SYNTHESIS, PROPERTIES AND BIOLOGICAL ACTIVITY OF 1-ARYL-7-METHYL(5,7-DIMETHYL)-4-OXO-1,4-DIHYDROPYRIDO[2,3-d] PYRIMIDINES

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According to data outlined in the patents [7-9] 4-oxo-1,4-dihydropyrido[2,3-d]pyrimidines display analgesic and anti-inflammatory properties.

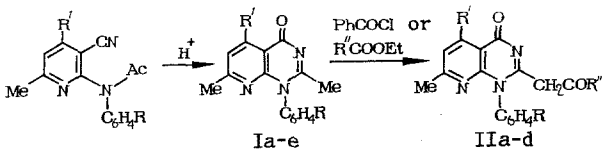
In order to find new biologically-active substances in this series of compounds and to extend the scope of the synthesis method that we put forward in a previous work [6], we have obtained the 1-aryl-2,7-dimethyl-4-oxo-1,4-dihydropyrido[2,3-d]pyrimidines Ia-d (Table 1) by cyclizing 2-(N-acetyl-N-arylamino)-6-methyl-nicotinonitriles. This was achieved by passing dry HCl through a solution of these compounds in benzene for 2 h. Higher yields were obtained than for the reaction in ethanol [6].

Our efforts to cyclize 2-(N-acetyl-4-bromanilino)-4,6-dimethylnicotinonitrile by treating it with HCl in both benzene and ethanol did not meet with success. This was probably due to steric hindrance caused by the methyl group at the C(4) atom shielding the CN group. The compound was successfully cyclized to 1-(4-bromphenyl)-2,5,7-trimethyl-4-oxo-1,4-dihydropyrido[2,3-d]pyrimidine (Ie) by reacting it with the stronger perchloric acid in a mixture of AcOH and Ac_2O.

Compounds Ia-e are colorless, crystalline substances, whose IR spectra show a carbonyl band at 1645-1650 cm^{-1}, but, unlike the spectra of the starting compounds, exhibit no nitrile group band at 2230 cm^{-1}. PMR spectra reveal methyl group protons at 1.93-2.40 ppm, aromatic proton multiplets at 7.10-7.33 ppm and pyridine ring protons in the from of doublets at 8.27-8.40 ppm (Ia-d) or as a singlet at 6.70 ppm (Ie).

Reference has been made in a previous work [6] to the fact that in type I compounds the hydrogen atoms at C_2 are labile and on treatment with Ac_2O they are replaced by an acetyl group. In the present work the example of compounds Ia, Ib, and Ie illustrates that they react with benzoyl chloride in pyridine, yielding the 4-oxo-2-phenacyl-1,4-dihydropyrido[2,3-d]pyrimidine derivatives IIa-c (see Table 1). Compound IIa is also formed by condensing Ia with ethyl benzoate in the presence of MeONa.

When compound Ia takes part in an ester condensation reaction with diethyl oxalate in the presence of MeONa in MeOH, it is converted into 7-methyl-2-methoxallylmethyl-4-oxo-1-phenyl-1,4-dihydropyrido-[2,3-d]pyrimidine (IId), ie. ester interchange is observed alongside the basic reaction.



Ia-e IIa-d

I: R = H(a), 2-CH_3(b), 2-Cl(c), 2-Br(d), 4-Br(e); R′ = H(Ia-d), CH_3(e);
II: R = H(a,d), 2-CH_3(b), 4-Br(c); R′ = H(a,b,d), CH_3(c); R″ = C_6H_5(a-c), $COOCH_3$(d)

The data cited shows that the methyl group at the C(2) atom of type I compounds possesses considerable CH-acidity and is more reactive than the analogous group at C(7).

The structure of compounds IIa-d is corroborated by IR and PMR spectroscopy (see Experimental).

In view of the fact that the PMR spectra of compounds IIa-d reveal ethylene proton signals at 5.00-5.27 ppm and a chelate ring proton at 13.90-14.40 ppm, it may be supposed

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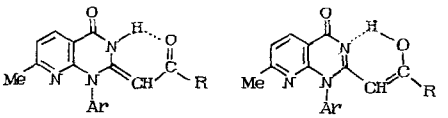
TABLE 1. Characteristics of the Synthesized Compounds

Compound	Yield, %	mp, °C	R_f	Empirical formula
Ib	82	161—3	0,57	$C_{16}H_{15}N_3O$
Ic	80	190—2	0,43	$C_{15}H_{12}ClN_3O$
Id	90	179—81	0,41	$C_{15}H_{12}BrN_3O$
Ie	93	206—8	0,91	$C_{16}H_{14}BrN_3O$
IIa	38(36)	238—40	0,85	$C_{22}H_{17}N_3O_2$
IIb	68	246—8	0,86	$C_{23}H_{19}N_3O_2$
IIc	64	244—6	0,81	$C_{23}H_{18}BrN_3O_2$
IId	75	215—7	0,75	$C_{18}H_{15}N_3O_4$
III	89	203—5	...	$C_{14}H_{11}N_3O$
IV	48	258—60	...	$C_{14}H_{11}N_3OS$

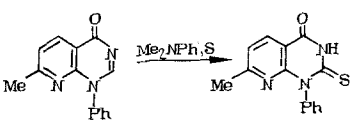
Note. The figure in brackets shows the yield of IIa obtained by reacting compound Ia with ethyl benzoate.

that the compounds exist in the enaminocarbonyl (A) and enol (B) tautomeric forms with a powerful intramolecular chelate-type hydrogen bond.



A B

In a previous work [3] reference is made to a new nucleophilic substitution reaction in the quinazoline series in which the hydrogen atom at position 4 of quinazolone-2 is replaced by an aminoaryl group. To ascertain whether a similar reaction is possible in the 1-aryl-4-oxo-1,4-dihydropyrido[2,3-d]pyrimidine series, we synthesized 7-methyl-4-oxo-1-phenyl-1,4-dihydropyrido[2,3-d]pyrimidine (III), which was then reacted with dimethylaniline in the presence of sulfur. Under these conditions it would appear that the sulfur atom joins to compound III at position 2; dimethylaniline takes no part in the reaction, probably due to steric hindrance by the ortho-substitutent.



III IV

EXPERIMENTAL (CHEMICAL)

IR spectra were taken in Vaseline using a UR-20 instrument; PMR spectra were recorded on an RS-60 magnetic resonance spectrometer for 5% solutions of the compounds in $CDCl_3$ (I and II) and DMSO-d_6 (III and IV), internal standard HMDS; TLC was performed on Silufol US-254 plates in a 1:1 butanol-benzene system for compounds Ib-e and in ethyl acetate for compounds IIa-d. Elemental analysis data was in line with calculated values.

1-Aryl-2,7-dimethyl-4-oxo-1,4-dihydropyrido[2,3-d]pyrimidines (Ia-d). Dry HCl was passed into a solution of 0.01 moles of the corresponding 2-(N-acetyl-N-arylamino)-6-methylnicotinonitrile [1] in 15 ml of dry benzene for 2 h; the resultant precipitate of I hydrochloride salt was filtered off and dried. It was then converted into the base using AcONa and crystallized from ethanol.

1-(4-Bromphenyl)-2,5,7-trimethyl-4-oxo-1,4-dihydropyrido[2,3-d]pyridine (Ie). To 30 ml of Ac_2O was added 3 ml of 50% perchloric acid with cooling. Then 3.5 g of 2-(N-acetyl-4-bromanilino)-4,6-dimethylnicotinonitrile [2] were dissolved in this mixture, which was kept at room temperature for 48 h. The resultant precipitate was filtered off, treated with an NaOH solution and crystallized from ethanol.

1-Aryl-7-methyl-4-oxo-2-phenacyl-1,4-dihydropyrido[2,3-d]pyrimidines (IIa-c). A solution of 0.01 moles of compound Ia (Ib) [6] and 3.5 g (0.025 moles) of benzoyl chloride in 20 ml of pyridine was boiled for 5 h, then poured into an $NaHCO_3$ solution. The resultant precipitate was filtered off and crystallized from a mixture of ethanol and IMF (1:1). Compound IIc was obtained in a similar way. IR spectrum of IIa: 1680 cm^{-1} (CO). PMR spectra,

TABLE 2. Biological Activity of the Synthesized Compounds

Compound	Analgesic activity (reflex time at peak effectiveness, sec)	Anti-inflammatory activity (% edema inhibition with respect to control)
Ib	15,6	No inhibition
Ic	14,6	» »
Id	15,6	+18,3
Ie	21,1	+36,0
IIa	16,0	No inhibition
IIb	18,6	+18,4
IIc	20,1	No inhibition
Amidopyrine (100 mg/kg)	27,6	+42,0
Ortofen (10 mg/kg)	21,7	+43,3
Control (2% starch mucilage)	12,9	No inhibition

σ, ppm: 2.00-2.70 s (CH_3 group protons), 5.00-5.07 s (1 H, CH), 6.90-7.70 m (aromatic protons), 6.73 s (1 H of IIc pyridine), 8.20-8.27 s (2 H of IIa and IIb pyridine), 14.23-14.40 s (1 H, NH).

7-Methyl-4-oxo-2-phenacyl-1-phenyl-1,4-dihydropyrido[2,3-d]pyrimidine (IIa). A solution of 1 g (0.004 moles) of compound Ia, 0.6 g (0.004 moles) of ethyl benzoate and 0.22 g (0.004 moles) of MeONa in 15 ml of dry MeOH was boiled for 10 h. After cooling and diluting with water the resultant precipitate was filtered off and crystallized. Yield 0.5 g (36%), mp 238-240°C. A sample mixed with substance IIa did not lower the melting point.

7-Methyl-2-methoxallylmethyl-4-oxo-1-phenyl-1,4-dihydropyrido[2,3-d]pyrimidine (IId). A solution of 1 g (0.004 moles) of Ia, 0.58 g (0.004 moles of diethyl oxalate and 0.22 g (0.004 moles) of MeONa in 15 ml of dry MeOH was boiled for 10 min. After filtering the resultant precipitate was washed with water and crystallized from ethanol. IR spectra, ν_{max}, cm^{-1}: 1700, 1720 (C=O). PMR spectrum, δ, ppm: 2.30 s (3 H, CH_3), 3.70 s (3 H, CH_{3O}), 5.27 s (1 H, CH), 6.93-7.50 m (aromatic protons), 13.9 s (1 H, NH).

7-Methyl-4-oxo-1-phenyl-1,4-dihydropyrido[2,3-d]pyrimidine (III). A mixture of 3.3 g of 2-anilino-6-methylnicotinic acid amide [5], 7.5 ml of $HC(OEt)_3$ and 15 ml of Ac_2O was boiled for 6 h. After filtering the resultant precipitatate was washed with ether and crystallized from ethanol. PMR spectrum, δ, ppm: 2.40 s (3 H, CH_3), 7.33 d (1 H, pyridine C(6)), 7.55 m (aromatic protons), 8.23 d (1 H, pyridine C(5)), 8.50 s (pyrimidine C(2)).

7-Methyl-4-oxo-2-thio-1-phenyl-1,4-dihydropyrido[2,3-d]pyrimidine (IV). A mixture of 2.37 g (0.01 moles) of compound III, 1.21 g (0.01 moles) of N,N-dimethylaniline and 1.92 g (0.06 moles) of sulfur was heated at 170°C for 2 h. After cooling the mixture was treated with a 10% HCl solution and filtered. The residue was dissolved in conc. HCl and the solution obtained was diluted with five times its volume of water. The precipitated substance was filtered off and crystallized from ethanol. PMR spectrum, δ, ppm: 2.31 s (3 H, CH_3), 7.17 d (1 H, pyridine C(6)), 7.45 m (aromatic protons), 8.17 d (1 H, pyridine C(5)), 12.67 s (1 H, NH).

EXPERIMENTAL (PHARMACOLOGICAL)

Compounds Ib-e and IIa-c were tested for anti-inflammatory, analgesic and diuretic activity.

Analgesic activity was assessed using the "hot plate" method [10] with white mice weighing 16-18 g. The test substances were introduced by intraperitoneal injection in the form of suspensions in 2% starch mucilage in dosage of 50 mg/kg.

Anti-inflammatory activity was studied in accordance with the procedural instructions on experimental preclinical research into non-steroid pharmacological anti-inflammatory preparations laid down by the pharmacology committee of the USSR Health Ministry. Tests were carried out on white rats weighing 180-200 g using a simulation of acute inflammatory edema involving a plantar injection into the animal's rear paw of 0.1 ml of a 1% karragenin solution. The effect of the compounds was evaluated from the percentage increase in the size of the paw [4]. Experimental results were compared to data for two anti-inflammatory preparations, ortofen in dosage of 10 mg/kg, and amidopyrine in dosage of 100 mg/kg.

The effect of the substances on diuresis was tested with white rats weighing 150-200 g. Observations of the animals were conducted over a period of 2 h after administration of the test preparations. Results were compared to the control preparation – a 45% NaCl solution.

Test results are given in Table 2. Compounds Ie and IIc displayed slight analgesic activity. Anti-inflammatory properties were detected in Id, Ie, and IIb, the other compounds showing no activity in this respect. The diuresis study revealed that none of the test compounds exhibit diuretic activity.

Compound Ie, which has a p-bromphenyl radical at position 1 and a methyl group at position 2, exhibits both analgesic and anti-inflammatory properties (see Table 2), while our data shows that biological activity is reduced in the analogous compound having a phenacyl group at position 2 (IIc).

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SYNTHESIS OF BIOLOGICALLY ACTIVE 4(3H)-QUINAZOLINONIUM PERCHLORATES

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In order to establish the influence of benzyl and substituted benzyl groups on the biological activity of quinazolinoium compounds, and in pursuance of earlier work [5], a method has been developed for the synthesis of arylamides of N-(2,4)- and -(3,4)-dimethoxybenzanthranilic acids.

TABLE 1. N-R^1-Benzylideneanthranilarylamides (IIIa-n)

Compound	Yield, %	Melting point, °C	Empirical formula
IIIa	63,0	105—6	$C_{20}H_{16}N_2O$
IIIb	65,0	140—2	$C_{21}H_{18}N_2O_2$
IIIc	90,0	118—20	$C_{22}H_{20}N_2O_2$
IIId	80,0	105—8	$C_{22}H_{20}N_2O_2$
IIIe	91,0	122—5	$C_{22}H_{20}N_2O_3$
IIIf	96,0	125—7	$C_{22}H_{20}N_2O_3$
IIIg	80,0	173—4	$C_{23}H_{22}N_2O_3$
IIIh	91,0	135—7	$C_{23}H_{22}N_2O_3$
IIIi	71,0	138—40	$C_{23}H_{22}N_2O_4$
IIIj	98,0	192—4	$C_{22}H_{19}ClN_2O_3$
IIIk	58,0	128—30	$C_{22}H_{20}N_2O_3$
IIIℓ	91,0	235—7	$C_{23}H_{22}N_2O_3$
IIIm	52,0	120—3	$C_{23}H_{22}N_2O_3$
IIIn	75,0	132—4	$C_{22}H_{19}ClN_2O_3$

*Here and in Tables 2-4, all the compounds were crystallized from ethanol.

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