S-(2-Methoxycarbonylethyl)-3-(4-methoxyphenyl)-5-phenyl-2-thioniabicyclo[4.4.0]decane Chloride Hydrate (XIII). From 0.5 g (0.0015 mole) of (III) there was obtained by the method described above 0.46 g (67%) of the chloride (XIII), mp 103-105°C.

S-(2-Carboxyethyl)-3,5-diphenyl-2-thioniabicyclo[4.4.0]decane Hexachloroplatinate (XIV). The chloride (XII) (0.2 g, 0.047 mmole) was added to a mixture of 2 ml of glacial acetic acid and 0.2 ml of acetic anhydride containing 0.41 g (0.1 mmole) of chloroplatinic acid. After 3 days, the reaction mixture was diluted with ether, and the oil which separated was dissolved in methylene chloride. Addition of hexane precipitated crystals of the salt (XIV). Yield 0.14 g (26%), mp 215°C (decomp.).

S-(2-Methoxycarbonylethyl)-3,5-diphenyl-2-thioniabicyclo[4.4.0]decane Hexachloroplatinate (XV). From 0.2 g of the chloride (XIII) there was obtained as described above 0.17 g (32%) of the hexachloroplatinate (XV), mp 159-161°C (decomp.).

EXPERIMENTAL BIOLOGICAL SECTION

The antiphage activity of the compounds was determined in a phage-bacterium system (DNA-containing phage T_6 and *E. coli*, and RNA-containing phage Ms-2 and *E. coli* HFrl). The number of surviving phage particles was determined by Grazia's agar slope method. Antiphage activity was expressed as percentage inactivation, calculated by the formula [3]: $[1 - (N_o/N_k)] \cdot 100\%$, where N_o is the number of surviving phage particles in the test, and N_k the number of surviving phage particles in the control.

Antimicrobial activity was measured by twofold serial dilution in Hottinger's bouillon of pH 7.2 with respect to the standard test microbes: *Staph. aureus* 209, *E. coli* 675, *Proteus vulgaris* 38, *Ps. aeruginosa* 165, *Candida albicans* 45. All the test compounds were dissolved in DMF followed by dilution with sterile distilled water.

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SYNTHESIS AND PHARMACOLOGICAL ACTIVITY OF 4-ARYL-1,4-DIHYDROPYRIDINES

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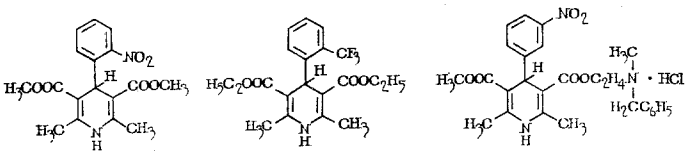
Derivatives of 1,3-dihydropyridine are known [1, 2] to exert a marked action on the cardiovascular system. The most active are the 4-aryl-1,4-dihydropyridines; these include the vasodilator nifedipine (adalat, corinfar)* — 2,6-dimethyl-3,5-dimethoxycarbonyl-4(o-nitrophenyl)-1,4-dihydropyridine [3], and the hypotensive agent SKF 24260 — 2,6-dimethyl-3,5-diethoxycarbonyl-4-(o-trifluoromethylphenyl)-1,4-dihydropyridine [4]. To these nicardipin (perdipin), 4-(3-nitrophenyl)-3-[2-(N-benzyl-N-methylamino)]ethoxycarbonyl-5-methoxycarbonyl-1,4-dihydropyridine, has recently been added [5]. The above compounds have a number of drawbacks: instability (nifedipine), high toxicity, and undesirable side effects.



Nifedipine (Fenigidin) SKF 24260 Nicardipin

*This compound was developed under the name "fenigidin" at the Institute of Organic Synthesis, Academy of Sciences of the Latvian SSR, and approved for use.

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TABLE 1. 1,4-Dihydropyridines Ia-e, and g-m

Compound	mp, deg C	Found/calculated, %			Empirical formula	UV spectra, nm (log ε)	IR spectra, cm^{-1} (absorption)	NMR spectra, δ ppm	R_f (system)	Yield, %
		C	H	N						
Ia	175—6	58,2 / 58,5	5,0 / 4,9	3,8 / 3,8	$C_{18}H_{16}F_3NO_4$	204 (4,2) 238 (4,2) 365 (3,7)	1624 (48) 1659 (46) 1697 (75) 3378 (70)	2,27s ($2,6\text{-}CH_3$) 3,57t (OCH_3) 4,96s (4H) 5,83s (NH) 7,31m (Ar, H)	0,24 (A) 0,54 (B)	46,8
Ib	144—5	60,0 / 60,4	5,6 / 5,3	3,7 / 3,5	$C_{20}H_{22}F_3NO_4$	204 (4,2) 240 (4,2) 360 (3,7)	1615 (73) 1647 (62) 1680 (78) 1700 (74) 3337 (63)	1,16t (CH_2CH_3) 2,22s ($2,6\text{-}CH_3$) 4,08q (CH_2CH_3) 5,57s (4H) 6,15s (NH) 7,41m (Ar, H)	0,32 (A)	65,0
Ic	124—8	60,8 / 60,4	5,7 / 5,3	3,7 / 3,5	$C_{20}H_{22}F_3NO_4$	211 (4,3) 240 (4,4) 366 (4,0)	1612 (80) 1642 (73) 1678 (82) 1698 (80) 3323 (82)	1,15t (CH_2CH_3) 2,28s ($2,6\text{-}CH_3$) 4,03q (CH_2CH_3) 4,96s (4H) 5,67s (NH) 7,37m (Ar, H)	0,47 (B)	48,2
Id	150—2	52,6 / 52,1	4,9 / 4,8	3,5 / 3,0	$C_{20}H_{22}F_3NO_6S$	205 (4,4) 238 (4,3) 286 (3,9) 375 (3,7)	1105 (88) 1308 (78) 1616 (66) 1645 (61) 1695 (82) 3334 (73)	1,17t (CH_2CH_3) 2,25s ($2,6\text{-}CH_3$) 4,08q (CH_2CH_3) 6,07s (NH) 6,18s (4H) 7,88m (Ar, H)	0,22 (A)	35,0
Ie	116—7	50,7 / 50,8	4,7 / 3,6	3,3 / 3,0	$C_{20}H_{17}F_3NO_7$	207 (4,6) 238 (4,6) 364 (4,1)	1107 (80) 1308 (78) 1616 (66) 1641 (56) 1682 (71) 1697 (70) 3345 (68)	1,0t (CH_2CH_3) 2,17s ($2,6\text{-}CH_3$) 3,93q (CH_2CH_3) 5,1s (4H) 7,3m (Ar, H) 8,86s (NH)	0,44 (B)	26,3

TABLE 1 (continued)

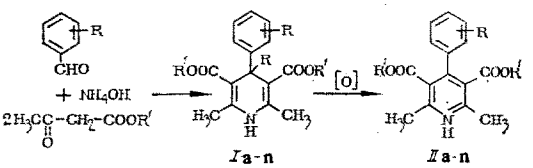
Compound	mp, deg C	Found/Calculated, %			Empirical formula	UV spectra, *nm* (*log* ϵ)	IR spectra, cm^{-1} (absorption)	NMR spectra, δ ppm	R_f (system)	Yield, %
		C	H	N						
Ig	127—8	60,0 / 60,1	6,1 / 5,8	3,7 / 3,5	$C_{20}H_{23}F_2NO_5$	206 (4,4) 241 (4,2) 367 (3,7)	1212 (65) 1620 (40) 1641 (35) 1672 (57) 3332 (42)	1,13t (CH_2CH_3) 2,23 s (2,6-CH_3) 3,98q (CH_2CH_3) 5,2 s (4H) 5,82s (NH) 7,01t (CHF_2; J= =37,4 Hz)	0,62 (A)	46,3
Ih	158—61	58,3 / 58,8	5,1 / 5,2	3,9 / 3,8	$C_{18}H_{19}F_2NO_5$	207 (4,2) 241 (4,3) 362 (3,8)	1216 (84) 1623 (62) 1643 (60) 1694 (80) 3336 (72)	2,25s (2,6-CH_3) 3,56s (OCH_3) 4,9 s (4H) 5,71 s (NH) 6,35t (CHF_2; J=74,0 Hz) 6,81—7,22m (Ar, H)	0,75 (C)	55,6
Ii	86—87	60,5 / 60,1	5,8 / 5,8	3,6 / 3,5	$C_{20}H_{23}F_2NO_5$	205 (4,1) 238 (4,3) 362 (3,8)	1212 (88) 1630 (66) 1647 (74) 1680 (74) 1702 (66) 3318 (72)	1,28t (CH_2CH_3) 2,33 s (2,6-CH_3) 4,1 q (CH_2CH_3) 4,9 s (4H) 6,6 s (CHF_2; J= =73,5 Hz) 7,14m (Ar, H) 8,15s (NH) (CCl_4 + ДМСО)	0,57 (A) 0,62 (C)	54,0
Ij	132—4	58,7 / 58,3	5,7 / 5,6	3,3 / 3,4	$C_{20}H_{23}F_2NO_4S$	206 (4,4) 240 (4,2) 371 (3,7)	1658 (86) 1714 (78) 3362 (89)	1,20t (CH_2CH_3) 2,27 s (2,6-CH_3) 4,08q (CH_2CH_3) 5,51s (4H) 5,75s (NH) 6,82t (CHF_2; J= =58,9 Hz) 7,0—7,6 m (Ar, H)	0,34 (A)	42,7

TABLE 1 (continued)

Compound	mp, °C	Found / Calculated, % C	H	N	Empirical formulas	UV spectra, mm (log ε)	IR spectra, cm^{-2} (absorption)	NMR spectra, δ ppm	R_f (system)	Yield, %
Ik	180—1	51,6 / 52,0	4,6 / 4,6	3,8 / 3,4	$C_{18}H_{19}F_2NO_6S$	205 (4,4) 238 (4,3) 285 (3,8) 378 (3,6)	1118 (74) 1332 (80) 1625 (49) 1650 (70) 1675 (75) 1703 (72) 3386 (72)	2,22 t (2,6-CH_3) 3,55 s (OCH_3) 5,78 s (4H) 6,12 s (NH) 6,93 t (CHF_2; J = 54,8 Hz) 7,65 m (Ar, H)	0,16 (A)	68,0
Il	151—2	54,3 / 54,2	5,2 / 5,2	2,9 / 3,1	$C_{20}H_{23}F_2NO_6S$	206 (4,3) 240 (4,3) 283 (3,8) 375 (3,8)	1163 (83) 1332 (80) 1632 (39) 1654 (50) 1678 (77) 1706 (67) 3492 (74)	1,10 t (CH_2CH_3) 2,20 s (2,6-CH_3) 4,03 q (CH_2CH_3) 5,9 s (NH) 6,09 s (4H) 7,1 t (CHF_2; J = 55 Hz) 7,62 m (Ar, H)	0,48 (B) 0,18 (A) 0,2? (B)	47,5
Im	159—60	54,6 / 54,2	5,3 / 5,2	3,5 / 3,1	$C_{20}H_{23}F_2NO_6S$	203 (4,2) 243 (4,2) 288 (3,6) 374 (3,6)	1122 (70) 1328 (62) 1624 (45) 1650 (46) 1700 (70) 3368 (64)	1,12 t (CH_2CH_3) 2,29 s (2,6-CH_3) 4,05 q (CH_2CH_3) 5,06 s (4H) 6,1 t (CHF_2; J = 53,5 Hz) 7,68 m (Ar, H)	0,23 (A)	43,0

In a search for cardiovascular agents without these disadvantages, we have synthesized a number of 4-aryl-1,4-dihydropyridines (Ia-n) with fluorine-containing substituents [6, 7]; one of the compounds — 2,6-dimethyl-3,5-dimethoxycarbonyl-4-(o-difluoromethoxyphenyl)-1,4-dihydropyridine (If) — is a hypotensive agent [7].

The 1,4-dihydropyridines Id-m with fluorinated aryl substituents were obtained by the condensation of acetoactic acid esters of the corresponding aldehyde [8] with ammonia in ethanol.



Ia-n IIa-n

a: R = *o*-CF_3; R^1 = Me;
b: R = *o*-CF_3; R^1 = Et (SKF24260);
c: R = m-CF_3; R^1 = Et;
d: R = *o*-SO_2CF_3; R^1 = Et;
e: R = *o*-OSO_2CF_3; R^1 = Et;
f: R = *o*-$OCHF_2$; R^1 = Me;
g: R = *o*-$OCHF_2$; R^1 = Et;
h: R = p-$OCHF_2$; R^1 = Me;
i: R = p-$OCHF_2$; R^1 = Et;
j: R = *o*-$SCHF_2$; R^1 = Et;
k: R = *o*-SO_2CHF_2; R^1 = Me;
l: R = *o*-SO_2CHF_2; R^1 = Et;
m: R = p-SO_2CHF_2; R^1 = Et;
n: R = *o*-NO_2; R^1 = Et **(adalat).**

All the 1,4-dihydropyridines synthesized were colorless, crystalline substances. The introduction of an electron acceptor on the aryl substituent caused a bathochromatic shift of the long-wave UV absorption bands: from 359 nm for 2,6-dimethyl-3,5-diethoxycarbonyl-4-phenyl-1,4-dihydropyridine to 375 nm for Id. In addition, the spectra of the compounds containing SO_2CHF_2 and SO_2CF_3 groups contain a fourth absorption maximum at about 280 nm.

The infrared spectra of compounds Ia-n are similar to the spectra of the 4-aryl-1,4-dihydropyridines [9]; compounds with an SO_2 group have sharp bands at 1130 and 1300 cm^{-1}, characteristic of symmetrical and asymmetrical vibrations of the SO_2 group. The ether link of the $OCHF_2$ group absorbs at 1200^{-1}.

The structure of the dihydropyridines Ia-n was also confirmed from NMR spectra. The proton of the CHF_2 group gives a triplet centered at about 6.1-7.1 ppm (Table 1).

The dihydropyridines Ia-n are stable in the solid state; after storage for 1.5 years, their UV spectra are unchanged. Solutions of compounds Ik-m in alcohol ($5 \cdot 10^{-5}$ moles) are oxidized in about 10 days; in the UV spectra, the long-wave maxima and the maxima at 240 nm disappear, and the spectra take the form characteristic for the corresponding derivatives of the pyridines IIa-n. The latter were obtained by the oxidation of the 1,4-dihydropyridines Ia-n with sodium nitrite in acetic acid. At higher concentrations ($1.5 \cdot 10^{-2}$ moles), the UV spectra does not change even after 45 days. Compounds Id and e are the most stable to oxidation; at a concentration of $5 \cdot 10^{-5}$ moles, the UV spectra change only after 2 months. The remaining dihydropyridines are even more stable, and in dilute solution in ethanol are not oxidized within 10-12 months.

A study of the biological activity of the compounds Ia-n (the known compounds Ia-c and n were also studied for comparison) showed that they exhibit coronary-dilating and hypotensive action.

TABLE 2. Effect of the 1,4-Dihydropyridines Ia-n on Hemodynamics, Acute Toxicity, and Coefficient of Distribution

Compounds	Tests on cats (0.1 mg/kg intravenously)				Hypotensive activity of SHR (10 mg/kg), mm Hg	LD_{50}, mg/kg (intraperitoneally)	log P ($M \pm m$)
	Increase in flow of blood from the coronary sinus, %	duration of effect, min	change in pulse rate, %	hypotensive activity, ED_{30}, mg/kg			
Ia	8	3	No change	0,052	28	700	4,01±0,08
Ib	72	15	13	0,022 (0,005—0,039)	27	38 (30—50)	4,46±0,04
Ic	10	5	15	0,04	17	500	4,87±0,02
Id	—	—	—	0,18 (0,16—0,2)	—	42 (35—50)	4,06±0,11
Ie	40	15	23	0,07 (0,02—0,12)	—	96 (67—136)	4,62±0,02
If	—	—	—	0,024 (0,018—0,03)	50	395 (250—466)	3,28±0,08
Ig	88	15	14	0,017 (0,015—0,019)	66	110 (84—143)	3,89±0,07
In	15	11	No change	1,45	56	1000	3,74±0,08
Ii	13	14	7	0,39 (0,26—0,52)	—	1000	3,33±0,09
Ij	110	30	25	0,037 (0,024—0,05)	41	125 (105—147)	4,09±0,06
Ik	58	6	12	0,05 (0,03—0,07)	—	49 (42—56)	2,87±0,02
Il	69	14	No change	0,018 (0,01—0,026)	28	355 (234—536)	3,58±0,04
Im	5	4	12	1,2 (0,2—2,2)	—	—	3,34±0,02
In	70—120	120—130	11	0,06	85	185 (119—287)	—

Note. Variation limits are given in parentheses.

Compound Ij caused a marked increase in the rate of flow of blood in the coronary sinus (Table 2). In doses of 0.1 mg/kg, this compound more than doubles the rate of flow of blood from the coronary sinus over a period of 30 minutes, exhibiting an action like that of adalat but of shorter duration. Compound Ij had a greater effect on the coronary bloodstream than SKF 24260. Substitution of the $SCHF_2$ group sulfur atom by oxygen led to a decreased effect on the flow of blood from the coronary sinus (compare Ig and Ij); the hypotensive activity is increased. Replacement of an oxygen atom by an SO_2 group decreases the hypotensive activity (compare If and Ik) and considerably increases the toxicity. In compounds with an ethoxycarbonyl group, the SO_2 shows no such effect on the hypotensive activity (Ig and Il); the coronary-dilating action of these compounds is also the same and differs little from that of SKF 24260.

Compounds Ih, i, and m, with p-substituents in the aryl group, have considerably less effect on the flow of blood from the coronary sinus and exhibit less hypotensive activity than compounds with an o-substituent; the p-substituted compounds are also less toxic.

In tests on cats, small doses of compounds Ia-n lowered the blood pressure and in tests on spontaneously hypertensive rats exhibited a hypotensive effect. The compounds had very little effect on respiration, and the majority did not decrease the rate of cardiac contractions (Table 2).

The lipophilic nature of the compounds, expressed as log P (P is the coefficient of distribution) is between 2.87 and 4.46. For compounds with an ethoxycarbonyl group, the toxicity increases with increasing lipophilicity; compounds with a methoxycarbonyl group exhibit the reverse effect. Methyl esters are less lipophilic than ethyl ethers with the same substituent (see Table 2).

Thus, some of the compounds studied were comparable to adalat and superior to SKG 24260 in coronary-dilating action. In hypotensive activity, some of the compounds were more active than adalat and equalled SKF 24260; moreover, they were considerably less toxic.

EXPERIMENTAL CHEMICAL SECTION

Infrared spectra of the compounds as suspensions in Nujol were taken on a UR-20 (GDR) instrument, UV-spectra on a "Specord UV-VIS" using ethanol as solvent ($5 \cdot 10^{-5}$ moles), NMR spectra were taken on a "Perkin-Elmer" using tetramethylsilane in $CDCl_3$ as a standard. Monitoring of the course of the reaction and identification of the compounds synthesized was carried out by TLC using Silufol UV-254 plates in chloroform–ethyl acetate–hexane, 1:1:3 (A), chloroform–ethyl acetate–hexane, 1:1:1 (B), and hexane-acetone, 1:1 (C).

2,6-Dimethyl-3,5-dimethoxycarbonyl-4-(o-difluoromethylsulfonylphenyl)-1,4-dihydropyridine (Ik). A mixture of 1.1 g (0.006 mole) of o-difluoromethylsulfonylbenzaldehyde, 1.38 g (0.012 mole) of methyl acetate, 2 ml of 25% aqueous ammonia, and 5 ml of ethanol was refluxed. After cooling, a precipitate separated and was recrystallized from 50% ethanol (see Table 1).

The remaining dihydropyridines Ia-j, l, and m were prepared in the same way.

2,6-Dimethyl-3,5-diethoxycarbonyl-4-(o-difluoromethoxysulfonylphenyl)pyridine (IIm). To a solution of 0.3 g of I in 10 ml of glacial acetic acid at 50-60°C was added in small portions 0.4 g of sodium nitrite. After all the sodium nitrite had been added, the mixture was heated for 1 h on the steam bath, followed by 2 h at room temperature. It was then poured into 100 ml of water and brought to pH 10.0-11.0 by the addition of 25% aqueous ammonia. The aqueous solution was extracted with ether (3 × 20 ml), and the ether extract washed with water, dried with anhydrous sodium sulfate, and evaporated using a vacuum water pump. The residue was recrystallized from ethanol to give 1.9 g (63.4%) of IIm, with mp 97-98°C. UV spectrum, λ_{max}, nm (log ε): 203 (4.3), 271 (3.6). IR spectrum, cm^{-1} (% absorption): 1568 (54), 1725(80). R_f (system 1): 0.77. Found, %: C 53.89; H 4.70; N 3.23. $C_{20}H_{21}F_2NO_6S$. Calculated, %: C 54.42; H 4.79; N 3.0.

Determination of the Distribution Coefficient in Octanol–water. Saturated solutions of the compounds in octanol (saturated with water) and in water (saturated with octanol) were prepared. The concentrations of the solution was obtained from the formula $c = (D \cdot \alpha)/\varepsilon$, where c is the concentration of the solution; D is the optical density of dilution; α is the dilution; ε is the extinction coefficient. The coefficient of distribution was determined from the formula

$$P = \log \frac{c \text{ in octanol}}{c \text{ in water}}$$

EXPERIMENTAL PHARMACOLOGICAL SECTION

Tests were carried out on cats narcotized with chlorazole (90 mg/kg intraperitoneally) weighing 2.4-3.8 kg. Blood pressure in the carotid artery was recorded electromanometrically. Transthoracic EKG and respiration were recorded by electrodes inserted under the skin of the thorax on a level with the fourth rib. All recordings were made on a Narko Bio-System physiograph.

Blood flow from the coronary sinus was measured by the method of N. V. Kaverin (1958).

The compounds were dissolved in 50% dimethylacetamide and injected intraperitoneally through a cannula inserted into the femural vein.

The systolic arterial pressure was measured on spontaneously hypertensive rats, SHR strain, using a pneumatic transducer pulse, and recorded on a physiograph. One dose of the compound (10 mg/kg) was tested on 5-7 rats. The test compounds were suspended in an isotonic solution of sodium chloride with Tween 80 and injected into the stomach in doses of 5 ml/kg.

Acute toxicity was studied on female white mice weighing 19-23 g; compounds were injected intraperitoneally into six mice. The animals were observed for 10 days after injection. Acute toxicity (LD_{50}) was determined by the method of Litchfield and Wilcoxon.

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SYNTHESIS AND ANTITUMOR ACTION OF SOME PYRIDO[2,3-b]PYRAZINES

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One of the goals of antitumor research is the synthesis of folic acid antimetabolites [1]. In earlier works on the synthesis of potential folic acid antagonists — compounds with pyrido[2,3-b]pyrazine [2, 3] or pyrido[3,4-b]pyrazine [4] systems — it was reported that some derivatives of pyrido[2,3-b]pyrazine exhibit antitumor activity [3, 5].

The present work describes the synthesis and antitumor action of some new derivatives of pyrido[2,3-b]pyrazine, prepared by the recently developed method for preparing 2,3-diaminopyridine derivatives [6].

The 6-R-pyrido[2,3-b]pyrazines (Ia-d) were synthesized by the cyclization of 6-R-2,3-diaminopyridines with 40% aqueous glyoxal as described in [7]; reaction of the bases Ia-d with methyl iodide in refluxing benzene gave the quaternary salts IIa-d.

The structures of compounds Ia-d were confirmed by NMR spectroscopy (Table 1). The chemical shifts for the H-2 and H-3 protons, together with the low values of the spin—spin

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