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SYNTHESIS AND PROPERTIES OF DERIVATIVES OF 1,4-DIHYDROPYRIMIDINE-5-CARBOXYLIC ACID

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1,4-Dihydropyrimidines were synthesized by reductive dethionation of the corresponding 2-thiono-4-aryl-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid derivatives, and some of their properties were studied.

1,4-Dihydropyrimidines are 3-aza analogs of 1,4-dihydropyridines, which attracted attention because of their broad spectrum of biological action. However, until now, there are no suitable methods available for the synthesis of 1,4-dihydropyrimidines, and only individual representatives of this class are known. The synthesis of derivatives of 1,4-dihydropyrimidine by intramolecular rearrangement of 1,2,3,4-tetrahydropyrimidine-2-thiones [1, 2] is not very promising, since it is complicated by splitting of the pyrimidine ring and recyclization into 1,3-thiazine derivatives. This method is also unsuitable for synthesizing 2-unsubstituted 1,4-dihydropyrimidines. The existence of 1-N-unsubstituted dihydropyrimidines in the form of 1,4-dihydro isomer has been strictly proved only in separate cases [3] because of tautomeric transitions [4]. In 1983 [5, 6], 1-substituted 4-methyl-1,4-dihydropyrimidines were synthesized by reductive dethionation of pyrimidine-2-thiones over a Raney nickel catalyst. We used this method for synthesizing 4-aryl derivatives of 1-substituted 1,4-dihydro-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid, which have so far been unknown. The reductive dethionation of 2-thiono-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid derivatives (I) which we synthesized was carried out in acetone and methanol. The reaction is complicated by side-processes. In the reduction of the bromo derivative Ib, debromination takes place, and the reaction product is 1,4-diphenyl-1,4-dihydropyrimidine (IIa). In the reduction of a methoxy derivative Id in methanol, a mixture of dihydropyrimidine IId and tetrahydropyrimidine IV is formed (in a 1:3 ratio, according to liquid chromatography data), and the main product of the reduction of the nitro derivative IIc is tetrahydropyrimidine III. Reduction of 1,2,3,4-tetrahydropyrimidine-2-thiones over Raney nickel in a hydrogen atmosphere (p = 1 atm, T = 60°C) does not lead to increase in the yield of II (see scheme on following page).

The synthesis of IIa by reductive splitting of 1,4-diphenyl-2-methylthio-5-ethoxy-6-methyl-1,4-dihydropyrimidine (V) is not explicitly preferential, since the starting compound V was obtained by alkylation of Ia. We took compounds IIa, e as an example, and showed that derivatives of 1,4-dihydropyrimidine-5-carboxylic acid have characteristic chemical properties. The ester grouping in IIa is readily hydrolyzed in an alkaline medium to 1,4-diphenyl-

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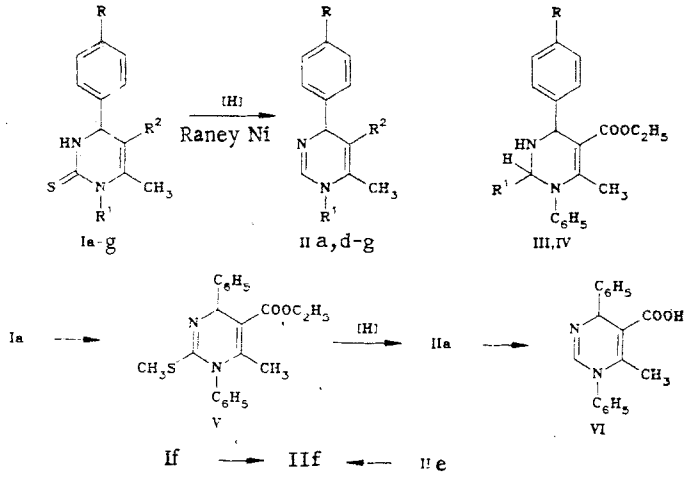
TABLE 1. PMR Spectra of Compounds Ia-g in DMSO-D_6 (ppm)

Compound	5-R^2	6-CH_3 (s, 3H)	1-R^1	4-Ar	4-H (d, 1H)	3-H (d, 1H)	J_{3H-4H}
Ia	1,02 (t, 3H); 3,98 (q, 2H)	1,96	7,34 (br.s, 10H)		5,22	9,90	4,00
Ib	1,06 (t, 3H); 4,02 (q, 2H)	1,97	7,04—7,42 (m, 7H)	7,58 (d, 2H)	5,21	9,99	4,00
Ic	1,06 (t, 3H); 4,01 (q, 2H)	2,00	7,06—7,44 (m, 5H)	7,59 (d, 2H); 8,24 (d, 2H)	5,34	10,02	4,00
Id	1,04 (t, 3H); 3,95 (q, 2H)	1,93	7,00—7,44 (m, 7H)	3,65 (s, 3H); 6,87 (d, 2H)	5,12	9,81	4,00
Ie	7,16 (br.s, 2H)	1,72	7,40 (br.s, 10H)		5,26	9,60	3,50
If		1,80	7,16—7,56 (m, 10H)		5,20	10,04	3,00
Ig	1,16 (t, 3H); 4,09 (q, 2H)	2,44	3,47 (s, 3H)	7,13—7,42 (m, 5H)	5,21	9,84	4,50

TABLE 2. PMR Spectra of Compounds IIa, d-g in DMSO-D_6 (ppm)

Compound	6-CH_3 (s, 3H)	4-H (s, 1H)	2-H	1-R^1	4-Ar	5-R^2
IIa	2,06	5,56	7,17—7,61 (m, 11H)			1,13 (t, 3H); 4,13 (d, 2H)
IId	2,04	5,51	7,13—7,62 (m, 8H)		6,88 (d, 2H); 3,73 (s, 3H)	1,13 (t, 3H); 4,04 (d, 2H)
IIe	2,10	5,51	7,14—7,60 (m, 11H)			5,21 (br.s, 2H)
IIf	1,87	5,33	7,22—7,71 (m, 11H)			
IIg	2,34	5,40	7,12 (s, 1H)	3,11 (s, 3H)	7,20 (s, 5H)	1,06 (t, 3H); 3,96 (q, 2H)
VI	2,07	5,58	7,18—7,64 (m, 11H)			12,0 (s, 1H)



I, IIa, d-g R=H, b R=Br, d R=NO_2, f R=OCH_3; a—d R^1=C_6H_5, g R^1=CH_3; a—f, g R^2=$COOC_2H_5$, e R^2=$CONH_2$, f R^2=CN; III R=NO_2, R^1=H; IV R=OCH_3, R^1=OH

6-methyl-1,4-dihydropyrimidine-5-carboxylic acid (VI), while the amide of this acid (IIe) reacts with phosphorus oxychloride to form 1,4-diphenyl-6-methyl-1,4-dihydropyrimidine-5-carbonitrile (IIf).

The structure of the synthesized compounds was confirmed by the sum total of the data of the spectral methods of investigation. In the PMR spectrum (Tables 1, 2) of 1-methyl derivative IIg, the signals of 2-H and 4-H protons appear in the form of four sharp singlets, and for 1,4-diaryl derivatives II, the 2-H proton signal and the multiplets of aromatic protons are superimposed. This character and disposition of the signals show that the alternative forms of the dihydro structure for II can be excluded. The mass spectra of all compounds II are characterized by a medium-intensity molecular ion peak and a parallel splitting of substituents from the pyrimidine ring (Table 3). It is also characteristic that no splitting of the 1-N substituent is observed. In the IR spectra of 5-ethyoxycarbonyl derivatives I and II the absorption frequency of the CO group is decreased to 1690 cm^{-1}, which is characteristic of the N—C=C—CO systems. Compounds II are more stable to oxidation than the known 4-methyl- and 4-unsubstituted 1,4-dihydropyrimidines [6]. In electrochemical oxidation on a rotating disk electrode, compounds II give only one-electron irreversible waves in the potential range of 0.7-1.0 V ($E_{1/2}$ for IIa 0.98, IId 0.92, IIe 0.84, and IIf 1.04), which is

TABLE 3. Characteristic Ions in Mass Spectra of 1,4-Dihydropyrimidines IIa, d-g

Compound	m/z values (intensity, %)					
	$M^{+\cdot}$	$[M-H]^+$	$[M-CH_3]^+$	$[M-C_6H_4R]$	$[M-R^2]^+$	other ions
IIa	320 (13)	319 (5)	305 (17)	243 (100)	247 (21)	291 (39) $[M-C_2H_5]^+$, 275 (5) $[M-OC_2H_5]^+$
IId	350 (28)	349 (16)	335 (13)	243 (51)	277 (33)	321 (100) $[M-C_2H_5]^{+*}$, 305 (7) $[M-OC_2H_5]^+$
IIe	291 (17)	290 (19)	276 (67)	214 (100)	247 (52)	
IIf	273 (36)	272 (19)	258 (2)	196 (100)	—	
IIg	258 (16)	257 (7)	243 (18)	181 (100)	185 (38)	229 (60) $[M-C_2H_5]^+$, 213 (13) $[M-OC_2H_5]^+$

*The composition of the ion was determined by high resolution 321.1215, calculated 321.1239; a metastable transition with m/z 350 → m/z 321 has been found.

TABLE 4. Characteristics of Compounds Synthesized Ia-g, IIa, d-g, III-VI

Compound	mp, °C	IR spectrum, cm^{-1}	UV spectrum, λ_{max}, nm (log ε)	Found, %			Empirical formula	Calculated, %			Yield, %
				C	H	N		C	H	N	
Ia	116—118	1700, 3170	305 (4.17)	68.4	5.8	7.9	$C_{20}H_{20}N_2O_2S$	68.2	5.7	8.0	70
Ib	158—160	1695, 3180	308 (4.23)	55.0	4.9	6.5	$C_{20}H_{19}BrN_2O_2S$	55.1	4.5	6.0	66
Ic	170—172	1695, 3340	298 (4.16)	60.0	4.6	10.4	$C_{20}H_{18}N_3O_4S$	60.4	4.9	10.6	76
Id	140—142	1702, 3185	307 (4.06)	65.7	5.7	7.3	$C_{21}H_{22}N_2O_3S$	65.9	5.9	7.3	90
Ie	220—222	1675, 3170, 3350	291 (4.13)	66.4	5.0	12.7	$C_{18}H_{17}N_3OS$	66.8	5.3	13.0	87
If	209—210	1695, 2205, 3150	303 (4.26)	70.4	5.2	14.1	$C_{18}H_{15}N_3S$	70.8	5.0	13.8	79
Ig	146—147	1640, 1705, 3200	305 (4.24)	62.3	6.0	9.9	$C_{15}H_{18}N_2O_2S$	62.0	6.2	9.6	83
IIa	77—79	1695	247 (3.94), 315 (3.74)	74.9	6.5	8.2	$C_{20}H_{20}N_2O_2$	75.0	6.3	8.7	67
IId	64—65	1690	223* (4.04), 252* (3.79), 310 (3.68)	72.4	6.7	8.3	$C_{21}H_{22}N_2O_3$	72.0	6.3	8.0	37
IIe	173—175	1685, 3150, 3370	264 (4.27)	74.5	5.7	14.0	$C_{18}H_{17}N_3O$	71.2 79.1	5.9 5.5	14.4 15.0	65 55
IIf	110—112	1675, 2198	247 (3.98), 292 (3.74)	78.9	5.3	15.1	$C_{15}H_{15}N_3$	69.7	7.0	10.8	56
IIg	76—77	1660, 1700	227* (4.07), 323 (3.76)	69.5	7.2	11.1	$C_{15}H_{18}N_2O_2$	60.4	5.8	11.5	61
III	158—160	1675, 3195	238* (4.06), 307 (4.09)	60.1	5.4	11.0	$C_{20}H_{21}N_3O_4$	68.5	6.5	7.6	50
IV	148—150	1683, 3312	223 (4.08), 309 (4.21)	68.3	6.0	7.1	$C_{21}H_{24}N_2O_4$				
V	92—94	1650, 1715	248* (4.15), 314 (3.49)	67.8	6.1	7.8	$C_{21}H_{22}N_2O_2S$	68.0	6.1	7.6	54
VI	196—198	1695, 3360	313 (3.58)	73.8	5.3	9.9	$C_{16}H_{16}N_2O_2$	74.0	5.5	9.6	

*Shoulder.

comparable with the values of potentials of 4-aryl derivatives of 1,4-dihydropyridine-3,5-dicarbonitriles [7]. The introduction of a carbamoyl grouping instead of ethoxycarbonyl (compounds IIa, e) shifts the value of the electrooxidation potential into a less anodic region and introduction of the nitrile group (IIf) shifts this potential into a more anodic region.

EXPERIMENTAL

The PMR spectra were run on a Bruker WH-90 spectrometer in DMSO-D_6, using TMS as internal standard; the IR spectra were taken on a Perkin-Elmer 580 spectrophotometer in mineral oil, the UV spectra, on a Specord M-40 spectrophotometer in ethanol at a concentration of $5 \cdot 10^{-5}$ mole/liter, and the mass spectra on an AEI MS-50 mass spectrometer with a direct introduction of the sample into an ionic source at 70 eV. The resolution in determination

of the elemental composition of the ions was 60,000. The metastable transitions were found by scanning the accelerating resolution. The electrooxidation potentials were determined by the method in [8]. The characteristics of the compounds synthesized are given in Tables 1-4.

1,2,3,4-Tetrahydropyrimidine-2-thiones (Ia-e, g) were obtained by the Biginelli condensation from ethyl ester or amide of acetoacetic acid, an aromatic aldehyde and N-methyl- or N-phenylthiourea in an acid medium by the method described in [9, 10].

1,4-Diphenyl-2-thiono-6-methyl-1,2,3,4-tetrahydropyrimidine-5-carbonitrile (If). A mixture of 2.0 g (6.2 mmoles) of compound Ie and 30 ml of $POCl_3$ is boiled for 30 min, and the solution is evaporated in vacuo. The residue is washed with water to a neutral reaction and crystallized from alcohol.

1,4-Diphenyl-5-ethoxycarbonyl-6-methyl-1,4-dihydropyrimidine (IIa). A 1.0 g portion (2.5 mmoles) of compound Ia is dissolved in 30 ml of acetone, ~3 g of Raney nickel are added, and the mixture is boiled for 2 h. It is then cooled, filtered, and the residue on the filter is washed with acetone. The combined filtrate is evaporated in vacuo. The oil formed is crystallized from hexane. Compounds IId-g are obtained in similar way.

1,4-Diphenyl-2-methylthio-5-ethoxycarbonyl-6-methyl-1,4-dihydropyrimidine (V). A 0.66 g portion (5 mmoles) of methyl iodide is added to 1.6 g (4.5 mmoles) of compound Ia in 50 ml of acetone, and the mixture is allowed to stand overnight. The crystals formed are filtered to give the hydroiodide salt of V; mp 154-156°C, yield 90%. The salt obtained is dissolved with heating in 50 ml of acetone, a 10% aqueous solution of ammonia is added to decolorize the yellow solution, which is then evaporated. The residue is crystallized from alcohol. PMR spectrum: 1.07 (t, 3H, OCH_2CH_3); 1.93 (s, 3H, 6-CH_3); 2.07 (s, 3H, SCH_3); 3.98 (q, 2H, OCH_2CH_3); 5.18 (d, 1H, 4-H); 7.16-7.53 ppm (m, 10H, 1- and 4-C_6H_5).

1-Phenyl-4-(p-nitrophenyl)-5-ethoxycarbonyl-6-methyl-1,2,3,4-tetrahydropyrimidine (III) and 1-phenyl-2-hydroxy-4-(p-methoxyphenyl)-5-ethoxycarbonyl-6-methyl-1,2,3,4-tetrahydropyrimidine (IV) were obtained by boiling 2.5 mmoles of compound IIc or IId with 6 g Raney nickel in 50 ml of methanol, as described above. The residue obtained after evaporation is crystallized from a mixture of benzene with hexane. Compound III, PMR spectrum ($CDCl_3$): 1.18 (t, 3H, OCH_2CH_3); 3.71 (s, 2H, 2-CH_2); 4.09 (q, 2H, OCH_2CH_3); 5.31 (d, 1H, 4-H); J_{3H-4H} = 3.00 Hz; 6.60 (d, 2H, 4-Ar); 7.11 (d, 2H, 4-Ar); 7.28-7.46 (m, 5H, 1-C_6H_5); 7.60 ppm (d, 1H, NH). Mass spectrum: 367 (61) $[M]^{+\cdot}$, 366 (11) $[M - H]^+$, 338 (61) $[M - C_2H_5]^+$, 307 (61) $[M - CH_3 - OC_2H_5]^{+\cdot}$, 294 (100) $[M - CO_2C_2H_5]^+$, 279 (24) $[M - CH_3 - CO_2C_2H_5]^+$, 275 (39) $[M - CH_3 - C_6H_5]^{+\cdot}$. Compound IV, PMR spectrum: 0.91 (t, 3H, OCH_2CH_3); 2.22 (s, 3H, 6-CH_3); 3.71 (s, 3H, OCH_3); 3.93 (q, 2H, OCH_2CH_3); 6.16 (d, 1H, 4-H); J_{3H-4H} = 9.50 Hz; 6.82 (d, 2H, 4-Ar); 7.04-7.50 (m, 7H, 1-C_6H_5 and 4-Ar); 8.18 (d, 1H, 2-H); J_{2H-3H} = 1.00 Hz; 8.36 (m, 1H, NH); 11.08 ppm (s, 1H, 2-OH). Mass spectrum: 368 (3) $[M]^{+\cdot}$, 322 (100) $[M - C_2H_5OH]^{+\cdot}$, 297 (27) $[M - C_2H_5OH - CO]^{+\cdot}$, 276 (5) $[M - C_2H_5OH - CO - H_2O]^{+\cdot}$, 205 (51).

1,4-Diphenyl-6-methyl-1,4-dihydropyrimidine-5-carbonitrile (IIf). A mixture of 0.4 g (1.5 mmole) of compound IIe with 15 ml of $POCl_3$ is heated to boiling and then allowed to stand for 2 h at 20°C. It is then evaporated in vacuo, and the residue is washed with water and recrystallized from alcohol. Yield 0.25 g (70%).

1,4-Diphenyl-6-methyl-1,4-dihydropyrimidine-5-carboxylic acid (VI). A mixture of 0.1 mmole of IIa with 0.2 mmole of KOH in 50% ethanol is boiled for 30 min. Alcohol is evaporated and the residue is neutralized with dilute HCl, the precipitate is ground with hexane, and recrystallized from methanol. Mass spectrum: 248 (32) $[M - CO_2]^{+\cdot}$, 247 (71) $[M - CO_2 - H]^+$, 233 (100) $[M - CO_2 - CH_3]^+$, 171 (52) $[M - CO_2 - C_6H_5]^{+\cdot}$.

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SYNTHESIS AND MESOMORPHIC PROPERTIES OF ARYL 5-ALKYL-(AND ALKOXY) PYRIMIDINE-2-CARBOXYLATES

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Some aryl 5-alkyl(and alkoxy)pyrimidine-2-carboxylates (I) and 5-alkylpyrimidinoyloxybenzoates (II) have been obtained. It has been found the former do not display mesomorphism, but the latter are nematic liquid crystals with a range over which the mesophase exists of 50-90°C. The transition to the liquid crystal state in these compounds takes place at approximately the same temperatures as in their benzene analogues, but the thermal stability of the mesophase is somewhat less. Cyano-derivatives of pyrimidine effectively increase the value of the dielectric anisotropy of the matrix mixture, but they have a marked effect on its clarification temperature.

It has been shown that substituted aryl 5-arylpyrimidine-2-carboxylates and pyrimidinoyloxybenzoates possess liquid crystal properties, forming a nematic phase [1]. However, the presence of a 5-aryl group in the pyrimidine ring results in high-melting and sparingly soluble compounds, presenting obstacles to their study. It would be expected that aryl 5-alkylpyrimidine-2-carboxylates would possess liquid crystal properties with lower mesophase temperatures.

We here report the preparation and study of the aryl 5-alkyl(and alkoxy)pyrimidine-2-carboxylates (I) and (II), which are analogues of the extensively studied arylbenzoates [2-5].

The starting 5-substituted pyrimidine-2-carboxylic acids (IIIa, b) were obtained by hydrolyzing the cyanopyrimidines (IV), which are readily accessible by introducing the cyano-group into the sulfones (V). Attempts to utilize information on the oxidation of 5-alkyl-2-methylpyrimidines [6] for the preparation of 5-heptylpyrimidine-2-carboxylic acid (IIIb) from 5-heptyl-2-methylpyrimidine (VIb) were unpromising, the yields of the acid (IIIb) being very small (see scheme on following page).

A frequently employed route to 2,5-disubstituted pyrimidines (including the mercapto-derivatives (VII, VIII)) [7, 8] makes use of various acrolein derivatives [9-11] (such as (IX) and (X)), obtained by a multistage synthesis from the acetals (IX) via the vinyl ethers (XII) and tetraethoxypropanes (XIII). This laborious route can be shortened by preparing the acroleins (X) directly from the acetals (XI), as described in [12].

5-Pentyloxypyrimidine-2-carboxylic acid (IIIc) was obtained by a convenient route for the preparation of 5-alkoxypyrimidines (from the 4-hydroxypyrimidines).

Acids (IIIa-c) were converted into their aryl esters (Ia-d) and (IIa-d) as described in [1].

Liquid Crystal Properties of (I) and (II). The p-cyanophenyl esters (Ia) and (Ic) and the hexyloxyphenyl ester (Id) did not display mesomorphism, in contrast to their benzene

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