SYNTHESIS AND SOME CONVERSIONS OF 6-METHYL- AND 1,6-DIMETHYL-5-NITRO-4-PHENYL-2-OXO-1,2,3,4-TETRAHYDROPYRIMIDINES

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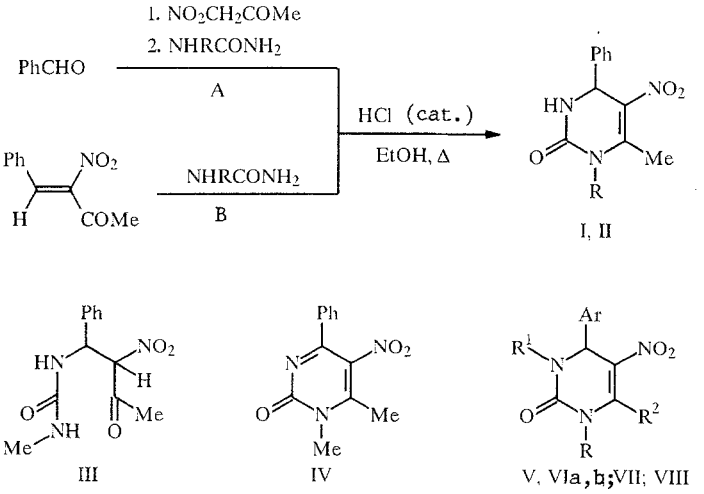
Using a modification of the Biginelli reaction, we have synthesized 6-methyl- and 1,6-dimethyl-5-nitro-4-phenyl-2-oxo-1,2,3,4-tetrahydropyrimidines. We have studied some of their chemical conversions involving the methyl group on the $C_{(6)}$ atom, the nitrogen atoms of the pyrimidine ring, and the phenyl substituent.

The application in medicine of calcium antagonists of the 1,4-dihydropyrimidine series, as highly effective cardiovascular agents (nifedipine, foridon, nicardipine, etc.), has stimulated interest in synthesis of aza analogs of these compounds. In recent years, many derivatives of di- and tetrahydrodiazines have been obtained [1-3], the investigation of the pharmacological properties of which has shown that they have an antihypertensive effect [4-8]. In this respect, the best studied have been 4-aryl-6-methyl-1,4(3,4)-di- and -1,2,3,4-tetrahydropyrimidines obtained from the Biginelli reaction [9-12], containing an ester group ortho to the germinal unit. In the literature, isolated examples have been described of synthesis of 1,2,3,4-tetrahydropyrimidines containing a nitro group on the $C_{(5)}$ atom [13-15].

Earlier, with the goal of obtaining new modulators for calcium uptake, we synthesized a series of 4-aryl-5-nitro-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidines [16]. Continuing the investigations in this area, in this paper we describe various approaches to synthesis of 6-methyl- (I) and 1,6-dimethyl-5-nitro-4-phenyl-2-oxo-1,2,3,4-tetrahydropyrimidine (II) and we have carried out some of their chemical conversions.

Scheme 1



I R = H; II R = CH_3; Va R = R^1 = H, R^2 = CH=CHN$(CH_3)_2$, Ar = C_6H_5; Vb R = R^1 = H, R^2 = $C_6H_4NO_2$-m, Ar = Ph; VIa R = H, R^1 = CHO, R^2 = CH_3, Ar = C_6H_5; VIb R = H, R^1 = CH_3CO, R^2 = CH_3, Ar = C_6H_5; VII R = R^1 = H, R^2 = CH_3, Ar = $C_6H_4NO_2$-m; VIII R = R^1 = R^2 = CH_3, Ar = C_6H_5

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Upon reaction of benzaldehyde, nitroacetone, and urea (in 1:1:2 ratio) in boiling ethanol in the presence of a catalytic amount of conc. HCl (method A), tetrahydropyrimidine I is formed. The latter is obtained under the same conditions as for reaction of 2-nitro-1-phenylbuten-3-one with a two-fold excess of urea (method B). Replacing urea by its N-methyl derivative when carrying out the reaction according to methods A and B leads to synthesis of tetrahydropyrimidine II. Furthermore, when carrying out this reaction according to method A at the temperature of 35-40°C, from the reaction mixture we also isolate N-methyl-N'-(2-nitro-1-phenylbutanon-3-yl)urea (III), which is an intermediate of the indicated cyclization. Formation of urea III in the first stage of the reaction obviously occurs as a result of condensation of aldehyde with nitroacetone and N-methylurea containing mobile hydrogen atoms. Compound II is cyclicized to tetrahydropyrimidine II upon boiling in ethanol in the presence of a catalytic amount of conc. HCl.

The PMR spectra of compounds I and II (Table 1) are characterized by the presence of signals from the protons of the phenyl ring (7.38-6.97 ppm), the methyl groups on the $C_{(6)}$ atom (2.64 and 2.67 ppm for I and II, respectively) and on the nitrogen atom of the pyrimidine ring for II (3.21 ppm). The doublet character of the signal from the geminal proton (5.71 and 5.31 ppm for I and II respectively) allows us to assign it to signals from the protons of the NH groups, and also to establish the position of the N-methyl group for compound II. Furthermore, dehydration of the latter by dichlorodicyanobenzoquinone, which leads to 1,6-dimethyl-5-nitro-4-phenyl-2-oxo-1,2-dihydropyrimidine (IV), serves as additional evidence for the presence of a methyl group on the $N_{(1)}$ atom. In the IR spectra of compounds I and II, there are intense absorption bands from the carbonyl (1680 and 1710 cm^{-1}) and NH group (3350 and 3320 cm^{-1}). The bands in the region 1315 and 1510 cm^{-1} are assigned to the symmetric and antisymmetric vibrations of the nitro group. In the UV spectra of compounds I and II, the long-wavelength absorption band (342 and 351 respectively) is evidence for the presence of the same conjugation chain in them. Thus, the spectral characteristics unambiguously prove the 1,2,3,4-tetrahydropyrimidine structure of compounds I and II. In the PMR spectrum of the substituted urea III (see the experimental part), the signals from the NH groups appear as a doublet (7.04 ppm) and a quartet (6.48 ppm). These data, and also the presence in the ^{13}C NMR spectrum of a signal in the 197.2 ppm region corresponding to the carbonyl group of the acetonyl fragment, confirm its acyclic structure.

The substituted tetrahydropyrimidine I has several reaction centers. In this paper, we have studied its reaction with some electrophilic agents. The vicinal nitro group considerably increases the mobility of the hydrogen atoms of the methyl group on the $C_{(6)}$ atom. In reaction of I with an equimolecular amount of dimethylformamide diethylacetal, we obtained the enamine (Va). Analogously, upon action of 3-nitrobenzaldehyde on I, the substituted styrene (Vb) is formed. In both cases, the tetrahydropyrimidine fragment remains unchanged.

Vilsmeier–Haack formylation of I and its acetylation with acetic anhydride occurs regioselectively at the $N_{(3)}$ atom. In this case, 3-formyl- and 3-acetyltetrahydropyrimidines (VIa and VIb respectively) are formed. In these two cases, the site of electrophilic attack is confirmed by the singlet character of the signal from the geminal proton in the PMR spectra (6.68 and 6.88 ppm for VIa and VIb respectively) (see Table 1).

Upon reaction of I with potassium nitrate in sulfuric acid, the nitronium ion attacks the meta position of the phenyl substituent. As a result, 6-methyl-5-nitro-4-(3'-nitrophenyl)-2-oxo-1,2,3,4,-tetrahydropyrimidine (VII) is formed, which is synthesized also according to method A.

Alkylation of I with methyl iodide is accomplished at the nitrogen atom of the pyrimidine ring. For a 1:1 reagent ratio, the $N_{(1)}$ atom is alkylated with formation of the monomethyl derivative II. In the case of a two-fold excess of base and methyl iodide, a mixture of mono- and dimethyl (VIII) derivatives is formed.

EXPERIMENTAL

The PMR spectra were recorded on the Bruker WP-200 spectrometer in DMSO-d_6, $CDCl_3$, and acetone-d_6; internal standard TMS. The IR spectra were taken on the Specord M-80; the UV spectra were taken on the Specord M-40. The course of the reaction and the purity of the synthesized compounds were monitored by TLC on Silufol UV-254 plates in chloroform (visualization in UV light).

The elemental analysis data for the synthesized compounds with respect to C, H, and N correspond to the calculated values.

Nitroacetone and 2-nitro-1-phenylbuten-3-one were obtained by the technique in [17] and [18] respectively.

6-Methyl-5-nitro-4-phenyl-2-oxo-1,2,3,4-tetrahydropyrimidine (I). A. Concentrated HCl (1.0 ml) was added with stirring to a mixture of 6.2 g (58.4 mmoles) benzaldehyde, 6.0 g (58.3 mmoles) nitroacetone, and 7.0 g (116.6 mmoles) urea in 100 ml absolute ethanol. The reaction mixture was boiled for 6 h. The separated residue I was filtered and dried.

TABLE 1. Characteristics of Synthesized Compounds

Compound	Empirical formula	Tmp, °C (from ethanol)	UV spectrum, λ_{max}, nm (lg ε) (in methanol)	PMR spectra, δ, ppm* (spin–spin coupling constant J, Hz)						Yield, %
				$N_{(1)}H$, s	$N_{(3)}H$, d	CH	$C_{(6)}-CH_3$, s	C_6H_5, m	other signals	
I	$C_{11}H_{11}N_3O_3$	199...202	342 (3,9)	10,20	8,18 (3,0)	5,71 d, (3,0)	2,64	7,38...7,24	–	91**
II	$C_{12}H_{13}N_3O_3$	168...170	351 (3,8)	–	8,56 (3,8)	5,31 d, (3,8)	2,67	7,30...6,97	3,21 (s, $N_{(1)}CH_3$)	64**
IV	$C_{12}H_{11}N_3O_2$	164...166	263 (4,1), 321 (3,9)	–	–	–	2,54	7,62...7,34	3,67 (s, $N_{(1)}CH_3$)	69
Va	$C_{14}H_{16}N_4O_3$	235...237	268 (4,3), 438 (4,6)	9,39	8,19 (2,0)	5,56 d, (2,0)	–	7,33...7,12	8,12, 6,70 (2 d, CH=CH); 3,17, 2,93 (2 s, $N(CH_3)_2$)	93
Vb	$C_{18}H_{14}N_4O_5$	249...250	265 (4,6), 367 (4,1)	10,09	8,44 (2,4)	5,58 d, (2,4)	–	7,40...7,32	7,88...7,58 (m, C_6H_4); 8,24, 8,09 (2 d, CH=CH)	38
VIa	$C_{12}H_{11}N_3O_4$	147...149	326 (4,0)	8,93	–	6,68 s	2,62	7,41...7,32	9,29 (s, CHO)	17
VIb	$C_{13}H_{13}N_3O_4$	161...163	253 (4,0), 324 (4,0)	9,72	–	6,88 s	2,41	7,29...7,18	2,58 (s, $COCH_3$)	79
VII	$C_{11}H_{10}N_4O_5$	241...242	259 (4,1), 336 (4,0)	10,20	8,12 (2,0)	5,88 d, (2,0)	2,94	–	7,74...7,52 (m, C_6H_4)	67**
VIII	$C_{13}H_{15}N_3O_3$	131...132	238 (3,7), 356 (4,0)	–	–	5,66 s	2,65	7,33...7,27	3,37 (s, $N_{(3)}CH_3$); 2,96 (s, $N_{(1)}CH_3$)	17

*Spectra of compounds I, Va, Vb, VII were obtained in DMSO-d_6; II, IV, VIII, in $CDCl_3$; VIa, VIb, in acetone-d_6.

**Method A.

Analogously, from N-methylurea we obtained 1,6-dimethyl-5-nitro-4-phenyl-2-oxo-1,2,3,4-tetrahydropyrimidine (II), and from 3-nitrobenzaldehyde we obtained 6-methyl-5-nitro-4-(3'-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine (VII).

B. A mixture of 0.2 g (1.05 mmoles) 2-nitro-1-phenylbuten-3-one, 0.126 g (2.6 mmoles) urea, and 0.05 ml conc. HCl was boiled in 10 ml ethanol for 6 h. This was treated according to method A. Yield of I, 0.2 g (77%).

Analogously, we obtained II from N-methylurea. Yield, 23%.

N-Methyl-N'-(1-nitro-2-phenylbutanon-3-yl)urea (III, $C_{12}H_{15}N_3O_4$). Concentrated HCl (0.1 ml) was added with stirring to a mixture of 0.5 g (4.7 mmoles) benzaldehyde, 0.5 g (4.8 mmoles) nitroacetone, and 0.72 g (9.7 mmoles) N-methylurea. The reaction mixture was held at 35-40°C for 15 min. The precipitated colorless residue III was filtered and dried. Yield, 0.65 g (52%), mp 135-137°C (ethanol). IR spectrum (KBr): 3300-3900 (N–H), 1738 and 1660 cm^{-1} (C=O). UV spectrum (in methanol), λ_{max} (logε): 256 (3.6), 333 nm (3.7). PMR spectrum (DMSO-d_6): 7.39-7.15 (5H, m, C_6H_5); 7.04 (1H, d, NH); 6.62 (1H, d, $CHNO_2$); 6.48 (1H, q, $NHCH_3$); 6.00 (1H, m, CH); 2.56 (3H, d, $NHCH_3$); 2.34 ppm (3H, s, CH_3), ^{13}C NMR spectrum (DMSO-d_6): 197.22; 177.50 (2 C=O); 128.70; 127.96; 126.51; 123.20 (C_6H_5); 103.90 ($CHNO_2$); 60.04 (CHC_6H_5); 26.80 (NCH_3); 26.24 ppm (CH_3).

Boiling III in ethanol in the presence of a catalytic amount of conc. HCl leads to II. Yield, 87%.

1,6-Dimethyl-5-nitro-4-phenyl-2-oxo-1,2-dihydropyrimidine (IV). Dichlorodicyanobenzoquinone (0.64 g, 2.8 mmoles) was added with stirring to a suspension of 0.7 g (2.8 mmoles) compound II in 30 ml absolute benzene. The reaction mass was boiled for 6 h. The separated hydroquinone was filtered, the mother liquor was evaporated to dryness, and IV was separated from the residue by chromatography on silica gel (20 g; eluting agent, chloroform), which after removal of the solvent was crystallized.

6,(2'-Dimethylaminoethenyl)-5-nitro-4-phenyl-2-oxo-1,2,3,4-tetrahydropyrimidine (Va). DMF diethylacetal (0.56 g, 4.2 mmoles) was added with stirring to a solution of 0.5 g (2.1 mmoles) compound I in 3 ml DMF. The reaction mixture was held at 130°C for 4 h. The solvent was removed under vacuum by a water-jet aspirator. The residue was treated with ether (3 × 50 ml).

5-Nitro-6-(3'-nitrostyryl)-4-phenyl-2-oxo-1,2,3,4,-tetrahydropyrimidine (Vb). Piperidine (0.4 ml) was added to a suspension of 1.0 g (4.2 mmoles) compound I and 0.63 g (4.2 mmoles) 3-nitrobenzaldehyde in 30 ml ethanol. The reaction mixture was boiled with stirring for 2 h. The precipitated residue of Vb was filtered and dried.

6-Methyl-5-nitro-4-phenyl-3-formyl-2-oxo-1,2,3,4,-tetrahydropyrimidine (VIa). Phosphorus oxychloride (0.4 ml) was added with stirring over the course of 15 min to a suspension of 1.0 g (4.2 mmoles) compound I in 5 ml DMF at −10°C. The temperature of the reaction mixture was brought up to room temperature, and then the mixture was held at 70°C for 45 min. The reaction mass was poured over ice (30 g); the precipitated residue was filtered, dried in air, and then VIa was separated by chromatography on a column with silica gel (20 g; eluting agent, a 3:1 chloroform–ethyl acetate mixture).

3-Acetyl-6-methyl-5-nitro-4-phenyl-2-oxo-1,2,3,4-tetrahydropyrimidine (VIb). A suspension of 0.5 g (2.1 mmoles) compound I in 5 ml freshly distilled acetic anhydride was boiled with stirring for 3 h. The reaction mixture was poured into water (25 ml). The precipitated oily product VIb crystallized over time.

6-Methyl-5-nitro-4-(3'-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine (VII). A solution of 0.87 g (9.1 mmoles) potassium nitrate in 8 ml conc. H_2SO_4 was added over the course of 30 min to a solution of 1.0 g (4.2 mmoles) compound I in 10 ml conc. H_2SO_4 at −5°C. The reaction mixture was stirred at room temperature for 1 h and then poured into water (100 ml). The precipitated residue VII was filtered. Yield, 0.78 g (65%). The product VII was identical to the sample obtained by method A.

Reaction of Compound I with Methyl Iodide. An 80% suspension of sodium hydride (0.37 g, 12.3 mmoles) was added with stirring under a stream of argon to a solution of 1.5 g (6.3 mmoles) compound I in 15 ml DMF. Methyl iodide (0.81 ml, 12.9 mmoles) was added to the reaction mixture 1 h after evolution of hydrogen was complete. After 20 h, the reaction mixture was diluted with water (300 ml) and extracted with chloroform (3 × 200 ml). The extract was dried over $MgSO_4$. The solvent was removed under vacuum with a water-jet aspirator and the residue was chromatographed on silica gel (30 g; 30:1 chloroform–methanol), eluting 1,3,6-trimethyl-5-nitro-4-phenyl-2-oxo-1,2,3,4-tetrahydropyrimidine (VIII) and then tetrahydropyrimidine II. Yield, 0.32 g (20%).

Under analogous conditions, for reagent ratio 1:1:1, as the only product we obtained tetrahydropyrimidine II. Yield, 59%.

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