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# SYNTHESIS AND BIOLOGICAL ACTIVITY OF SOME N-SUBSTITUTED 1,2-DIHYDROPYRIDINES

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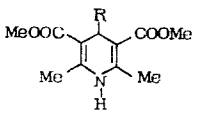
Derivatives of 1,4-dihydropyridine (1,4-DHP) possess cardiovascular, heptaoprotective, antitumor, and antimutagen activities [1]. Examples of drugs from this category which are used as hypotensive agents are nifedipine, nicardipine, nitrendipine, and riodipine (foridone), which have been synthesized at the Institute of Organic Synthesis of the Latvian Academy of Sciences.

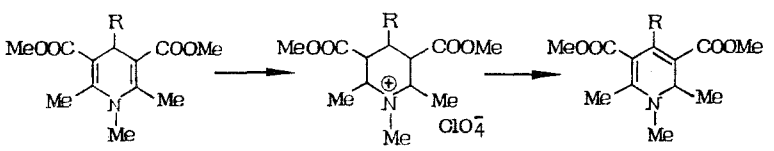


R = $C_6H_4NO_2$-*o* (nifedipine)
$OCHF_2$-*o* (riodipine)

Derivatives of 1,2-dihydropyrindine (1,2-DHP) have been much less studied. In this work, we have used structural analogues of nifedipine and riodipine to compare the biological properties of 1,4- and 1,2-DHPs. Due to the instability of derivatives of 1,2-DHP unsubstituted at position 1, it was only possible to compare N-methylated 1,2-DHPs with the corresponding N-methylated 1,4-DHPs.

4-(o-R-phenyl)-3,5-dimethoxycarbonyl-1,2,6-trimethyl-1,2-dihydropyridines (IIIa, b) were synthesized by $NaBH_4$ reduction of the corresponding pyridinium salts (IIa, b), obtained from the isomeric 1,4-DHPs (Ia, b).

Analysis of the PMR spectra indicates that the 1,2-DHPs exist in the form of two rotamers.



*I* a,b *II* a,b *III* a,b

R = $C_6H_4NO_2$-*o* (*I*a-*III*a), $C_6H_4OCHF_2$-*o* (*I*b-*III*b)

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TABLE 1. Lipophilicity, ESA, and Hypotensive Properties of Nifedipine, Riodipine, and Their Analogues

| Compound | Lipophilicity | ESA | Effect on hemodynamic parameters in experiments on narcotized cats | | | | |
|---|---|---|---|---|---|---|---|
| | | | dose, mg/kg | systemic AP, % | HR, % | coronary blood flow | |
| | | | | | | change, % | duration, min |
| Nifedipine | 2,90±0,06 | 1,9±0,1 | 0,01 | 10↓ | 13↑ | 61↑ | 15 |
| Ia | 3,61±0,05 | 1,5±0,1 | | | | | |
| IIIa | 2,03±0,07 | 1,3±0,1 | 0,01 | 0 | 0 | 20↑ | 5 |
| | | | 0,1 | 0 | 0 | 60↑ | 30 |
| | | | 1,0 | 0 | 0 | 33↑ | 25 |
| Riodipine | 3,31±0,01 | 1,3±0,1 | 0,01 | 12↓ | 10↑ | 55↑ | 17 |
| Ib | 3,92±0,05 | 1,2±0,1 | 0,01 | 0 | 0 | 7↑ | 12 |
| | | | 0,1 | 28↓ | 1↑ | 15↑ | 17 |
| | | | 1,0 | 32↓ | 27↓ | 3↑ | 5 |
| IIIb | 2,75±0,03 | 1,0±0,1 | 0,01 | 0 | 0 | 0↑ | 0 |
| | | | 0.1 | 0 | 0 | 28↑ | 30 |
| | | | 1.0 | 10↓ | 0 | 33↑ | 10 |

Notes. AP – arterial pressure; HR – heart rate.

## EXPERIMENTAL (CHEMISTRY)

PMR spectra were recorded on a WH 90 instrument, with tetramethylsilane as internal standard. Values found in elemental analyses agreed with those calculated.

4-(o-Difluoromethoxyphenyl)-3,5-dimethoxycarbonyl-1,2,6-trimethyl-1,4-dihydropyridine) (Ib). To 0.1 mole portions of the methyl esters of β-N-methylaminocrotonic and α-(o-difluoromethoxybenzylidene) acetoacetic acids in 20 ml MeOH was added 2 drops HCl, and this was boiled for 4 h and then cooled. A colorless precipitate formed, which was recrystallized from MeOH. Yield 63%, mp 141-143°C; $C_{19}H_{21}F_2NO_5$. PMR spectrum ($CDCl_3$), δ, ppm: 2.34 (s, 6H, 2.6-$CH_3$), 3.12 (s, 3H, 1-$CH_3$), 3.56 (s, 6H, 3.5-$CO_2CH_3$), 5.34 (s, 1H, 4-H), 6.39 (t, 1H, $OCHF_2$, J = 74.5 Hz), 6.99 (s, 4H, Ar).

4-(o-Difluoromethoxyphenyl)-3,5-dimethoxycarbonyl-1,2,6-trimethylpyridinium Perchorate (IIb) was obtained according to [3]; mp 177-179°C (from i-PrOH), yield 72%. PMR spectrum (DMSO), δ, ppm: 2.82 (s, 6H, 2.6-$CH_3$), 3.54 (s, 6H, 3.5-$CO_2CH_3$), 4.16 (s, 3H, 1-$CH_3$), 7.31 (t, 1H, $OCHF_2$, J = 74.5 Hz), 7.04-7.71 (m, 4H, Ar).

4-(o-Difluoromethoxyphenyl)-3,5-dimethoxycarbonyl-1,2,6-trimethyl-1,2-dihydropyridine (IIIb) was obtained by reduction of pyridinium perchlorate IIb according to [3]. Yield 76%, mp 125-127°C (from MeOH). PMR spectrum of a mixture of rotamers, A:B = 5:1 ($CDCl_3$), δ, ppm: 3.08 and 3.20 (s, 3H, 1-$CH_3$), 1.22 (d, 3H, 2-$CH_3$, J = 6.5 Hz), 4.58 and 4.56 (q, 1H, 2-H, J = 6.5 Hz), 3.20 and 3.23 (s, 3H, 3-$CO_2CH_3$), 3.46 and 3.38 (s, 3H, 5-$CO_2CH_3$), 6.47 and 6.27 (t, 1H, $OCHF_2$, J = 75.0 Hz), 2.42 and 2.33 (s, 3H, 6-$CH_3$), 6.84-7.33 (m, 4H, Ar).

4-(o-Nitrophenyl)-3,5-dimethoxycarbonyl-1,2,6-trimethyl-1,2-dihydropyridine (IIIa) was synthesized from Ia according to [6]. Yield 65%, mp 144-146°C (from MeOH).

## EXPERIMENTAL (BIOLOGY)

To determine the partition coefficient (lipophilicity), saturated solutions of compounds in n-octanol (saturated with water) and distilled water (saturated with n-octanol) were prepared. The saturated solutions were left for 24 h at room temperature in the dark, filtered the octanol filtrate was diluted 100-300 fold with ethanol, and spectra were recorded on a Hitachi 557 spectrophotometer. The partition coefficieint (P) was determined using the formula

$$P = \frac{C_{\text{octanol}}}{C_{\text{water}}},$$

where C is the molar concentration of the test substance in octanol and water, respectively.

Hemolysis with hydrochloric acid was done according to [4]. Washed erythrocytes were diluted with 1000 volumes of 0.9% NaCl, giving a suspension containing on average $6 \cdot 10^3$ cells/ml. The optical density of the suspension at 576 nm was close to 1. To 2.4 ml of a washed erythrocyte suspension in a spectrophotometric cuvette was added 25 μl of a $5 \cdot 10^{-3}$ M solution of the test substance in ethanol. This was incubated 20 min at 37°C. Hemolysis was initiated with 0.1 ml of 0.05 N HCl (concentration of HCl in the cuvette was 0.002 N).

The kinetics of the change in optical density at 576 nm were recorded on a Hitachi 557 spectrophotometer. The inhibitory effect (IE) of the compounds was assessed as the relative prolongation of the time to 50% hemolysis: $IE = \tau/\tau_0$, where $\tau$ is time to 50% hemolysis with the test substance, and $\tau_0$ is the time without the compound.

Pharmacologic experiments were carried out on cats (2.4-3.6 kg) narcotized with chloralose (90 mg/kg intraabdominally). Systemic arterial pressure was registered electromanometrically by means of a MPU-0.1 pressure sensor (Nikhon Kohden, Japan), and recorded by a RM-6000 polygraph (Nikhon Kohden). The rate of coronary blood flow as determined by the outflow of venous blood from the coronary venous sinus [2]. Electrocardiograms were recorded on a standard single-lead instrument. All compounds were given intravenously through cannulas inserted in the femoral vein. Substances studied were dissolved in 50% dimethylacetamide, and each dose was given in a volume of 0.1 ml/kg. Prior to the experiment, the same volume of solvent was injected. As a rule, the solvent was not found to significantly effect hemodynamic parameters.

## RESULTS AND DISCUSSION

We compared the following properties of the compounds: lipophilicity, erythrocyte stabilizing activity (ESA), and cardiovascular activity. The experimental results obtained are given in Table 1.

Lipophilicity is frequenty used to characterize compounds; there are data on the correlation of biological activity with the partition coefficient [5]. It was found that in most cases there is a parabolic dependence, i.e., for a given lipophilicity, the biological activity is expressed to a greater degree.

The lipophilicity of 1,4-DHPs is increased by introducing a $CH_3$ group onto the nitrogen atom, whereas N-substituted 1,2-DHPs are more soluble in water and less lipophilic than N-methyl 1,4-DHPs.

Studies of the effects of the compounds on acid hemolysis shows that the inhibitory effect on hemolysis in both series of compounds is decreased by introducing a $CH_3$ group onto the N-atom; the lipophilicity of 1,4-DHPs is increased, whereas N-substituted 1,2-DHPs are more soluble than 1,2-DHPs. However, the ESA of compound III is equal to that of riodipine. In this case, there is no correlation between lipophilicity and ESA, although in the literature there are data on such a dependence in other classes of compounds. For example, in the case of phenolic anesthetics the correlation coefficient between lipophilicity and ESA is equal to 0.963 [7]. For 3,5-diethoxycarbonyl derivatives of 1,4-DHPs with furyl substituents at position 4, there is a parabolic dependence of ESA on lipophilicity, with a maximum at log P = 3.6 [4]. However, in the case of nifedipine there is pronounced ESA with much less lipophilicity. It is likely that such a correlation may only hold for certain series of compounds.

Compounds were tested in pharmacological experiments at doses of 0.01-1 mg/kg. Compound IIIa (an analogue of nifedipine) was not found to affect arterial pressure, and IIIb had some depressor activity only at a dose of 1 mg/kg. Both derivatives of 1,2-DHP were not found to affect heart rate, while having some regional vasodilatory effect, judging from the rate of coronary blood flow.

The greatest coronary dilating activity (as well as ESA) among the 1,2-DHPs is displayed by IIIa. Changing the structure of riodipine by introducing a methyl group onto the nitrogen atom gives rise to weakened vasodilating properties. This activity is also decreased by going to a 1,2-DHP structure (a similar tendency was seen in the case of the inhibitory effect on hemolysis).

The studied 1,2-DHPs are inferior to the corresponding 1,4-DHP analogues in their coronary dilating activity and ESA. However, 1,2-DHPs are less lipophilic than 1,4-DHPs. The high lipophilicity of derivatives of 1,4-DHPs sometimes interferes with their use both as experimental and as medicinal substances.

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# SYNTHESIS AND PSYCHOTROPIC PROPERTIES OF 4-AMINO-3-CYANO-1,2-DIHYDROSPIRO(NAPHTHALENE-2,1'CYCLOPENTANE) DERIVATIVES

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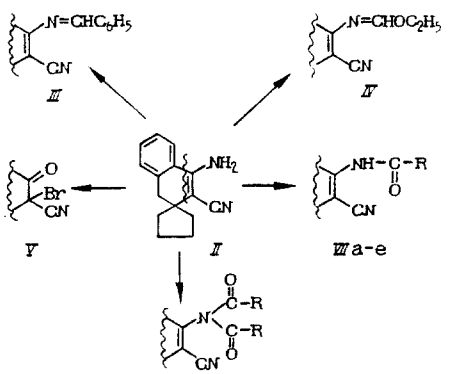
It is reported in the literature that spirocyclic derivatives of naphthalene exhibit a high psychotropic activity [2-4]. It was therefore of interest to develop a method of synthesis of derivatives of 4-amino-3-cyano-1,2-dihydrospiro(naphthalene-2,1'-cyclopentane) and to examine the psychotropic properties of the synthesized compounds.

Condensation of cyclopentylidenemalononitrile with benzylmagnesium chloride gave 1-benzyl-1-dicyanomethylcyclopentane (I), whose cyclization in sulfuric acid led to the formation of 4-amino-3-cyano-1,2-dihydrospiro-(naphthalene-2,1'-cyclopentane) (II).

By condensation of aminonitrile II with benzaldehyde and orthoformic ester, the Schiff base III and the ethoxymethylene compound IV were obtained. Bromination of aminonitrile II in glacial acetic acid and subsequent treatment with a base gave 3-bromo-4-oxo-3-cyano-1,2,3,4-tetrahydrospiro(naphthalene-2,1'-cyclopentane) (V). the reaction of aminonitrile II with carboxylic acid chlorides was studied and the following patterns were discovered. The condensation of the above aminonitrile with acetyl chloride leads to the formation of the diacetylamino compound VI. when chloroacetyl chloride is used, depending on the amount of the reagent, a mono- (VIIa) or disubstituted product (VIb) can be obtained. In the reaction of aminonitrile II with propionyl, benzoyl and phenylacetyl chlorides, the monosubstituted compounds (VIIb-e) are the only products




R=CH3(VIIa), CH2Cl(VIb, VIIa), C2H5(VIIb), C3H7(VIIc), C6H5(VIId), C6H5CH2(VIIe)

The structure of the synthesized compounds was confirmed by IR, PMR and mass spectral and elemental analysis data. The results of the elemental analyses correspond to the calculated data.

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