PYRIDO[2,3-d]PYRIMIDINES.

2.* REACTIONS OF 2,4,5-TRIOXO-7-AMINO-8H-PYRIDO[2,3-d]PYRIMIDINES WITH ELECTROPHILIC AGENTS

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1,3-Dimethyl-2,4,5-trioxo-7-amino-8H-pyrido[2,3-d]pyrimidine has been brominated, chlorosulfonated, treated with potassium nitrite in acidic medium, and with the Vilsmeier reagent. Acylation and alkylation of 1,3-dimethyl-2,4,5-trioxo-6-bromo-7-aminopyrido[2,3-d]pyrimidine is also discussed.

A study of the reactivity of 1,3-dimethyl-2,4,5-trioxo-7-amino-8H-pyrido[2,3-d]pyrimidine (I) has shown it to be acylated readily at the amino group and, under more severe conditions, at the pyridone ring nitrogen [1]. Attempts to acylate at the C_6 position using catalysts and high temperatures were unsuccessful.

Continuing studies of I, we have successfully chlorosulfonated it at C_6 to give the sulfochloride IIa which is readily hydrolyzed to the sulfonic acid IIb. Reaction of I with potassium nitrite in a mixture of glacial acetic acid and concentrated sulfuric acid gives two products. These were the 6-nitroso-7-hydroxypyridopyrimidine III (as the main product) and 6-nitro-7-hydroxypyridopyrimidine IV.

Reaction of I with the Vilsmeier reagent (DMFA–$SOCl_2$) in chloroform takes place at the amino group to give the enamine V. By analogy with the literature reaction for 1,3-dimethyl-6-aminouracil [2], the product expected was that due to reaction at the pyridine C_6, but spectral data (see Table 1) unequivocally favored structure V. Additional evidence came from the observed hydrolysis of V to the known 7-formamide derivative VI [1].

6-Bromopyridopyrimidine VII is produced in quantitative yield by treating I with bromine in chloroform. As expected, the bromine atom shows low reactivity and reaction with amines and potassium acetate gives only recovered starting VII. Attempts to exchange the bromine for a nitrile group were unsuccessful and only the 7-aminopyridopyrimidine dehalogenation product is obtained. The reaction was carried out in hexamethapol at a temperature of 110–150°C by treating VII with sodium cyanide and sodium iodide.

Interesting results were obtained when alkylating VII with methyl polyphosphate. When the reaction is carried out at 140°C the product is the 6-bromo-7-dimethylaminopyridopyrimidine VIII. Further heating to 200°C and holding at this temperature for 1 h causes total loss of VIII (TLC analysis). The product is IX (yield 13.7%) and combined spectral and elemental analytical data confirm the structure as 1,3,6-trimethyl-2,4,5-trioxo-7-dimethylamino-8H-pyrido[2,3-d]pyrimidine. The PMR spectrum of IX showed the absence of a proton signal at C_6. In addition to the two methyl group signals for the pyrimidine ring there were observed a dimethylamino group singlet (six protons) at 3.00 ppm, a signal for the N_8 proton at 12.02 ppm, and a methyl group singlet attached to C_6 at 2.04 ppm. Evidently, as in attempts to introduce a nitrile group at position 6 in the ring, a high temperature and severe reaction conditions lead to dehalogenation of the bromo derivative.

*For Communication 1, see [1].

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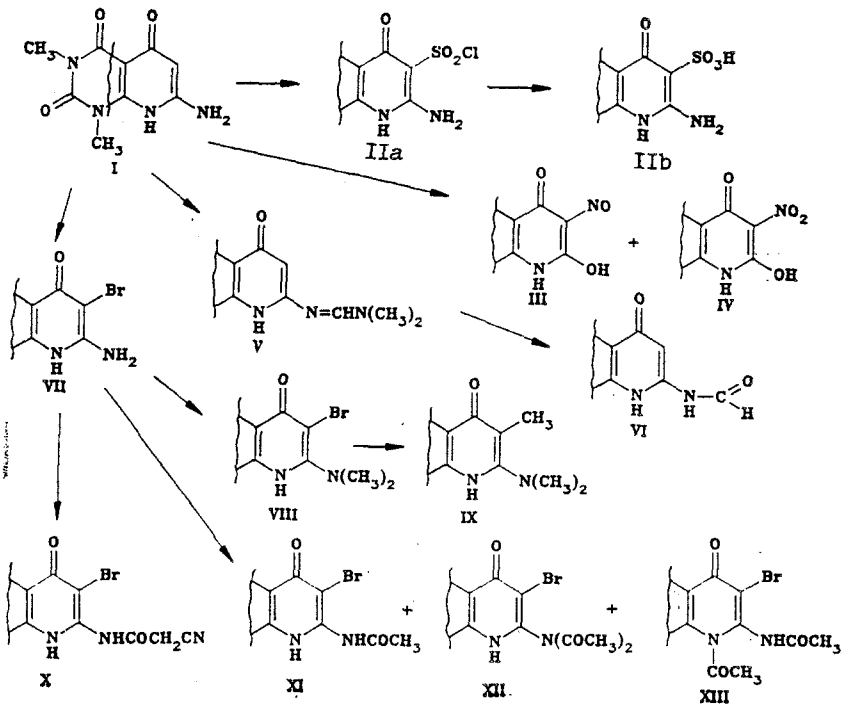

Acylation of VII did not encounter any kind of difficulty and can occur both at the amino group and at the cyclic nitrogen depending on the conditions. Refluxing of VII in acetic anhydride or reaction with cyanoacetic acid in the presence of acetic anhydride yields the mono acyl derivatives X and XI. Their PMR spectra show signals for the NH protons attached to C_7 at 8.15 ppm and for the 8-NH groups at 12.91 and 10.45 ppm, respectively. Prolonged refluxing of VII in acetic anhydride gives mainly the diacetyl product XII (59%) and also XI and XIII which are separated by column chromatography in about 7 and 28% yields, respectively.

TABLE 1. PMR Spectra of II–XIII

Compound	PMR spectrum, δ, ppm*
IIa	3,09 (3H, s, NCH_3); 3,35 (3H, s, NCH_3)
IIb	3,16 (3H, s, NCH_3); 3,36 (3H, s, NCH_3); 7,46 (2H, br. s, NH_2)
III	3,08 (3H, s, NCH_3); 3,44 (3H, s, NCH_3)
IV	3,28 (3H, s, NCH_3); 3,48 (3H, s, NCH_3)
V	3,33 (3H, s, $N_{(1)}$—CH_3); 3,53 (3H, s, $N_{(3)}$—CH_3); 3,07 (3H, s, N—CH_3); 3,10 (3H, s, NCH_3); 6,10 (1H, s, $C_{(6)}$—H); 8,48 (1H, s, N=CH); 11,90 (1H, s, 8-NH)
VII	3,23 (3H, s, NCH_3); 3,39 (3H, s, NCH_3); 7,28 (2H, br. s, NH_2)
VIII	3,35 (3H, s, NCH_3); 3,51 (3H, s, NCH_3); 3,18 (6H, s, $N(CH_3)_2$); 12,68 (1H, s, 8-NH)
IX	3,32 (3H, s, NCH_3); 3,48 (3H, s, NCH_3); 3,00 (6H, s, $N(CH_3)_2$); 2,04 (3H, s, $C_{(6)}$—CH_3); 12,02 (1H, s, 8-NH)
X	3,27 (3H, s, NCH_3); 3,60 (3H, s, NCH_3); 4,04 (2H, s, $COCH_2CN$); 10,45 (1H, s, 8-NH)
XI	3,40 (3H, s, NCH_3); 3,58 (3H, s, NCH_3); 2,56 (3H, s, $COCH_3$); 8,15 (1H, s NH); 12,91 (1H, s, 8-NH)
XII	3,43 (3H, s, NCH_3); 3,57 (3H, s, NCH_3); 2,27 (6H, s, $N(COCH_3)_2$); 13,13 (1H, s 8-NH)
XIII	3,34 (3H, s, NCH_3); 3,60 (3H, s, NCH_3); 2,44 (3H, s, $COCH_3$); 2,58 (3H, s, $COCH_3$); 8,19 (1H, s, $C_{(7)}$—NH)

*PMR spectra of IV, VII in DMF-D_7; IIa, III in CF_3COOD; IIb, X in DMSO-D_6; and V, VIII, IX, XI–XIII in $CDCl_3$.

EXPERIMENTAL

IR spectra were recorded on a Specord IR-75 spectrometer for KBr tablets and PMR spectra on a Tesla BS-497 instrument with HMDS internal standard. Mass spectra were obtained on a Varian MAT-311A with direct introduction of the sample into the ion source. Column chromatography was performed on L 100/250 micron grade silica gel (h = 40 cm, d = 1.5 cm). Thin layer chromatography was performed on Silufol UV-254.

Elemental analytical data for C, H, N, Br, Cl, and S agreed with those calculated.

1,3-Dimethyl-2,4,5-trioxo-6-chlorosulfonyl-7-amino-8H-pyrido[2,3-d]pyrimidine (IIa, $C_9H_9N_4ClO_5$) and 1,3-Dimethyl-2,4,5-trioxo-7-amino-8H-pyrido[2,3-d]pyrimidine-6-sulfonic acid (IIb, $C_9H_{10}N_4O_6S$). A mixture of the pyridopyrimidine I (5 g, 22.5 mmoles) and chlorosulfonic acid (10.4 ml, 18.35 g, 157.5 mmoles) was heated with stirring to 110°C and held at this temperature for 1 h. It was then cooled to room temperature and poured onto ice (100 g). The precipitated solid was filtered off, washed with cold water (100 ml) and the precipitated solid dried to give IIa (3 g, 41.6%) with mp 197–199°C (from dioxane). IR spectrum: 1625, 1650, 1710 (C=O), 3200, 3370, 3480 (NH, NH_2), 1150, 1350 cm^{-1} (SO_2). Mass spectrum, m/z (%): 285 (100), 237 (83), 321 (63, M^+), 57 (48), 136 (49), 221 (47), 68 (46), 82 (40), 36 (38).

The aqueous acid (pH ~1) was left overnight in a refrigerator and the precipitated solid filtered off, washed with acetone (5 ml) and dried to give IIb (2.2 g, 32.3%, based on I) with mp 335–337°C (from water). IR spectrum: 1609, 1631, 1705 (C=O), 3360, 3473 (NH_2), 3227 (OH), 1053, 1155 cm^{-1} (SO_2).

1,3-Dimethyl-2,4,5-trioxo-6-nitroso-7-hydroxy-8H-pyrido[2,3-d]-pyrimidine (III, $C_9H_8N_4O_5$) and 1,3-Dimethyl-2,4,5-trioxo-6-nitro-7-hydroxy-8H-pyrido[2,3-d]pyrimidine (IV, $C_9H_8N_4O_6$). Glacial acetic acid (10 ml) and concentrated sulfuric acid (1 ml) were added to pyridopyrimidine I (1 g, 4.5 mmoles). Sodium nitrite (0.77 g, 0.1 mmole) was added portionwise with stirring over 1 h and the product kept at 18–20°C for 2 h. The product was poured onto ice (20 g), neutralized with aqueous ammonia, and the precipitate filtered off, washed with water (10 ml), and dried to give 0.77 g of solid. The two products present were separated by column chromatography on silica gel. The first fraction was eluted with ethyl acetate and the solvent removed to give IV (0.12 g, 9.9%) with mp 275–276°C (decomp., from DMF). R_f 0.65 (ethyl acetate). IR spectrum: 1667, 1700, 1731 (C=O), 1328, 1535 cm^{-1} (NO_2). Mass spectrum, m/z (%): 268 (100, M^+), 83 (72), 193 (58), 208 (46), 182 (41), 69 (39), 56 (35), 30 (75), 250 (34), 70 (32).

The second fraction was eluted by methanol and the solvent removed to give III (0.5 g, 44.0%) with mp 237–239°C (decomp., from water). R_f 0.2. Yellow crystals. IR spectrum: 1640, 1713, 1731 (C=O), 1500 cm^{-1} (N=O). Mass spectrum, m/z (%): 208 (100), 252 (90, M^+), 83 (70), 222 (34), 238 (26), 30 (26), 110 (26), 82 (24), 70 (22), 68 (21).

1,3-Dimethyl-2,4,5-trioxo-7-dimethylaminomethyleneimino-8H-pyrido-[2,3-d]pyrimidine Hydrochloride (V, $C_{12}H_{10}N_5O_3 \cdot HCl$). Thionyl chloride (11.9 g, 100 mmoles) was added dropwise with stirring over 5 min at 0-5°C to a mixture of I (2 g, 9 mmoles) in dry chloroform (25 ml) and DMF (4.73 g, 10 mmoles). The product was stirred for 1 h at 0-5°C, heated to 60°C and held for a further hour. This was evaporated in vacuo, and anhydrous ethanol (20 ml) added to the residue. Filtration and washing with ether (10 ml) gave V (2.4 g, 83.3%) with mp 273°C (decomp.).

1,3-Dimethyl-2,4,5-trioxo-7-formamido-8H-pyrido[2,3-d]pyrimidine (VI). A suspension of I (1 g, 3.2 mmoles) in water (20 ml) was refluxed for 1 h until total dissolution of V. The solution was cooled and the precipitated solid filtered off, washed with water, and dried to give the product (0.6 g, 74%) with mp 301–304°C, identical to a known sample in physicochemical properties [1].

1,3-Dimethyl-2,4,5-trioxo-6-bromo-7-amino-8H-pyrido[2,3-d]-pyrimidine (VII, $C_9H_9BrN_4O_3$). A solution of bromine (37 g, 232 mmoles) in chloroform (200 ml) was added dropwise with stirring to a suspension of I (50 g, 225 mmoles) in chloroform (500 ml) and stirred at room temperature for 1 h. The precipitate was filtered off and washed with water (100 ml) to give VII (67 g, 99%) with mp 277–278°C (decomp., from DMF). IR spectrum: 1628, 1671, 1693 (C=O), 3213, 3336 cm^{-1} (NH, NH_2).

1,3-Dimethyl-2,4,5-trioxo-6-bromo-7-dimethylamino-8H-pyrido[2,3-d]pyrimidine (VIII, $C_{11}H_{13}BrN_4O_3$). A mixture of VII (1 g, 3.3 mmoles) and methyl polyphosphate (10 g) was heated for 5 h at 140°C, cooled to 20°C, water (10 ml) poured in, and the product neutralized with ammonia solution (5%). The precipitate was filtered off (0.5 g) and refluxed with hexane (3 × 20 ml). Evaporation of solvent gave VIII (0.1 g, 9.2%) with mp 161–163°C (decomp., from hexane). IR spectrum: 1620, 1667, 1700 cm^{-1} (C=O).

1,3,6-Trimethyl-2,4,6-trioxo-7-dimethylamino-8H-pyrido[2,3-d]-pyrimidine (IX, $C_{12}H_{16}N_4O_3$). A mixture of VII (5 g, 16.6 mmoles) and methyl polyphosphate (50 g) was heated at 200°C for 1 h, cooled to 20°C, diluted with water (15 ml), and neutralized with ammonia solution. The precipitate was filtered off, washed with water (5 ml), and dried to give solid (2 g). This was refluxed with hexane (3 × 150 ml) and the solvent evaporated to give IX (0.6 g, 13.7%)

with mp 167°C (from hexane). Mass spectrum, m/z (%): 264 (100, M^+), 249 (97), 235 (91), 44 (64), 221 (40), 82 (40), 42 (35), 233 (22), 164 (21), 80 (20).

1,3-Dimethyl-2,4,5-trioxo-6-bromo-7-cyanacetamido-8H-pyrido[2,3-d]pyrimidine (X, $C_{12}H_{10}BrN_5O_5$). Cyanoacetic acid (4.7 g, 55 mmoles) was added with stirring at 80°C over 15 min to a solution of VII (3.3 g, 11 mmoles) in acetic anhydride (5.6 g, 55 mmoles heated to 60°C) and then cooled to 20°C. Dilution with water (20 ml), filtration, and washing the precipitate with water (10 ml) and acetone (5 ml) gave X (3 g, 74%) with mp 252–254°C (from glacial AcOH). IR spectrum: 1713 (C=O), 2271 (CN), 3327 cm^{-1} (NH).

1,3-Dimethyl-2,4,5-trioxo-6-bromo-7-acetamido-8H-pyrido[2,3-d]pyrimidine (XI, $C_{11}H_{11}BrN_4O_4$). Substance VII (1.1 g, 3.7 mmoles) was refluxed in acetic anhydride (10 ml) to complete solution (15 min), cooled to 20°C, and the precipitate filtered, washed with water (5 ml) and acetone (3 ml), and dried to give white XI (1 g, 79.4%) with mp 224.5–225.5°C (from $CHCl_3$). IR spectrum: 1710 (C=O), 3280 cm^{-1} (NH).

Products of Reaction of 1,3-Dimethyl-2,4,5-trioxo-6-bromo-7-amino-8H-pyrido[2,3-d]pyrimidine VII with Acetic Anhydride. A mixture of VII (0.8 g, 2.6 mmoles) and acetic anhydride (16 g, 156.8 mmoles) was refluxed for 1 h, excess anhydride distilled off in vacuo, and the residue diluted with water (20 ml). The precipitate was filtered to give 1 g of solid which chromatography showed to contain three products (Silufol UV-254 plates, benzene–AcOH 15:1). They were separated on a silica gel column using benzene eluent. The first fraction gave **1,3-dimethyl-2,4,5-trioxo-6-bromo-7-diacetamido-8H-pyrido[2,3-d]pyrimidine (XII, $C_{13}H_{13}BrN_4O_5$)** in a yield of 0.6 g (58.8%) with mp 191–193°C (from acetone). R_f 0.3. IR spectrum: 1720, 1740 cm^{-1} (C=O).

After removal of solvent the second fraction gave 0.06 g (6.6%) of **1,3-dimethyl-2,4,5-trioxo-6-bromo-7-acetamido-8H-pyrido[2,3-d]pyrimidine (XI)** with mp 224–225°C and R_f 0.2. The third fraction gave 0.28 g (27.5%) of **1,3-dimethyl-2,4,5-trioxo-6-bromo-7-acetamido-8-acetylpyrido[2,3-d]pyrimidine (XIII, $C_{13}H_{13}BrN_4O_5$)** with mp 217–219°C (from dioxane) and R_f 0.15. IR spectrum: 1720, 1787 (C=O), 3280 cm^{-1} (NH).

LITERATURE CITED

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