H NMR spectrum of compound III contains signals at 2.60 and 3.23 ppm ($N-CH_3$) and 7.42 ppm (phenyl) plus a signal for the C(5)−H protons at 13.12 ppm, while the signal for the C(6)−H proton at 5.50 ppm, present in the starting material Ic, is absent. The molecular ion peak $M^{+\cdot}$ at 660 is present in the mass spectrum of III.

Evidently chlorination of pyridopyrimidine molecules at C(6) is facilitated by the presence of two electron donor groups at positions 5 and 7, e.g., two hydroxy groups (compound Ia) or a hydroxy and an azido group (compound Ib). If electron acceptors are present at positions 5 and 7, for example, chlorine atoms, then chlorination at C(6) by $SOCl_2$−DMF does not take place [4].

The directed synthesis of compound IIa was carried out by heating 5,7-dihydroxy-6-chloropyridopyrimidine hydrochloride IV [8] with $SOCl_2$-DMF for 3 h (90% yield). By shortening the reaction time to 1 h it was possible to isolate compound IIa and 5-hydroxy-6,7-dichloropyridopyrimidine V [1] in a ratio of 4:3. The structure of compound V was confirmed by its synthesis from 6-chloro-7-aminopyrimidine VI under the influence of sodium nitrite in hydrochloric acid solution. Compound VI was synthesized in its turn by reaction of the 7-amino derivative VII [9] with sulfuryl chloride at 20°C.



Interesting results were obtained from a study of the reaction of 5,7-dihydroxy-6-nitropyrido[2,3-d]pyrimidin-2,4-dione VIII [10] with $SOCl_2$-DMF. When the reaction was carried out for 2 h it gave the 5,7-dichloro-6-nitro derivative IX in 84% yield, but on more prolonged heating (6 h) the trichloro derivative IIa was unexpectedly obtained along with compound IX.

Ipsosubstitution of a nitro group by a chlorine atom was recently examined in the reactions of a series of 3,6-dinitro-4-chloro- and 3,6-dinitro-4-hydroxycoumarins with $POCl_3$ in DMF [11]. In our example, ipsosubstitution of the nitro group at C(6) by chlorine accompanied replacement of the C(5) and C(7) hydroxy groups of compound VIII by chlorine.

EXPERIMENTAL

IR spectra of KBr disks were recorded with a Specord IR-75 instrument. Mass spectra were obtained with a Varian MAT-311 A machine with direct insertion of the samples into the ion source.

^1H NMR spectra were recorded with a Tesla Bs-497 spectrometer (100 MHz) with hexamethyldisiloxane as internal standard. Silicagel L 100/250 μm was used for column chromatography and Silufol UV-254 plates were used for TLC.

Elemental analyses found for C, H, Cl, N, and S corresponded to calculated values.

1,3-Dimethyl-5,6,7-trichloropyrido[2,3-d]pyrimidin-2,4-dione (IIa, $C_9H_6Cl_3N_3O_2$). **A.** A suspension of compound Ia (3 g, 13 mmole), $SOCl_2$ (20 ml), and DMF (2 ml) was heated under reflux for 6 h, the excess $SOCl_2$ was removed in vacuum, and the residue was poured into water. The precipitate was filtered off, dried, and placed on a silicagel column (3 × 60 cm, benzene eluent). The first fraction was collected and evaporated to give compound IIa (0.8 g, 20%), m.p. 168-170°C (from benzene). IR spectrum: 1662, 1726 cm^{-1} (CO). ^1H NMR spectrum ($CDCl_3$): 3.43 (3H, s), 3.65 ppm (3H, s).

B. A suspension of compound IV (1 g, 3.4 mmol), $SOCl_2$ (20 ml), and DMF (0.4 ml) was refluxed for 3 h, poured into water, and the precipitate filtered off. Yield 0.9 g (90%).

C. A suspension of compound IV (2 g, 6.8 mmol), $SOCl_2$ (20 ml), and DMF (0.4 ml), was refluxed for 1 h, the reaction mixture was poured into water, and the residue filtered off. The latter was dried and chromatographed on silicagel with chloroform as eluent to give compound IIa (0.8 g, 40%), R_f 0.8 (methyl acetate) and compound V (0.5, 30%), R_f 0.7, identical in physicochemical and spectroscopic properties with a sample described previously [1].

1,3-Dimethyl-5,6-dichloro-7-azidopyrido[2,3-d]pyrimidin-2,4-dione (IIb, $C_9H_6Cl_2N_6O_2$). A suspension of compound Ib (1 g, 4 mmol), $SOCl_2$ (15 ml), and DMF (0.8 ml) was refluxed for 8 h, the excess of thionyl chloride was distilleed off, and the residue was poured into water. The precipitate was filtered off a chromatographed on a silicagel column with chloroform as eluent to give IIb (0.35 g, 29%), m.p. 147-149.5°C (from acetone), R_f 0.35 (chloroform). IR spectrum: 2156 (N_3), 1669, 1723 cm^{-1} (CO). ^1H NMR spectrum (in $CDCl_3$): 3.40 (3H, s), 3.63 ppm (3H, s). Mass spectrum, m/z (J/J_{max}, %): 152 (100, 187 (48), 189 (31), 154 (31), 215 (24), 100 (22), 67 (19), 56 (17), $M^{+\cdot}$ 300 (17), (M + 2) 302 (13), (M + 4) 304 (2).

6,6′-Dithiobis[1,3-dimethyl-5-hydroxy-8-phenylpyrido[2,3-d]-pyrimidin-2,4,7-trione] (III, $C_{30}H_{24}N_6O_8S_2$). A suspension of compound Ic (1 g, 3.3 mmol) in $SOCl_2$ (5 ml) was refluxed for 0.5 h, cooled to 20°C, the residue filtered off and washed on the filter with acetone to give III (0.9 g, 41%), m.p. > 300°C (from acetic acid). IR spectrum: 1667, 1716 cm^{-1} (CO).

1,3-Dimethyl-6-chloro-7-amino-8H-pyrido[2,3-d]pyrimidin-2,4,5-trione (VI, $C_9H_9ClN_4O_3$). A suspension of 7-aminopyridopyrimidine VII (4 g, 18 mmol) in SO_2Cl_2 (16 ml) was stirred for 1 h at 20°C, the precipitate was filtered off and washed with water to give VI (yield, 4.4 g, 95%), m.p. 271-273°C (from acetic acid). IR spectrum: 3527, 3356 (NH_2); 1653, 1680, 1720 cm^{-1} (CO). Mass spectrum: $M^{+\cdot}$ 256 (100), (M + 2) 258 (33).

1,3-Dimethyl-5-hydroxy-6,7-dichloropyrido[2,3-d]pyrimidin-2,4-dione (V). The pyridopyrimidine VI (0.5 g, 1.9 mmol) dissolved in 35% HCl (100 ml) on heating, the solution was cooled to 0 to 5°C and sodium nitrite (3 g, 43 mmol) was added in portions. The solution was stirred at this temperature for 1 h, and the precipitate was filtered off and washed with water to give V (0.4 g, 74%).

1,3-Dimethl-5,7-dichloro-6-nitropyrido[2,3-d]pyrimidin-2,4-dione (IX, $C_9H_6Cl_2N_4O_4$). **A.** A suspension of compound VIII (5 g, 18.6 mmol) in $SOCl_2$ (50 ml) and DMF (2 ml) was boiled for 2 h, the excess thionyl chloride was removed in vacuum, and the residue was added to ice water. The precipitate was filtered off and washed with water to give IX (4.75 g, 84%), m.p. 177-179°C (from 1:1 ethanol-chloroform). IR spectrum: 1673, 1723, (CO), 1540, 1369 cm^{-1} (NO_2). Mass spectrum, m/z (J/J_{max}, %): 286 (100), 228 (440, 171 (42), $M^{+\cdot}$ 304 (39), 288 (36), 174 (34), (M + 2) 306 (29), 256 (28), 82 (26), 76 (26), (M + 4) 308 (6).

B. A suspension of compound VIII (0.8 g, 3 mmol) in $SOCl_2$ (8 ml) and DMF (0.5 ml) was refluxed for 6 h, the excess thionyl chloride was removed in vacuum, water was added to the residue, the precipitate (0.68 g) was filtered off and chromatographed on a silicagel column with benzene as eluent to given compound IX (0.35 g, 42%), R_f 0.43 (benzene–methanol, 10:0.1, and compound IIa (0.26 g, 32%), R_f 0.34.

REFERENCES

1. I. D. Bystryakova, O. A. Burova, N. M. Smirnova, and T. S. Safonova. Khim. Geterotsikl. Soedin., No. 11, 1563 (1991).
2. B. S. Hulbert, K. W. Ledig, R. Stenbuch, B. F. Valenti, and G. H. Hitchings, J. Med. Chem., **11**, 703 (1968).
3. T.-L. Su, J.-T. Huang, J. H. Burchenal, K. A. Watanabe, and J. J. Fox, J. Med. Chem., **29**, 709 (1986).
4. O. A. Burova, N. M. Smirnova, V. I. Polyshakov, G. S. Chernov, G. A. Losev, and T. S. Safonova, Khim. Geterotsikl. Soedin., No. 5, 674 (1991).

5. O. A. Burova, I. D. Bystryakova, N. M. Smirnova, and T. S. Safonova, Khim. Geterotsikl. Soedin., No. 4, 497 (1991).
6. J. M. Goldman, J. Org. Chem., **34**, 3285 (1969).
7. Sadao Nishigaki, Keitaro Senda, and Fumio Yoneda. Chem. Pharm. Bull., **18**, 1925 (1970).
8. I. D. Bystryakova, O. A. Burova, G. M. Chelysheva, N. M. Smirnova, and T. S. Safonova. Khim.-farm. Zh., No. 12, 31 (1991).
9. N. M. Smirnova, N. M. Cherdantseva, O. A. Burova, V. M. Nesterov, and T. S. Safonova. Khim. Geterotsikl. Soedin., No. 7, 971 (1990).
10. O. A. Burova, I. D. Bystryakova, N. M. Smirnova, and T. S. Safonova. Khim. Geterotsikl. Soedin., No. 5, 662 (1990).
11. T. Ya. Mokhaeva, O. L. Samsonova, and V. L. Sovel'ev. Khim. Geterotsikl. Soedin., No. 9, 1287 (1988).