PYRIDO[2,3-d]PYRIMIDINES.

1. ACYLATION OF 2,4,5-TRIOXO-7-AMINO-8H-PYRIDO [2,3-d]PYRIMIDINES

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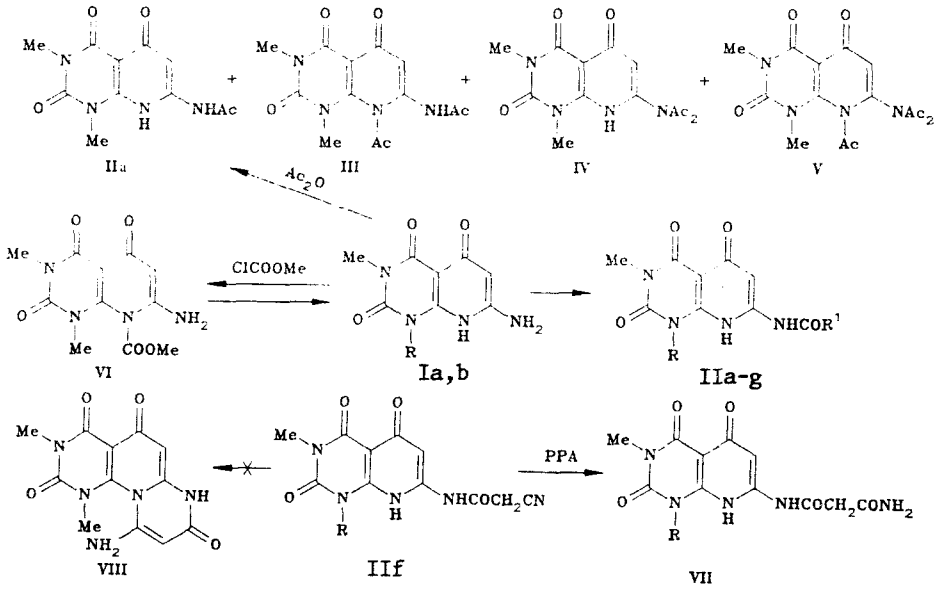
Reaction of 2,4,5-trioxo-7-aminopyrido[2,3-d]pyrimidines with acylating agents takes place both at the amino group and at the cyclic nitrogen atom. Reaction of these compounds with formic acid, chloroacetyl chloride in pyridine, cyanoacetic acid in the presence of acetic anhydride, and oxalyl chloride leads to monoacylation at the amino group but with methyl chloroformate it is the product of acylation at the cyclic nitrogen. Refluxing in acetic anhydride gave mono-, di-, and triacetyl derivatives. The structures of these compounds were proved using spectral data.

We have previously developed a method for preparing 2,4,5-trioxo-7-amino-8H-pyrido[2,3-d]pyrimidines (Ia, b) [1]. In the present work we have studied the reactions of Ia, b with acylating agents.

By analogy with [2, 3] it would be expected that the action of acylating agents with Ia, b would occur both at the amino group and at the cyclic nitrogen atom. In fact, we have found that Ia reacts with acetic anhydride to give a mixture of four products. Column chromatography on silica gel gave the monoacetamido (IIa, 14%) and diacetyl derivatives III (62%) and IV (3%), together with the product of complete acetylation V (3%).



Ia R=Me, b R=Et; IIa R=R¹=Me, b R=Me, R¹=H, c R=Et, R¹=H, d R=Me, R¹=CH_2Cl, e R=Et, R¹=CH_2Cl, f R=Me, R¹=CH_2CN, g R=Me, R¹=COOH

The 7-monoacetamido structure for IIa was proposed on the basis of the amide NH and CO absorptions at 3370 and 1720 cm^{-1} in the IR spectra and by the presence in the PMR spectra of an acetyl proton singlet at 2.19 ppm, a singlet for C_6 at 7.40 ppm, and for the exchangeable NH protons at 7.40 and 10.68 ppm.

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TABLE 1. PMR Spectra of II-VII*

Compound	Chemical shift, δ, ppm (Spin-spin coupling, J, Hz)
IIa	2,19 (3H, s, $COCH_3$); 3,27 (3H, s, $N—CH_3$); 3,41 (3H, s, $N—CH_3$); 7,40 (1H, s, CH); 7,70 (1H, br.s, $C_{(7)}—NH$); 10,68 (1H, s, 8-NH)
IIb	3,14 (3H, s, $N—CH_3$); 3,42 (3H, s, $N—CH_3$); 6,40 (1H, s, CH); 8,30 (1H, s, COH)
IIc	1,19 (3H, t, CH_3CH_2, $J=5,0$); 3,25 (3H, s, $N—CH_3$); 4,16 (2H, q, CH_2CH_3, $J=5,0$); 6,62 (1H, s, CH); 9,12 (1H, br.s, $C_{(7)}—NH$)
IId	3,17 (3H, s, $N—CH_3$); 3,35 (3H, s, $N—CH_3$); 4,32 (2H, s, CH_2Cl); 7,15 (1H, s, CH); 10,80 (1H, s, $C_{(7)}—NH$); 11,98 (1H, s, 8-NH)
IIe	1,50 (3H, t, CH_3CH_2, $J=5,0$); 3,59 (3H, s, $N—CH_3$); 4,44 (2H, s, CH_2Cl); 4,59 (2H, q, CH_2CH_3, $J=5,0$); 6,84 (1H, s, CH); 10,10 (1H, s, $C_{(7)}—NH$)
IIf	3,26 (3H, s, $N—CH_3$); 3,40 (3H, s, $N—CH_3$); 4,11 (2H, s, CH_2CN); 7,32 (1H, s, CH); 11,10 (1H, s, 8-NH)
IIg	3,26 (3H, s, $N—CH_3$); 3,43 (3H, s, $N—CH_3$); 7,22 (1H, s, CH); 7,68 (1H, br.s, $C_{(7)}—NH$); 10,50 (1H, s, 8-NH); 12,28 (1H, s, COOH)
III	2,20 (3H, s, $NHCOCH_3$); 3,32 (3H, s, $N—CH_3$); 3,53 (3H, s, $N—CH_3$); 2,37 (3H, s, $N—COCH_3$); 7,74 (1H, s, OH); 8,00 (1H, br.s, NH)
IV	2,25 (6H, s, $N(COCH_3)_2$); 3,34 (3H, s, $N—CH_3$); 3,58 (3H, s, $N—CH_3$); 7,40 (1H, s, CH); 13,10 (1H, s, 8-NH)
V	2,29 (6H, s, $N(COCH_3)_2$); 2,37 (3H, s, $N—COCH_3$); 3,35 (3H, s, $N—CH_3$); 3,60 (3H, s, $N—CH_3$); 6,78 (1H, s, CH)
VI	3,14 (3H, s, $COOH_3$); 3,34 (3H, s, $N—CH_3$); 3,77 (3H, s, $N—CH_3$); 6,03 (1H, s, CH); 7,37 (2H, s, NH_2)
VII	3,23 (3H, s, $N—CH_3$); 3,40 (3H, s, $N—CH_3$); 3,50 (2H, s, $NHCH_2$); 7,24 (2H, s, NH_2); 7,35 (1H, s, CH); 7,74 (1H, br.s, $C_{(7)}—NH$); 10,89 (1H, s, 8-NH)

*PMR spectra of IIa, c, f, g, VII in DMF-D_7, III-V in $CDCl_3$, IIb, e in CF_3COOH, IId, VI in DMSO-D_6.

The PMR spectrum of III shows signals for the two acetyl groups, the C_6 proton, and the exchangeable NH proton at C_7 (Table 1).

In the PMR spectrum of IV, two acetyl groups appear as a singlet with double intensity. The nonequivalence of the two acetyl groups in III and their equivalence in IV allows assignment of III and IV to 7-acetamido-8-acetyl- and 7-N,N-diacetamidopyridopyridines, respectively.

In the IR spectra of III, IV two bands are observed for the absorptions of amide CO and one for the NH groups.

The structure of the fully acetylated V was confirmed by the presence in the IR spectrum of three amide CO groups at 1714, 1730, and 1785 cm^{-1} and by the PMR spectral data (Table 1).

The acetylation reaction under milder conditions (heating Ia with acetic anhydride for 0.5 h at 130°C) leads to formation of the monoacetyl product IIa.

It has been found that treatment of Ia, b with 99% formic acid, chloroacetyl chloride in the presence of pyridine, cyanoacetic acid in the presence of acetic anhydride, and oxalyl chloride gives, in high yield, the 7-acetamidopyridopyrimidines IIb-g whose structures were shown similarly to IIa (Tables 1 and 2). 7-Formamidopyrido[2,3-d]pyrimidine IIb was also obtained by thermal decarboxylation of acid IIg at 230°C for 1 h. In compounds IIb, c the formyl proton signals were seen in the range 8.30-9.12 ppm in the PMR spectra.

Refluxing Ia in methyl chloroformate gives the single product 7-amino-8-carbomethoxypyridopyrimidine VI. The structure was proved by the presence of a primary amino group at 3500 and 3367 cm^{-1} in the IR spectrum and the broad two-proton NH_2 signal and the absence of the 8-NH in the region 10-14 ppm in the PMR spectrum. Compound VI is thermally deacetylated at 240°C to the starting Ia.

Attempts to cyclize IIe in PPA to the tricyclic system VIII were unsuccessful, the product being the mono-substituted malonic diamide VII, as shown by IR, PMR, and mass spectrometry.

In summary, we have developed a preparative method for 7-monoacylamidopyrido[2,3-d]pyrimidines as intermediates in the synthesis of bioactive compounds. It has also been shown that reaction of 2,4,5-trioxo-7-aminopyrido[2,3-d]pyrimidines with acylating agents occurs both at the amino group and at the cyclic nitrogen atom.

TABLE 2. Synthesis and Constants for II-VI

Compound	Empirical formula	Reagents	t, h*	mp, °C	IR spectrum, ν, cm^{-1}	Yield, %
IIa	$C_{11}H_{12}N_4O_4$	Ac_2O	0,5	300	1720 (CO); 3370, 3150 (NH)	98
IIb	$C_{10}H_{10}N_4O_4$	HCOOH	2	310...311	1713 (CO); 3386 (NH)	89
IIc	$C_{11}H_{12}N_4O_4$	HCOOH	1	265	1700 (CO); 3150 (NH)	99
IId	$C_{11}H_{11}ClN_4O_4$	$ClCH_2COCl$, pyridine	1	209	1720 (CO); 3375, 3150 (NH)	90
IIe	$C_{12}H_{13}ClN_4O_4$	$ClCH_2COCl$, pyridine	1	203	1715 (CO); 3370, 3150 (NH)	99
IIf	$C_{12}H_{11}N_5O_5$	$CNCH_2COOH$, Ac_2O	1	246...248	1720 (CO); 3335 (NH); 2265 (CN)	92
IIg	$C_{11}H_{10}N_4O_6$	ClCOCOCl	2	244 (decomp.)	1767, 1715 (CO); 3327 (NH); 3200 (OH)	62
III	$C_{13}H_{14}N_4O_5$	Ac_2O	10	260...262	1775, 1720 (CO); 3380 (NH)	62
IV	$C_{13}H_{14}N_4O_5$	Ac_2O	10	162...163	1733, 1715 (CO)	3
V	$C_{15}H_{16}N_4O_6$	Ac_2O	10	151...153	1786, 1730, 1714 (CO)	3
VI	$C_{11}H_{12}N_4O_5$	$ClCOOCH_3$	2	263...265 (decomp.)	1760, 1727 (CO); 3500, 3367, 3250 (NH_2)	74

*t) Acylation time.

EXPERIMENTAL

IR spectra were recorded on a Specord IR-75 spectrophotometer for KBr tablets and Vaseline mull. Mass spectra were recorded on a Varian MAT-311A with direct introduction of the sample into the ion source. PMR spectra were recorded on a Tesla BS-497 (100 MHz) instrument with HMDS internal standard. Monitoring of the reaction was carried out by TLC on silufol UV-254 plates.

Data for the synthesized compounds are given in Tables 1 and 2. Elemental analytical data for C, H, Cl, and N agreed with that calculated.

1,3-Dimethyl-2,4,5-trioxo-7-amino-8H-pyrido[2,3-d]pyrimidine (Ia). A sample of VI (0.5 g, 1.8 mmoles) was placed in a round-bottomed, single-necked flask with an air condenser and immersed for 1 h in an oil bath which had previously been heated to 270°C. A vigorous effervescence occurred. The flask was cooled to 20°C, water (10 ml) added, and the solid filtered off, washed with water, alcohol, and dried to give product (0.35 g, 88%), identical to that obtained earlier [1].

Products of Reaction of 1,3-Dimethyl-2,4,5-trioxo-7-amino-8H-pyrido[2,3-d]pyrimidine (Ia) with Acetic Anhydride. A mixture of Ia (2 g, 9 mmoles) and acetic anhydride (40 ml) was refluxed with a condenser for 10 h, the excess anhydride distilled off, and the residue treated with acetone (5 ml). The solid was filtered off to give 2.4 g, which was chromatographed (benzene–AcOH 3:1) as a mixture of four products. They were separated by chromatography on silica gel (benzene eluent) to give the **1,3-dimethyl-2,4,5-trioxo-derivatives of -7-N,N-diacetamido-8H-pyrido[2,3-d]pyrimidine (IV)** (R_f 0.65), **-7-N,N-di-acetamido-8-acetylpyrido[2,3-d]pyrimidine (V)** (R_f 0.85), **-7-acetamido-8H-pyrido[2,3-d]pyrimidine (IIa)** (R_f 0.3), and **-7-acetamido-8-acetylpyrido[2,3-d]pyrimidine (III)** (R_f 0.2).

1-Alkyl-3-methyl-2,4,5-trioxo-7-acylamido-8H-pyrido[2,3-d]pyrimidine (IIa-g). A suspension of Ia or Ib (10 mmoles), acylating agent (10-100 mmoles), and pyridine (0-10 mmoles) was heated to reflux with stirring, held for 0.5-2 h, cooled to 0°C, and the solid produced washed with water and dried. Compounds IIa, b, d, f were recrystallized from acetic acid, IIc from ethanol, IIe from ethyl acetate, and IIg from acetone.

1,3-Dimethyl-2,4,5-trioxo-7-formamido-8H-pyrido[2,3-d]pyrimidine (IIb) was obtained by decarboxylation of IIg (similarly to Ia) in quantitative yield. Physicochemical data were identical to the product of formylation.

1,3-Dimethyl-2,4,5-trioxo-7-amino-8-carbomethoxypyrido[2,3-d]pyrimidine (VI). A suspension of Ia (3 g, 13.5 mmoles) in methyl chloroformate (30 g, 317 mmoles) was refluxed with vigorous stirring for 2 h using a reflux condenser. Cooling to 20°C, filtration of the solid and washing with water and acetone gave the product with $M^{+\cdot}$ 280 (mass spectrum).

N-(1,3-Dimethyl-2,4,5-trioxo-8H-pyrido[2,3-d]pyrimid-7-yl)malondiamide (VII, $C_{12}H_{13}N_5O_5$). A suspension of IIf (5 g, 17.3 mmoles) in polyphosphoric acid (50 ml) was heated to 100°C, held for 1 h, cooled to 50°C, and poured into water (50 ml). Neutralization with aqueous ammonia, filtration of the solid produced, washing with water, alcohol, and drying gave 5 g (94%) with mp 254-255°C (AcOH). IR spectrum: 1650, 1693, 1720 (C=O), 3460, 3288, 3200 cm^{-1} (NH, NH_2). Mass spectrum, m/z (%): 249 (100), 222 (59), 307 (52, $M^{+\cdot}$), 43 (37), 68 (35), 44 (34), 110 (34), 59 (29), 193 (25), 42 (24).

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