(MRI-0.5, Nichon-Kogden, Japan) on both carotid arteries. The maximum dp/dt and electrocardiogram were recorded on a RM-6000 polygraph (Nichon-Kogden).

Test compounds were dissolved in 50% dimethylacetamide and injected intravenously (0.05 ml/kg) through a cannule in the femoral vein.

In tests on stimulated spontaneously hypertensive male rats weighing 180-220 g (Okamoto-Aoki strain) [8] aged 7-12 months the arterial systolic pressure was measured with a plethysmograph. Rats were placed in the chamber at 45 ± 5°C for 5 min. The arterial pressure was measured on injection and 0.5, 1, 3, 6, and 24 h after injection of the test substance. Groups of 5-6 rats were used. For tests, a dose of 10 mg/kg of the substance was injected into the stomach as an aqueous suspension in Tween-80 (5 ml/kg). Recordings were made on a Harko Bio-systems physiograph.

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SYNTHESIS AND PHARMACOLOGICAL ACTIVITY OF 4-(2-DIFLUOROMETHOXYPHENYL)-1,4-DIHYDROPYRIDINES

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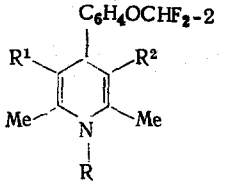
In continuing work [2] in the search for new effective cardiovascular substances in the 1,4-dihydropyridine series, we synthesized 2,6-dimethyl-3,5-dimethoxycarbonyl-4-(2-difluoromethoxyphenyl)-1,4-dihydropyridine (Ih), which possessed high anti-hypertensive activity [3].



Ia-h

a: R = H, R^1 = CN, R^2 = COOMe; b: R = H, R^1 = CN, R^2 = COOEt; c: R = H, $R^1 = R^2$ = CN; d: R = H, $R^1 = R^2$ = Ac; e: R = H, $R^1 = R^2$ = CONHCPh; f: R = H, $R^1 = R^2$ = $CONHC_6H_4OMe$-p; g: R = C_6H_4·OMe-p, $R^1 = R^2$ = COOMe; h: R = H, $R^1 = R^2$ = COOMe.

With the aim of studying the cardiovascular activity and toxicity of 1,4-dihydropyridines as a function of the substituents in positions 3 and 5 of the dihydropyridine ring, the nitriles Ia-c and amides Ie,f of 1,4-dihydropyridine-3,5-dicarboxylic acid were synthe-

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TABLE 1. 1,4-Dihydropyridines Ia-h

Compound	Mp, °C	Found/Calculated, %			Empirical formula	UV spectrum, nm (log ε)	IR spectrum, ν_{max}, cm^{-1} (absorption, %)	PMR Spectrum, δ, ppm	R_f (system)	Yield, %
		C	H	N						
Ia	158—60	61,64 / 61,04	4,87 / 4,82	8,39 / 8,38	$C_{17}H_{16}F_2N_2O_3$	212 (4,2) 228 (4,2) 357 (3,7)	1654 (74) 1672 (80) 1709 (58) 2215 (74) 3118 (60) 3242 (68) 3318 (78)	1,98 s (2-Me) 2,26 s (6-Me) 3,45 s (OMe) 4,94 s (4-H) 5,78 s (NH) 6,45 q (CHF_2) J^1=73 Hz, J^2=75 Hz 7,14 m (ArH)	0,34 (A)	45
Ib	129—31	61,31 / 62,06	5,35 / 5,20	8,07 / 8,04	$C_{18}H_{18}F_2N_2O_3$	212 (4,2) 228 (4,2) 357 (3,6)	1658 (77) 1698 (78) 2208 (75) 3105 (67) 3235 (68) 3326 (76)	1,0 t (CH_2Me) 1,96 s (2-Me) 2,26 s (6-Me) 3,92 q (CH_2Me) 4,94 s (4-H) 5,71 s (NH) 6,45 q (CHF_2) J^1=73 Hz; J^2=76 Hz 7,1 m (ArH)	0,37 (A)	51
Ic	174—5	63,54 / 63,78	4,21 / 4,35	13,66 / 13,95	$C_{16}H_{13}F_2N_3O$	214 (4,6) 348 (3,8)	1661 (62) 2217 (79) 3124 (65) 3241 (71) 3292 (68)	1,84 s (2,6-Me) 4,67 s (4-H) 6,45 t (CHF_2) J=73 Hz 6,5 s (NH) 7,25 m (ArH)	0,20 (A)	47
Id	200—1	63,91 / 64,27	5,80 / 5,99	4,47 / 4,17	$C_{18}H_{20}F_2NO_3$	206 (4,3) 257 (4,2) 380 (3,9)	1628 (78) 1675 (81) 3184 (77) 3180 (77) 3304 (78)	2,14 s (2,6-Me) 5,21 s (4-H) 7,04 m (ArH) 7,16 t (CHF_2) J=74,2 Hz 8,84 (NH)	0,18 (B)	49
Ie	197—9	68,4 / 68,7	5,5 / 5,2	7,9 / 8,6	$C_{28}H_{25}F_2N_3O_3$	206 (4,7) 165 (4,3) 354 (3,8)	1658 (56) 1677 (62) 3300 (74) 3425 (68)	2,04 s (2,6-Me) 5,21 s (4-H) 6,76 t (CHF_2) J=75,7 Hz 6,84—7,53 (ArH) 9,15 s (NHCO)	0,13 (A)	57
If	181—4	65,1 / 65,3	5,3 / 5,7	7,6 / 7,6	$C_{30}H_{31}F_2N_3O_5$	211 (4,7) 262 (4,3) 291 (4,3) 353 (4,1)	1640 (78) 1690 (43) 3197 (68) 3302 (66) 3420 (61)		0,19 (B)	50
Ig	136—8	62,8 / 63,3	5,2 / 5,5	2,8 / 3,0	$C_{35}H_{36}F_2O_6$	208 (4,4) 242 (4,4) 348 (3,7)	1645 (75) 1685 (86) 1700 (82)	1,96 s (2,6-Me) 3,58 s (3,5-OMe) 3,78 s (OMe) 5,41 s (4-H) 6,51 t ($OCHF_2$) J=75 Hz 6,95—7,24 (ArH)	0,82 (A)	58

TABLE 2. Acute Toxicity and Influence on Hemodynamic Parameters of 1,4-Dihydropyridines Ia-h

Compound	Dose, mg/kg (intravenously)	Hypotensive activity, %		Coronary-dilating activity on cats (effect, %)	Prolongation, min	Instantaneous heart volume, %	Frequency of heart contractions, %	LD_{50}, mg/kg (intraperitoneally in mice)
		acute experiments on cats	experiments on SHR (10 mg/kg)					
Ia	0,05	—	...	20↑	15	25↑	6↑	>5000
	1,0	25↓	...	26↑	15	23↓	4↓	
Ib	0,05	—	—	10↑	15	16↑	7↑	>5000
	1,0	10↓	—	6↑	5	24↓	14↓	
Ic	0,1	—	—	7↑	9	41↑	—	
	1,0	12↑	...	13↑	14	27↑	5↓	...
Id	0,1	20↓	—	15↑	10	31↓	4↓	...
	1,0	47↓	—	46↑	21	42↓	15↓	
Ie	0,1	—	...	10↑	5	...	—	>5000
	1,0	—	...	15↑	7	...	—	
If	0,1	8↑	—	8,6↑	7	13↑	3↑	>5000
	1,0	8↑	—	33↑	38	21↑	1↑	
Ig	0,1	20↑	...	3↑	2	11↓	3↓	>5000
	1,0	20↓	...	6↑	3	26↑	21↓	
Nifedipine	0,05	23↓	44	94↑	33	46↓	42↓	185
Ih	0,024	30↓	50	...	...	...	...	395

sized, as well as 3,5-diacetyl-4-(2-difluoromethoxyphenyl)-1,4-dihydropyridine (Id) and an N-substituted-1,4-dihydropyridine derivative (Ig).

The nitriles Ia-c were obtained by condensation of β-aminocrotonitrile with the corresponding aldehyde and β-aminocrotonate ester (for the case of Ia and b) in acetic acid solution. It is necessary to add the aminocrotonitrile to the reaction mixture last, since it easily undergoes a self-condensation reaction [5] to form 4,6-dimethyl-5-cyano-2-pyridone.

Compound Ig was formed by condensation of methyl acetoacetate, 2-difluoromethoxybenzaldehyde, and p-anisidine.

All of the synthesized 1,4-dihydropyridines were colorless, crystalline materials except for the yellow Id. UV spectra of Ia-h were analogous to the spectra of other 4-aryl-1,4-dihydropyridines [2]. Introduction of acetyl groups into positions 3 and 5 (Id) produced a significant bathochromic shift of the long wavelength absorption band ($\Delta \sim 15$ nm) relative to Ia. Other substituents in positions 3 and 5 (Ia-c, e and f) showed a hypsochromic shift of the long wavelength band (Δ = 5-12 nm) compared to the ester groups.

The structures of the dihydropyridines Ia-h also were verified by IR and PMR spectra (Table 1). In the PMR spectra of compounds Ia and b containing unequal substituents in the 3 and 5 positions and 2,6-dimethyl groups show two separate signals at δ 1.98 and 2.26 ppm; the $-CHF_2$ proton in Ia and b is a quartet because of the non-equivalence of the fluorine atoms.

Compounds Ia-h are stable in the solid state. In alcoholic solution ($c = 5 \cdot 10^{-5}$ M), Ia-d did not show a change in the UV spectra over one month, while amides Ie and f oxidized 13-25% in the same period. The lower stability of 1,4-dihydropyridines containing amide groups instead of esters is recorded in the literature [1].

In a study of the biological activity of the synthesized compounds Ia-g (the known coronary dilator nifedipine [4] was included for comparison), it was found (Table 2) that they possessed insignificant coronary dilating and hypotensive action, but three of the compounds (Ic,f,g) showed a pressor effect.

Compounds Ic,f,g insignificantly influenced the frequency of cardiac contraction, but produced an increase in the instantaneous heart volume and coronary flow, while Ic more strongly influenced the instantaneous heart volume, and If more strongly increased the coronary flow for a longer time. Compounds Ia and b at lower doses increased, and in larger doses decreased the instantaneous heart volume. The coronary dilating effect was the least significant for the N-substituted 1,4-dihydropyridine Ig, and the most significant and prolonged for compounds Id and f. Compound Ie in the doses used did not influence the pulse frequency, and compounds Ia and b in doses of 0.1 mg/kg somewhat increased, and in a dose of 1 mg/kg decreased the frequency of heart contractions. In experiments on spontaneously hypertensive rats the studied compounds were found not to be hypotensive.

Thus, the substitution of ester groups in positions 3 and 5 of the dihydropyridine ring by other substituents leads to a decrease both in hypotensive and coronary-dilating activity, and the hypotensive activity is decreased the most. The toxicity of the compounds is significantly decreased in this case. For some compounds, the appearance of a pressor effect was noted, which was also observed recently in a series of other derivatives of 1,4-dihydropyridines [6].

EXPERIMENTAL CHEMISTRY

IR spectra were recorded on a Perkin-Elmer instrument in Nujol suspension, UV spectra were recorded on a Specord UV-Vis instrument in ethanol ($c = 5 \cdot 10^{-5}$ M), and PMR spectra were obtained on a Perkin-Elmer instrument in $CDCl_3$ with TMS as standard. The course of the reactions and the purification of the synthesized compounds was monitored by TLC on Silufol UV-254 plates in $CHCl_3$-ethylacetate-hexane (1:1:1, A) and cyclohexane-ethyl acetate (1:1, B).

2,6-Dimethyl-3,5-dicyano-4-(2-difluoromethoxyphenyl)-1,4-dihydropyridine (Ic). A mixture of 4.85 g (0.028 mole) of 2-difluoromethoxybenzaldehyde and 4.6 g (0.056 mole) of β-aminocrotononitrile in 30 ml of glacial acetic acid was boiled for three hours and poured into ice water. The residue was crystallized from 50% ethanol (Cf. Table 1).

2,6-Dimethyl-3-cyano-5-methoxycarbonyl-4-(2-difluoromethoxyphenyl)-1,4-dihydropyridine (Ia). A mixture of 4 g (0.035 mole) of methyl β-aminocrotonate, 2.83 g (0.035 mole) of β-aminocrotononitrile, and 6 g (0.035 mole) 2-difluoromethoxybenzaldehyde in 30 ml of glacial acetic acid was boiled for 2 h. The mixture was poured into ice water, extracted with ether (3 × 30 ml), and dried with anhydrous Na_2SO_4. The ether was distilled under vacuum, and the oily residue was crystallized from petroleum ether and recrystallized from 50% ethanol (Cf. Table 1).

Ib was prepared in an analogous manner.

2,6-Dimethyl-4-(2-difluoromethoxyphenyl)-1,4-dihydropyridine-3,5-dicarboxyanilide (Ie). A mixture of 1.72 g (0.01 mole) of 2-difluoromethoxybenzaldehyde, 3.54 g (0.02 mole) of acetoacetanilide, 2 ml of 25% aqueous ammonia, and 6 ml of MeOH was boiled for 3 h. A white crystalline precipitate formed upon cooling, which was recrystallized from 50% aqueous ethanol (Cf. Table 1).

If was prepared analogously.

N-(p-Methoxyphenyl)-2,6-dimethyl-3,5-dimethoxycarbonyl-4-(2-difluoromethoxyphenyl)-1,4-dihydropyridine (Ig). A mixture of 3.46 g (0.02 mole) of 2-difluoromethoxybenzaldehyde, 3.44 g (0.02 mole) of p-anisidine, and 4.64 g (0.04 mole) of methyl acetoacetate in 30 ml of ethanol was boiled for 13 h. The colorless crystalline precipitate separated after cooling (Cf. Table 1).

2,6-Dimethyl-3,5-diacetyl-4-(2-difluoromethoxyphenyl)-1,4-dihydropyridine (Id). A mixture of 3.46 g (0.02 mole) of 2-difluoromethoxybenzaldehyde, 3.9 ml (0.04 mole) of acetylacetone, and 3 ml of 25% aqueous ammonia in 5 ml of ethanol was boiled for 3 h. The yellow precipitate formed after cooling (Cf. Table 1).

EXPERIMENTAL PHARMACOLOGY

In experiments on narcotized, chloralosed (90 mg/kg, intraperitoneally) cats of both sexes weighing 2.4-3.7 kg with open chest cavities a cannula was introduced into the coronary venous sinus through the right auricle and the venous blood flow was measured. The systemic arterial pressure was registered electromanometrically from the carotid artery (pressure transducer MRU-0.5) and with a computer dp/dt_{max} (mm Hg/sec) was calculated for the pressure. Electrocardiograms were recorded for I by standard methods. The instantaneous heart volume was recorded electromagnetically with a Nichon Kogden (Japan) flowmeter with the transducer positioned on the rising part of the aorta. An RM-6000 polygraph (Nichon Kogden, Japan) was used for recording. The study materials were dissolved in 50% dimethylacetamide solution and introduced intravenously in a volume of 0.05 mg/kg through the cannula tied into the femoral vein.

In experiments on spontaneously hypertensive rats (SHR) of the Okamoto-Aoki strain, 6-8 months old (180-205 g), the systolic arterial pressure was registered by plethysmography. The rats were placed in chambers warmed to 45 ± 5°C in 5 min. The systolic arterial pressure

was measured upon introduction and 0.5, 1, 3, 6, and 25 h after introduction of the substances, which were used at a dose of 10 mg/kg. Five to six rats were used to study each dose. Recordings were made on a physiograph (DMP-4B, Harko Bio-systems, USA).

The compounds were introduced into the stomach in a volume of 5 ml/kg as aqueous suspensions prepared with Tween-80 (0.05 ml of 6% Tween per 5 ml of material).

The acute toxicity was studied on both sexes of white mice weighing 19-23 g by intraperitoneal injection. Each dose was studied with 6 mice, and the mice were observed for 10 days after treatment. Acute toxicity was obtained by the Litchfield-Wilcoxon method.

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SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF ACETYLENE DERIVATIVES OF AZABICYCLONONANE

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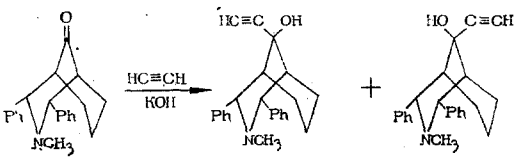
Acetylene-containing compounds with a variety of biological activities including antimicrobial are widely known since they are often more active, less toxic, and more easily assimilated by the organism than the olefinic compounds [5]. The decreased toxicity and strong adsorption and metabolism of some drugs apparently is connected with the presence of the triple bond in these molecules.

In a synthesis program conducted with the aim of obtaining preparations with high activity and low toxicity, we carried out the synthesis of acetylenic alcohols, their acetates, and diacetylene derivatives.



I II III

The isomeric acetylenic derivatives were synthesized in a Favorskii reaction by the interaction of 2,4-diphenyl-3-methyl-3-azabicylo[3,3,1]-nonan-9-one (I) with acetylene in the presence of potassium hydroxide in liquid ammonia.

The isomeric 2,4-diphenyl-3-methyl-9-ethynyl-3-azabicyclo[3,3,1]nonan-9-ols (II and III) were stable and usually crystalline substances, easily soluble in organic solvents (ethanol, acetone, benzene, dioxane) and insoluble in water.

The 2,4-diphenyl-3-methyl-9-ethynyl-3-azabicyclo[3,3,1]nonan-9-yl acetates (IV and V) were prepared by the interaction of the isomeric acetylenic alcohols I and II with acetic anhydride; the reaction products were crystalline materials, soluble in organic solvents and insoluble in water.

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