PYRIDO[2,3-d]DIPYRIMIDINES
8.* SYNTHESIS OF PYRROLO(2′,3′:4,5)PYRIDO[2,3-d]PYRIMIDINES

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The reaction of 1,3-dimethyl-5-chloro-6-nitropyrido[2,3-d]pyrimidine-2,4-dione with CH-acids yielded 5-substituted pyridol[2,3-d]pyrimidines which were used in the synthesis of pyrrolo(2′,3′:4,5)pyrido[2,3-d]pyrimidines.

It is known that derivatives of pyrido[2,3-d]pyrimidine have a wide spectrum of biological activity [2, 3]. In a continuation of our studies [4-8] we have carried out the synthesis of new representatives of this heterocyclic system with the aim of examining their chemical and biological properties.

A preparative method for obtaining 1,3-dimethyl-5-chloro-6-nitropyridol[2,3-d]pyrimidine-2,4-dione (I) has been proposed [8]. In the reaction of this compound with CH-acids (1,3-dicarbonyl compounds and nitromethane being used for this purpose) in DMF in the presence of NaH at 25°C, 5-substituted pyridopyrimidines (IIa-e) were obtained in high yield. The presence of signals for hydroxyl group protons in the 12.92-16.96 ppm region of the PMR spectrum of compounds IIa-c (Table 1) shows that in $CDCl_3$ solution these compounds exist in their enol forms stabilized by intramolecular hydrogen bonds.

I → IIa-e

IIa-c R = C(R¹)(R²)(C=O)(C=O)H; a R¹ = Me, R² = OEt; b R¹ = R² = Me; c R¹ = R² = Ph

IId R = $CH(COOEt)_2$; IIe R = CH_2NO_2

In studies of the reduction of pyridopyrimidines IIa, b and IId it was observed that under catalytic hydrogenation, not only was the nitro group reduced but intramolecular cyclization occurred forming the previously unreported pyrrolo-(2′,3′:4,5)pyrido[2,3-d]pyrimidines (IIIa, b and IV), respectively. In the PMR spectra of compounds IIIa, b and IV (Table 2) there are signals of substituents at $C_{(1)}$ and $C_{(2)}$ of the pyrrolopyridopyrimidine system and downfield (11-12 ppm) signals are recorded for the proton on the nitrogen of the pyrrole ring. In the case of derivative IV a singlet signal from the methine proton of $C_{(1)}$ was also observed (see top of following page).

With the object of preparing pyrrolo(2′,3′:4,5)pyrido[2,3-d]pyrimidine having, in contrast to compounds IIIa, b and IV, an unsubstituted pyrrole ring, a derivative of the malonoester IId was heated at bp for 4 h in 18% HCl. Under these conditions, in addition to saponification of the ethoxycarbonyl group, decarboxylation occurs resulting in the formation of 1,3,5-trimethyl-6-nitropyridol[2,3-d]pyrimidine-2,4-dione (V). Reaction of the latter with the diethylacetal of DMF in DMF at 70°C gave the enamine (VI) catalytic hydrogenation of which led to the formation of the desired pyrrolopyridopyrimidine (VII). In

*For Communication 7, see [1].

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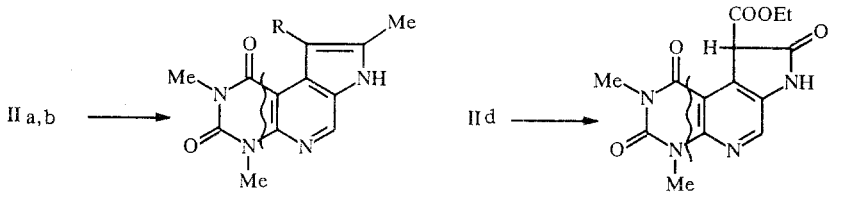
TABLE 1. Physicochemical Characteristics of 5-Substituted-6-nitropyrido[2,3-d]pyrimidines IIa-e, V, and VI

Compound	mp, °C	PMR spectrum, δ, ppm (J Hz)**				Yield, %
		$C_{(7)}H$, s	OH, s	$N_{(1)}$—CH_3, s $N_{(3)}$—CH_3, s	other protons	
IIa	171...173	9,11	12,92	3,40; 3,77	1.05 (3H, t, J = 7, CH_3); 1.65 (3H, s, CH_3); 4.12 (2H, q, J = 7, CH_2)	92,5
IIb	204...206	9,11	16,15	3,41; 3,78	1.75 (6H, s, $2CH_3$)	85,0
IIc	176...178	8,75	16,96	3,21; 3,55	6.9-7.5 (10H, arom., H)	88,5
IId	109...110	9,25		3,41; 3,75	1.22 (6H, t, CH_3CH_3); 4.2 (3H, q, CH_2CH_2); 6.91 (1H, s, $C_{(5)}$—CH)	91,2
IIe	162 decomp	9,40		3,27; 3,62	6.41 (2H, s, CH_2) 2.85 (3H, s, CH_3)	63,6
V	177...178	9,11		3,29; 3,58	3.05 (6H, s, $N(CH_3)_2$);	91,9
VI	199...201	8,45		3,40; 3,62	6.92 (2H, s, CH, CH)	87,7

*Compound IIc crystallized from ethanol, IIa, b from aqueous isopropanol, IId from methanol, IIe and V from acetic acid, VI from ethylacetate.

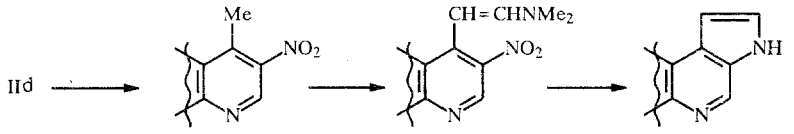
**PMR spectra of compounds IIa-e and VI run in $CDCl_3$, compound V in DMSO-D_6.



III a, b IV

IIIa R = COOEt, b R = COMe

the PMR spectrum of the tricyclic derivative VII (Table 2) there were signals from the protons of the pyrrole ring in the form of doublets with coupling constants = 4 Hz and a signal from the NH proton in the form of a broad singlet. The mass spectrum of VII showed a molecular ion peak $M^{+\cdot}$ 230 of maximum intensity which corresponds to the calculated molecular weight.



V VI VII

When several of these compounds were examined at the All-Union Science Center for Biologically Active Substances (Kupavna station) it was discovered that the pyridopyrimidine IIb possessed mild activity towards the vaccinia virus. The derivative IIa displayed activity bordering on toxic action on the cells in relation to the vaccinia virus, the ECHO-6 Venezuelan equine encephalomyelitis virus, and the classical birdpox virus. Compound V showed activity against the herpes virus.

EXPERIMENTAL

PMR spectra were run on a Tesla BS-497 instrument at 100 MHz with HMDS as internal standard. A Varian MAT-311 A was used to obtain mass spectra, with direct injection of the sample into the ion source. Progress of the reactions was

TABLE 2. Physicochemical Characteristics of Pyrrolo(2′,3′:4,5)pyrido[2,3-d]pyrimidines IIIa, b, IV, and VII

Compound	mp, °C	PMR spectra, δ, ppm (J Hz)**				Yield, %
		$C_{(4)}$—H, s	N(3)—H	$N_{(6)}$—CH_3, s $N_{(8)}$—CH_3, s	other protons	
IIIa	250...251	8,65	12,36	3,35; 3,60	2.55 (3H, s, CH_3) 1.24 (3H, t, J = 7, CH_3); 4.32 (2H, J = 7, CH_2)	73,7
IIIb	299...302	8,64	12,25	3,28; 3,54	2.23 (3H, s, CH_3); 2.43 (3H, s, CH_3)	83,3
IV	> 300	8,30	11,04	3,21; 3,49	1.10 (3H, t, J = 7, CH_3); 4.08 (2H, q, J = 7, CH_2); 4.94 (1H, s, CH)	86,8
VII	> 300	8,84	12,00	3,27; 3,63	7.18 (1H, d, J = 4, $C_{(1)}$—H); 7.87 1(H, d, J = 4, $C_{(2)}$—H)	92,7

*Compounds IV, VII crystallized from ethanol, IIIa from aqueous ethanol, IIIb from isopropanol.

**PMR spectra of compounds IIIa, IIIb run in DMSO-D_6, compounds IV, VII in DMF-D_7.

monitored and the purity of the compounds assessed by means of TLC on Silufol UV-254 plates. The characteristics of the compounds prepared are set out in Tables 1 and 2.

Results of elemental analysis were in agreement with those calculated.

General Method for the Preparation of Pyridol[2,3-d]pyrimidines (IIa-e). The CH acid was added to a suspension of NaH in DMF, keeping the temperature at 25-30°C. The mixture was stirred at this temperature for 15 min and then compound I added and the mixture kept at 25°C for 0.5-1.0 h, until the TLC spot of the starting material with R_f 0.66 had disappeared (10:1 benzene–acetone). The reaction mixture was diluted with 20-100 ml water, acidified with CH_3COOH to pH 5-6 and the precipitated product II filtered off and recrystallized.

(1,3-Dimethyl-2,4-dioxo-6-nitro-1,2,3,4- tetrahydropyridol[2,3-d]pyrimidinyl-5) Acetoacetic Ester (IIa, $C_{15}H_{16}N_4O_7$) was prepared from 2 g (7.39 mmoles) compound I, 2.8 ml (22.16 mmoles) acetoacetic ester, and 0.53 g (22.08 mmoles) NaH in 12 ml DMF. Yield 2.5 g. Mass spectrum, m/z (I/I_{max}, %): $M^{+\cdot}$ 364 (0.7).

(1,3-Dimethyl-2,4-dioxo-6-nitro-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine-5)acetylacetone (IIb, $C_{14}H_{14}N_4O_6$) was prepared from 2 g (7.39 mmoles) compound I, 2.3 ml (22.28 mmoles) acetylacetone, and 0.53 g (22.08 mmoles) NaH in 12 ml DMF. Yield 2.1 g. Mass spectrum m/z (I/I_{max} %): $M^{+\cdot}$ 334 (4).

(1,3-Dimethyl-2,4-dioxo-6-nitro-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine-5)dibenzoylmethane (IIc, $C_{24}H_{18}N_4O_6$) was prepared from 1 g (3.695 mmoles) compound I, 2.07 g (9.23 mmoles) dibenzoylmethane, and 0.22 g (9.14 mmoles) NaH in 5 ml DMF. The oily product which precipitated on dilution with water and acidification crystallized on treatment with 50 ml hexane. Yield 1.42 g. Mass spectrum m/z (I/I_{max} %): $M^{+\cdot}$ 458 (0.8).

(1,3-Dimethyl-2,4-dioxo-6-nitro-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine-5)malonic ester (IId, $C_{16}H_{18}N_4O_8$) was prepared from 5.0 g (18.48 mmoles) compound I, 8.4 ml (55.59 mmoles) malonic ester, and 1.33 g (55.42 mmoles) NaH in 20 ml DMF. Yield 6.65 g.

1,3-Dimethyl-5-nitromethylene-6-nitro-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine-2,4-dione (IIe, $C_{10}H_9N_5O_6$) was prepared from 0.5 g (1.85 mmoles) compound I, 0.3 ml (5.6 mmoles) nitromethane, and 0.132 g (5.5 mmoles) NaH in 8 ml DMF. Yield 0.35 g. Mass spectrum m/z (I/I_{max} %): $M^{+\cdot}$ 295 (24).

General Method for the Preparation of Pyrrolo(2′,3′:4,5)pyrido[2,3-d]pyrimidines (IIIa, b and IV). The nitrocompounds IIa, b and IId were hydrogenated in alcohol over 10% PdO/C until no more hydrogen was absorbed. The catalyst was filtered off and washed with alcohol. The combined filtrates were evaporated under vacuum and the residue triturated with ether for crystallization.

2,6,8-Trimethyl-1-ethoxycarbonyl-6,7,8,9-tetrahydro-3H-pyrrolo(2′,3′:4,5)pyridol[2,3-d]pyrimidine (IIIa, $C_{15}H_{16}N_4O_4$) was prepared from 2.5 g (6.86 mmoles) compound IIa in 100 ml CH_3OH in the presence of 1.8 g 10% PdO/C.

Yield 1.6 g. Mass spectrum m/z (I/I_{max} %): $M^{+\cdot}$ 316 (74), $(M-OC_2H_5)$ 271 (100), $(M-C_2H_5OH)$ 270 (54), $(M-COOC_2H_5)$ 244 (32).

2,6,8-Trimethyl-1-acetyl-6,7,8,9-tetrahydro-3H-pyrrolo(2′,3′:4,5)pyrido[2,3-d]pyrimidine (IIIb, $C_{14}H_{14}N_4O_3$) was prepared from 2.1 g (6.28 mmoles) compound IIb in 100 ml CH_3OH in the presence of 1.2 g 10% PdO/C. Yield 1.5 g. Mass spectrum m/z (I/I_{max} %): $M^{+\cdot}$ 286 (30), $(M-CH_3)$ 271 (100), $(M-CO-CH_2)$ 244 (77).

6,8-Dimethyl-1-ethoxycarbonyl-1,2,6,7,8,9-hexahydro-3H-pyrrolo(2′,3′:4,5)pyrido[2,3-d]pyrimidine (IV, $C_{14}H_{14}N_4O_5$) was prepared from 3.0 g (7.61 mmoles) compound IId in 100 ml C_2H_5OH in the presence of 1.5 g 10% PdO/C. Yield 2.1 g. Mass spectrum m/z (I/I_{max} %): $M^{+\cdot}$ not recorded, $(M-C_2H_5OH)$ 272 (100).

1,3,5-Trimethyl-6-nitro-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine-2,4-dione (V, $C_{10}H_{10}N_4O_4$). Compound IId (3 g, 7.61 mmoles) was heated at bp in 50 ml 18% HCl for 4 h until the TLC spot of the starting material (R_f 0.21, chloroform) was no longer detected. Water (50 ml) was added to the reaction mixture at 25°C and the precipitated product V filtered off. Yield 1.75 g. Mass spectrum m/z (I/I_{max} %): $M^{+\cdot}$ 250 (37).

1,3-Dimethyl-5-(dimethylaminoethenyl)-6-nitro-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine-2,4-dione (VI, $C_{13}H_{15}N_5O_4$). A mixture of 2.2 g (4.795 mmoles) compound V, 3 ml DMF, and 1.5 ml (6.42 mmoles) 70% DMF diethylacetal was kept at 70-75°C for 1.5 h until the TLC spot of the starting material (R_f 0.6, chloroform) had disappeared. The reaction mixture was cooled to 25°C, diluted with 10 ml ether, and the precipitated product VI filtered off. Yield 1.28 g. Mass spectrum m/z (I/I_{max} %): $M^{+\cdot}$ 305 (37).

6,8-Dimethyl-6,7,8,9-tetrahydro- 3H-pyrrolo(2′,3′:4,5)pyrido[2,3-d]pyrimidine-7,9-dione (VII, $C_{11}H_{10}N_4O_2$). Compound VI (2.0 g, 6.55 mmoles) was hydrogenated in 150 ml C_2H_5OH over 1 g 5% PdO/C until hydrogen was no longer absorbed. The reaction mixture was further diluted with 150 ml chloroform, heated to boiling, and the catalyst filtered off. The filtrate was evaporated, the residue triturated with water (50 ml), and the product VI filtered off. Yield 1.4 g. Mass spectrum m/z (I/I_{max} %): $M^{+\cdot}$ 230 (100).

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