SYNTHESIS AND STUDY OF THE PHARMACOLOGIC PROPERTIES OF DERIVATIVES OF 1,2,3,4-TETRAHYDRO-5-NITROPYRIMIDINE

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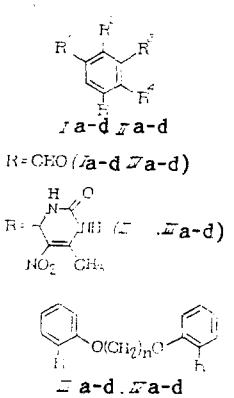
Many compounds of the 4-aryl-1,4-dihydropyridine series are effective cardiovascular preparations (Nifedipine, Nicardipine, Nitrendipine, Phoridone, etc.). They are successfully used to treat hypertension, ischemic heart disease, and arthritis [5], and are thought to act as calcium-channel blockers (calcium antagonists). Compounds of the 1,2,3,4-tetrahydropyrimidine series, containing a complex ether group at position 5 of the heterocyclic ring, have similar properties [1, 8, 15].

The recent development of synthesis methods for 1,4-dihydropyridines [16] allows one to bestow pharmacologic properties on these compounds [3, 4, 6, 12]. In particular, it has been found that the presence of different substituents at positions 3 and 5 of the 1,4-dihydropyridine ring (for example, the preparations Bay K 8644 and CGP 28 392) transforms these substances from calcium antagonists to agonists [10, 17].

For the purposes of discovering new modulators of calcium entry and studying their pharmacologic properties, we have, for the first time, obtained compounds of the 1,2,3,4-tetrahydropyrimidine series with a nitro group at position 5. Synthesis of these compounds was carried out by means of a modification of the classic Biginelli reaction [9, 11].

By reacting aromatic aldehydes (Ia-d) with nitroacetone and urea in boiling ethanol in the presence of a catalytic amount of hydrochloric acid, we obtained 1,2,3,4-tetrahydro-4-aryl-5-nitro-6-methylpyrimidin-2-ones (IIa-d).



R^1 = H(Ia-c; IIa-c), OCH_3(Id, IId); R^2 = H(Ia, c; IIa, c), OCH_3(Ib, d; IIb, d); R^3 = H(Ia-c; IIa-c), OCH_3(Id; IId); R^4 = H(Ia, b, d, IIa, b, d). OCH_3(Ic, IIc) n = 1 (IIIa; IVa), 2 (IIIb; IVa), 3 (IIIc; IVc), 4 (IIId; IVd).

Pyrimidines IIa-d were isolated as high-melting crystalline substances, soluble in polar aprotic solvents. The structures of the compounds synthesized were confirmed by spectral data. The PMR spectra are characterizes by the presence of the signals of protons of the phenyl ring (7.05-7.50) and of the methyl group (2.43-2.82). In addition, a doublet (5.42-5.84), belonging to the signal of the geminal proton of the pyrimidine ring, permits the assignment

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of the signals of the CH protons (Table 1). The IR spectra of IIa-d display intense carbonyl (1680-1710 cm^{-1}) and NH-group (3350 cm^{-1}) absorption. Bands in the regions of 1300 and 1500 cm^{-1} may be assigned to symmetric and antisymmetric vibrations of the nitro group. In the UV spectra of the obtained tetrahydropyrimidines, long-wave absorption bands are evidence of the presence of equivalent conjugated bonds in fragments of these compounds. Thus, the spectral data uniquely prove the 1,2,3,4-tetrahydropyrimidine structure of the compounds synthesized.

It is known that many crown ethers, cryptands, and podands that have chelating properties are calcium antagonists [7, 14]. With the aim of increasing the chelating abilities of derivatives of 1,2,3,4-tetrahydro-5-nitropyrimidine, we have synthesized compounds (IIIa-d), in which the bonding between the phenyl fragments of the molecule is accomplished by methylene bridges. These compounds were obtained by the reaction of dialdehydes (IVa-d) with nitroacetone and urea, under conditions analogous to those for the formation of IIa-d.

The spectral characteristics of compounds IIIa-d (see Table 1) were analogous to pyrimidines IIa-d, which allows one to assign them the same 1,2,3,4-tetrahydropyrimidine structure.

EXPERIMENTAL (CHEMISTRY)

IR spectra were recorded on a Specord IR-71 instrument in KBr tablets, and PMR spectra on a Bruker WP-200 (200 MHz); shifts were measured relative to hexamethyldisilazane; UV spectra were recorded on a Specord UV-VIS.

The course of reactions and the purity of products were checked on TLC on Silufol UV-254 plates in the system chloroform–methanol (9:1), with visualization by UV light. The characteristics of compounds IIa-d and IIIa-d are given in Table 1. The results of elemental analysis corresponded to the calculated values.

1,2,3,4-Tetrahydro-4-phenyl-6-methylpyrimidin-2-one (IIa). To a mixture of 5.8 g (56.5 moles) benzaldehyde, 5.8 g (56.5 moles) of nitroacetone, and 6.8 g (113 mmoles) urea in 100 ml absolute ethanol was added, with stirring, 20 drops of concentrated HCl. The reaction mixture was boiled for 6 h. The resulting residue was filtered and recrystallized from ethanol. Compounds IIb-d were obtained similarly.

Bis(1,2,3,4-tetrahydropyrimidinones) (IIIa-d). These were obtained analogously to IIa-d from 7.3 moles of the corresponding dialdehyde IVa-d [13], 14.6 mmoles of nitroacetone, and 29.2 mmoles of urea. They were recrystallized from dimethylformamide.

EXPERIMENTAL (BIOLOGY)

The effects of these compounds on the hemodynamic system were studied in acute tests on Wistar rats of both sexes weighing 250-300 g. Under hexenal or thiopental anesthesia (50 mg/kg), the right carotid artery was catheterized with a polyethylene catheter (0.7 × 22 mm, Medicut, USA). Arterial pressure was recorded electromanometrically (TP-200T, Nichon Kohden, Japan). Cardiac pumping function was assessed by measuring the stroke and minute volumes (SV and MV), for which first-derivative rheograms were obtained with a P 04-02 rheograph by tetrapolar rheography [2], with subsequent calculation of SV using Kubichek's formula:

$$SV = K \cdot \varrho \frac{l^2}{L^2} > A_D T_{ex},$$

where K is the coefficient of error; ρ is the specific resistance of the blood; ℓ is the distance between chest electrodes; L is the electrical impedance; A_D is the amplitude of the differential rheogram; and T_{ex} is the expulsion time.

To assess vasodilation, we calculated the total peripheral resistance (TPR) with the formula

$$TPR = \frac{AP_m}{MV} \cdot 1333.$$

where AP_m is the mean arterial pressure.

During the course of the experiment, the EKG was continuously monitored with a second instrument (an AB-6019 amplifier, Nichon Kohden, Japan). Simultaneous recording of the AP_m, EKG, and SV were done by a Polygraph System 8000 (Nichon Kohden, Japan).

TABLE 1. Constants for Compounds IIa-d and IIIa-d

Compound	Yield, %	mp, °C	Empirical formula	PMR spectrum, δ, ppm
II a	77	199—202	$C_{11}H_{11}N_3O_5$	2,64(3H,s,CH_3); 5,71(1H,d,CH); 7,38(5H,m, C_6H_5); 8,18(1H,d,NH); 10,2(H1,s,NH)
II b	84	227—8	$C_{12}H_{13}N_3O_4$	2,43(3H,s,CH_3); 3,67(3H,s,OCH_3); 5,42(1H,d,CH); 6,82(2H,d,C_6H_2); 7,17(2H,d,C_6H_2); 8,14(1H,d,NH); 9,92(1H,s,NH)
II c	94	196—8	$C_{12}H_{13}N_3O_4$	2,49(3H,s,CH_3); 3,78(3H,s,OCH_3); 5,73(1H,d,CH); 7,08(4H,m,C_6H_4); 7,95(1H,d NH); 10,02(1H,s,NH)
II d	80	243—5	$C_{14}H_{17}N_3O_6$	2,82(3H,s,CH_3); 3,87(3H,s,OCH_3); 3,97(6H,s,$2OCH_3$); 5,84(1H,d,CH); 6,87(2H,s,C_6H_2); 8,36(1H,d,NH); 10,15(1H,s,NH)
IIIa*	63	(dec.) —	$C_{23}H_{22}N_6O_7$	2,66(3H,s, CH_3) 5,91(1H,s, CH_2); 5,99(1H,d, CH); 7,01—7,48(4H,m, C_6H_4); 7,99(1H, d,NH); 10,12(1H, s,NH)
IIIb*	96	—	$C_{24}H_{24}N_6O_7$	2,47(3H,s,CH_3) 4,36(2H,s,CH_2); 5,78(1H,d,CH); 6,80—7,35(4H,m, C_6H_4); 7,83(1H,d,NH); 10,01(1H,s,NH)
IIIc*	80	-	$C_{25}H_{26}N_6O_8$	2,71(3H,s,CH_3) 4,39(3H,m,CH_2); 6,00(1H,d,CH); 7,05- 7,50(4H,m,C_6H_4); 8,21(1H,d,NH); 10,30(1H,s,NH)
IIId*	91	—	$C_{26}H_{28}N_6O_8$	2,72(3H,s,CH_3) 4,30(4H, br.s,CH_2); 6,02(1H,d,CH); 7,05- 7,50(4H,m,C_6H_4); 8,09(1H,d,NH); 10,24(1H,s,NH)

*Does not melt; decomposes on heating above 250°C.

The compounds being studied were dissolved in dimethylacetamide and physiological solution, and given intravenously (into the jugular vein) in doses of 0.1 and 1 mg/kg. The ratio of the volume of solvent to physiological solution in the mixture given did not exceed 1:100, and was found not to affect the hemodynamic indices under investigation.

In the next series of experiments, the effects of the synthesized compounds on myocardial contractility was studied. Experiments were carried out on the papillary muscles of the left ventricles of the rat heart, contracting in an isometric regime under the influence of electrical stimulation, using platinum electrodes arranged parallel to the muscle in the working chamber. Square-wave stimulatory impulses were used with a duration of 5 msec, with a current exceeding the threshold by 10-25% and a frequency of 1 Hz. The solution was oxygenated with carbogen (95% O_2 and 5% CO_2). In all experiments the pH was maintained at 7.3. The strength of contractions, close to isometric, was recorded by means of a 6 MKh ZS mechanograph. Perfusion of muscle was carried out with Tyrode buffer containing the compounds under investigation in concentrations from 10^{-8}-10^{-3} M, under conditions of normal oxygenation, with a ratio of solvent to nutrient solution of 1:100. The results obtained were treated according to a statistical variance method (Student's test).

In Table 2 are given the results of studying the effects of the synthesized compounds on indices of the hemodynamic system and on the contractility of isolated myocardium compared with the structurally similar calcium antagoist Nifedipine. All compounds studied showed vasodilating activity, with a resultant lowering of AP_m by 5-15% and TPR by 4-40%. The greatest activity was shown by compound IIc, which has a methoxy group in the ortho position of the phenyl ring. However, its activity was lower than that of Nifedipine.

The different directions of changes in indices of cardiac pumping function (SV, MV) under the influence of the preparations points out their differing affinity for the smooth muscle of vessel walls and myocardium. Thus, IIc and IId, which increase MV, are compounds which mainly act on vessels. At the dose investigated (0.1 mg/kg) they significantly decreased loading, changing myocardial contractility little, and in particular promoting more complete emptying of the heart. As the data obtained on isolated myocardium show, IIc and d lessen the tension developed by papillary muscles significantly less than IIa and b.

In the series of dimeric compounds, lower cardiovascular activity is observed with an increasing number of methyl groups in the chains of IIIa to IIId. Thus, whereas IIIa retains vasodilatory properties, IIId displays them irregularly.

Thus, compounds of the 1,2,3,4-tetrahydropyrimidine series, with a nitro group at position 5 of the pyrimidine ring, resemble the known calcium antagonist Nifedipine in their effect on the hemodynamic system and on myocardial contractility. Hence, they may be regarded as a group of calcium transport antagonists of somewhat lower activity. The results obtained support the conclusion that the synthesis of 1,2,3,4-tetrahydro-5-nitropyrimi-

TABLE 2. Effect of Compounds IIa-d and IIIa-d (in a dose of 0.1 mg/kg and 10^{-6} M) on the Hemodynamic System and Myocardial Contractility (in % of initial index)

Compound	AP_m	Heart rate	MV	SV	TPR	τ
IIa	12↓	—	3↓	4↓	7↓	12↓
IIb	15↓	8↓	12↓	7↓	—	18↓
IIc	25↓	3↓	7↑	8↑	40↓	5↓
IId	18↓	6↓	15↑	10↑	33↓	8↓
IIIa	14↓	10↓	5↑	8↑	18↓	20↓
IIIb	12↓	5↓	—	3↑	10↓	7↓
IIIc	9↓	—	2↑	2↑	10↓	8↓
IIId	5↓	—	—	—	6↓	4↓
Nifedipine	40↓	13↓	18↓	15↓	34↓	24↓

dines with different substituents is a potential way of developing highly effective modulators of calcium transport.

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