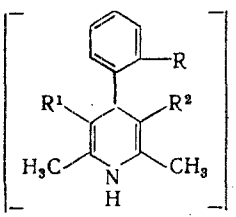
SYNTHESIS AND PHARMACOLOGICAL ACTIVITY OF ANALOGS OF THE HYPOTENSIVE DRUG FORIDON

V. V. Kastron, R. O. Vitolin', G. Ya. Dubur,
I. P. Skrastin'sh, and A. A. Kimenis

UDC 615.225.2:547.822.1].012.1

In continuation of our search for new effective cardiovascular agents in the 1,4-dihydropyridine series [2], we synthesized analogs of the original antihypertensive Foridon (riodipin) [3], i.e., 2,6-dimethyl-3,5-dimethoxycarbonyl-4-(o-difluoromethoxyphenyl)-1,4-dihydropyridine (Ia).



Ia-h

Ia: $R = OCHF_2$, $R^1 = R^2 = COOCH_3$; Ib: $R = OCHF_2$, $R^1 = R^2 = COOC_3H_7$; Ic: $R = OCHF_2$, $R^1 = R^2 = COOC_4H_9$-*i*; Id: $R = OCHF_2$, $R^1 = COOC_2H_5$, $R^2 = CONHC_6H_5$; Ie: $R = SCHF_2$, $R^1 = R^2 = COOCH_3$; If: $R = SCHF_2$, $R^1 = R^2 = COOC_3H_7$-*i*; Ig: $R = SCHF_2$, $R^1 = R^2 = COOC_5H_{11}$-*i*; Ih: $R = NO_2$, $R^1 = R^2 = COOCH_3$.

The following Foridon analogs were synthesized: 3,5-dicarboxylates of 1,4-dihydropyridines with a longer alkyl chain (Ib, c) and the monoanilide of 1,4-dihydropyridine 3,5-dicarboxylate (Id). In addition, we synthesized three compounds (Ie-g) in which the oxygen atom in the $OCHF_2$ group was replaced by a sulfur atom.

The 3,5-dicarboxylate esters Ib, c, e-g were synthesized by the condensation of o-difluoromethoxybenzaldehyde or o-difluoromethylthiobenzaldehyde and β-aminocrotonate esters. The monoanilide of 3,5-dicarboxylate Id was obtained by the condensation of o-difluoromethoxybenzaldehyde, β-aminocrotonate, and acetoacetic anilide.

The synthesized 1,4-dihydropyridines are colorless crystalline substances: Compounds Ie-g have a yellowish color. The UV spectra exhibit two absorption maxima, at 240 and 350-370 nm. The introduction of an amide group into position 5 (Id) induced a hypsochromic shift of the longwave absorption maximum ($\Delta \sim 15$ nm) in comparison to the complex ester group. Replacement of the oxygen atom by a sulfur atom in the aryl substituent (Ie-g) results in a certain bathochromic shift of the longwave maximum which diminishes as the lengths of the alkyl groups in positions 3 and 5 increase.

The structure of the dihydropyridines I was also verified by IR and PMR spectra (Table 1). The substituent in the aryl ring of 1,4-dihydropyridine influences the proton chemical shift in position 4 of the dihydropyridine ring. In compounds Ib-d with a $-OCHF_2$ group, the proton at C(4) yields a signal of approximately δ 5.2 ppm, and in compounds Ie-g with a $-SCHF_2$ group, the C(4) proton yields a signal in the region of δ 5.4-5.5 ppm. The proton of the $-OCHF_2$ group in Id yields a quartet because of the fluorine atom's nonequivalence.

The compounds I are stable as solids and their UV spectra did not change after 1-1.5 years of storage. The UV spectra of the dihydropyridines I also did not change when they were stored over a 4-5 month period as diluted alcohol solutions ($c = 5 \cdot 10^{-5}$ moles).

A study of the biological activity of the synthesized compounds Ib-g (the known coronary dilator Nifedipine was used as a comparison [4]) demonstrated that they exhibit coronary dilator and hypotensive activity.

The most significant increase in blood flow from the coronary venous sinus was brought about by compound Ie, which at a dose of 0.05 mg/kg doubled the coronary blood output

Institute of Organic Synthesis, Academy of Sciences of the Latvian SSR, Riga. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 21, No. 5, pp. 554-559, May, 1986. Original article submitted October 29, 1985.

0091-150X/87/2105-0327$12.50

TABLE 1. 1,4-Dihydropyridines I

Compound	Yield, %	mp, °C	Found/Calculated, %			Empirical formula	UV spectra, λ, nm(log ε)	IR spectra, ν, cm⁻¹	PMR spectra, δ, ppm	R_f (system)
			C	H	N					
Ib	72,5	97—8	62,4 62,4	6,4 6,4	3,9 3,3	$C_{22}H_{27}F_2NO_5$	238 (4,4) 362 (3,8)	1621 1675 3318	0,78 g (CH_3—Pr) 1,52 m (CH_2—Pr) 2,2 s (2,6—CH_3) 3,82 t (O—CH_2) 5,19 s (4—H) 5,7 s (NH) 6,37 t (CHF_2) J=75,1 Hz 7,25—6,95 m (Ar)	0,75 (I)
Ic	41	77—8	63,2 63,8	6,7 6,9	3,6 3,1	$C_{24}H_{31}F_2NO_5$	241 (4,3) 365 (3,9)	1640 1670 1690 3225 3330	0,8 q (CH_3—Bu) 1,84 m (CH—Bu) 2,22 s (2,6—CH_3) 3,75 d (—CH_2) 5,22 s (4—H) 5,81 s (NH) 6,45 t (CHF_2) J=75 Hz 7,40—7,70 m (ArH)	0,77 (I)
Id	35	212—4	64,8 65,2	5,6 5,5	6,5 6,3	$C_{24}H_{21}F_2N_3O_6$	247 (4,3) 350 (3,9)	1641 1678 3184 3300	1,2 t (CH_3—Et) 2,33 s (2,6—CH_3) 4,06 q (CH_2—Et) 5,22 s (4—H) 5,66 s (N—H) 6,66 q (CHF_2) J'=70 Hz J'=78 Hz 6,97—7,51 m (ArH) 7,88 (CONH)	0,42 (I) 0,44 (II)
Ie	53,2	173—5	56,2 56,4	4,9 5,0	3,3 3,6	$C_{18}H_{19}F_2NO_4S$	243 (4,3) 371 (3,8)	1646 1694 3352	2,21 s (2,6—CH_3) 3,53 s (OCH_3) 5,47 s (4—H) 6,78 t (CHF_2) J=58,5 Hz 7,18 m (ArH)	0,51 (II)
If	62	101—3	60,2 60,3	6,2 5,8	3,2 3,5	$C_{22}H_{27}F_2NO_4S$	240 (4,4) 368 (3,9)	1661 1705 3361	1,09 q (CH_3—Pr) 2,20 s (2,6—CH_3) 4,87 m (CH—Pr) 5,40 s (4—H) 5,58 s (N—H) 6,76 t (CHF_2) J=58 Hz 7,02—7,53 m (ArH)	0,40 (III)
Ig	53	97—99	62,9 63,0	7,1 7,1	3,5 2,9	$C_{26}H_{35}F_2NO_4S$	240 (4,3) 366 (3,8)	1649 1676 1702 3315	0,86 q (CH_3—Am) 1,56 m (—CH_2—CH<) 2,27 s (2,6—CH_3) 3,98 t (CH_2—O) 5,51 s (4—H) 5,84 s (N—H) 6,84 t (CHF_2) J=59 Hz 7,02—7,58 (ArH)	0,85 (I) 0,31 (III)

TABLE 2. Acute Toxicity of Foridon Analogs and Their Effect on the Hemodynamics of Anesthetized Cats and Active Spontaneously Hypertensive Rats

Compound	Dose, mg/kg	Increase in coronary circulation		Hypotensive activity		Cardiac minute volume, %
		%	duration, min	acute experiment, %	on ASH rats, 10 mg/kg	
Ib	0,1	27	10	22	22	50 ↑
	1,0	87	20	80		93 ↓
Ic	0,05	—	—	12	14	—
	0,1	10	14	34		10 ↓
	0,5	60	50	42		32 ↓
Id	0,1	49	45	—	—	10 ↓
	1,0	60	58	38		51 ↓
Ie	0,02	...	...	30		...
	0,05	103	30	...	54,8	20 ↓ /50 ↑
	0,1	150	65	...		60 ↓ /30 ↑
If	0,05	—	—	—	16	8 ↑
	0,1	—	—	—		34 ↑
	1,0	24	8	—		52 ↑
Ig	0,05	25	36	15	17	31 ↑
	0,1	27	5	53		83 ↓
Ih	0,05	94,4±15,2	33,8±8,6	...	44,8	25 ↓ /65 ↑
(Nifedipine)	0,06	...	...	30		...

Note. Arrows in last column signify decrease (↓) or increase (↑) of cardiac minute volume. ASH rats are active spontaneously hypertensive.

within 30 min, thus exhibiting the same cardiovascular effects as Nifedipine. There was less coronary dilation in the case of the isopropyl ester of If, and the isoamyl ester produced no significant increase in coronary flow, although the most active compound was still the methyl 3,5-dicarboxylate ester of Ie. The Foridon analogs Ib-d also increase blood flow in cardiac vessels, but to a lesser degree than does Nifedipine. Compounds Ib was the most active, but its action was of shorter duration. In comparison to the 3,5-dicarboxylic dianilide [2], the 3,5-dicarboxylic monoanildide exhibited stronger coronary dilator activity and its action laster longer.

Compound Ie's hypotensive action was approximately twice as effective as Nifedipine in acute experiments on cats, and exceeded the latter's action by 1.2 times when administered one time to spontaneously hypertensive rats. However, when compound Ie was administered additional times within 10 days (5 mg/kg once a day ip), its hypotensive effect did not differ from that of Nifedipine at the indicated dose.

The depressant action of the remaining 1,4-dihydropyridines (Ib-d, f, g) both in the acute experiments and in the spontaneous hypertensive rats was considerably weaker than that of Ie. Compound If did not alter arterial pressure in the acute experiment, but it did have some hypotensive effect in the experiments on spontaneously hypertensive rats. It should be noted that this compound increased cardiac minute volume at the tested doses.

Compound Ie, like Nifedipine, induced a two-phase change in cardiac minute volume, i.e., immediately after its administration it caused a short-term reduction in minute volume followed by an increase. Cardiac minute volume was increased by dihydropyridines Ib, g at smaller doses (0.05 mg/kg), but decreased that volume at higher doses (0.1-1.0 mg/kg).

When an oxygen atom was replaced by a sulfur atom (in comparing Ie to Ia) vasodilator activity was retained and even exceeded that of Foridon, although toxicity went up. Ie is three times more toxic than Foridon Ia (LD_{50} 93 and 395 mg/kg, respectively). The remaining compounds were less toxic (LD_{50} ~ 1000 mg/kg).

EXPERIMENTAL CHEMICAL

IR spectra were recorded on a Perkin-Elmer 580 B instrument in the form of a suspension in Nujol. UV spectra were recorded on a Specord UV-vis instrument in ethanol ($c = 5 \cdot 10^{-5}$ moles), and the PMR spectra were recorded on a WD 90/DS instrument (90 MHz), tetramethylsilane standard, in a $CDCl_3$ solution. The reactions and individuality of the synthesized

compounds were controlled with the aid of TLC on Silufol UV-254 plates in a 1:1:1 chloroform–ethylacetate–hexane system (I); a 1:1 cyclohexane–ethylacetate system (II), and a 1:1:3 chloroform–ethylacetate–hexane system (III).

Dimethyl-3,5-dipropoxycarbonyl-4-(o-difluoromethoxyphenyl)-1,4-dihydropyridine (Ib). A mixture of 2.56 g (0.015 moles) of o-difluoromethoxybenzaldehyde, 4.65 g (0.03 moles) of n-propyl acetoacetate, and 4.5 ml of 25% aqueous ammonia was boiled for 12 h in 10 ml of ethanol. The solvent was vacuum distilled, and the oily residue was treated with hexane and crystallized from a 1:1 ethylacetate and hexane mixture (see Table 1).

Compound Ic was obtained in the same manner.

2,6-Dimethyl-3-ethoxycarbonyl-4-(o-difluoromethoxyphenyl)-1,4-dihydropyridine-5-carboxylate (Id). A mixture of 1.72 g (0.01 moles) of o-difluoromethoxybenzaldehyde, 1.77 g (0.01 moles) of acetoacetic acid anilide, and 1.27 g (0.01 moles) of ethyl β-aminocrotonate was boiled for 12 h in 5 ml of methanol. After cooling 1 g of precipitate was formed.

2,6-Dimethyl-3,5-di(isopropoxycarbonyl)-4-(o-difluoromethylthiophenyl)-1,4-dihydropyridine (If). A mixture of 1.44 g (0.01 mole) of isopropyl acetoacetate, 1.43 g (0.01 mole) of isopropyl β-aminocrotonate, and 1.88 g (0.01 mole) of o-difluoromethylthiobenzaldehyde* was boiled for 10 h in 10 ml of isopropyl alcohol. The solvent was vacuum distilled, and the oily residue was treated with hexane and crystallized from a 1:1 mixture of ether and hexane (see Table 1).

Compound Ig was obtained in a similar manner.

2,6-Dimethyl-3,5-dimethoxycarbonyl-4-(o-difluoromethylthiophenyl)-1,4-dihydropyridine (Ie). A 6.8-g (0.04 mole) portion of o-difluoromethylthiobenzaldehyde, 9.26 g (0.08 mole) of methyl acetoacetate, 6.2 ml of 25% aqueous ammonia, and 20 ml of methanol was boiled for 3 h. The precipitate, compound Ie, was collected after cooling and crystallized from ethanol (see Table 1).

EXPERIMENTAL PHARMACOLOGICAL

The experiments were conducted on cats of both sexes weighing 2.6-3.7 kg and anesthetized by chloralose (90 mg/kg IP). Systemic arterial pressure was recorded electromagnetically from the common carotid with the aid of a MPU-0.5 pressure sensor (Nikon Koden). EKG was recorded in a II standard lead to the subdermal thoracic cage at the fourth intercostal level. The thoracic cavity was opened, an incision was made into the pericardium, and cannula was inserted into the coronary venous sinus from which effluent blood was collected [1]. A sensor was attached to the ascending segment of the aorta to record aortal circulation. A LPU-0.1 pressure sensor was used to record venous pressure in the right atrium. All of the recordings were made on a polygraph (Nikon Koden).

The test substances were administered IV through a cannula inserted into the femoral vein.

In the experiments on the active, spontaneously hypertensive Okamoto-Aoki breed rats, plethysmographic assays were made of the hypotensive action of the test substances before and after their oral administration at a dose of 10 mg/kg in the form of an aqueous suspension with a 6% solution of Tween-80 (0.05 ml per 5 mg of substance).

Acute toxicity was assayed on white mongrel mice weighing 18-23 g to which the test substances were administered ip. Each dose of the substance was tested on six mice and the LD_{50} was determined by the Litchfield–Wilcoxon method. A tentative lethal dose was determined on three mice. The mice were observed for 10 days following the administration of the test substances during which toxic effects and deaths were noted.

LITERATURE CITED

1. N. V. Kaverina, Farmakol. Toksikol., 21, No. 1, 39-43 (1958).
2. V. V. Kastron, G. Ya. Dubur, R. O. Vitolin', et al., Khim.-farm. Zh., No. 5, 545-549 (1985).

*o-Difluoromethylthiobenzaldehyde was synthesized at the Institute of Organic Chemistry, Academy of Sciences of the Ukrainian SSR.

3. V. V. Kastron, G. J. Dubur, V. D. Shatz, and L. M. Jagupolsky, Arzneim.-Forst., 35, 668-672 (1985).
4. E. Kusano, I. Asano, and K. Takeda, Arzneim.-Forst., 32, 1575-1580 (1982).

SYNTHESIS OF N_4-PROPYLAJMALINE BROMIDE AND A STUDY OF ITS ANTIARRHYTHMIC ACTIVITY

S. A. Minina, Ya. V. Kostin,
É. I. Gendenshtein, and E. I. Molokhova

UDC 615.22:547.944].012.1

It has been shown in recent years that the quaternary derivatives of some antiarrhythmic agents have a significantly greater antiarrhythmic action and of longer duration than their precursors. This relationship has been established for Lidocaine [14], Trimecaine [5, 6], and Anaprylin [10], and has already been successfully applied in medical practice to Ajmaline from which an effective new generation of antiarrhythmic preparations called Neo-Gilurythmal has been manufactured [12, 13, 16].

A study of the relationship between chemical structure and the pharmacological activity of the quaternary derivatives of ajmaline has established that N_4-propylajmaline bromide (N-PAB) exhibits the greatest activity [15]. N-PAB was synthesized at the I. F. Makarevich Kharkov Scientific Research Institute of Pharmaceutical Chemistry, and its pharmacological properties were investigated by É. I. Gendenshtein [2, 3]. N-PAB was clinically tested successfully in 1974 and was approved by the Pharmacology Committee of the Ministry of Health of the USSR for use in medical practice as an antiarrhythmic drug. However, because of the lack of domestic raw materials, this preparation was never manufactured.

The Leningrad Pharmaceutical Chemistry Institute devised a means of cultivating isolated cells of Rauwolfia serpentina [1] which provided a promising source for the production of ajmaline alkaloids [8] from which N-PAB was synthesized.

The present work offers a modified method of obtaining N-PAB and cites the results of a study of its antiarrhythmic activity as tested on experimental models of cardiac arrhythmia.

EXPERIMENTAL CHEMICAL

The starting material for the production of N-PAB was ajmaline which was isolated from the biomass of a Rauwolfia serpentina tissue culture and which corresponded to the requirements of the All-Union Pharmacology Committee 42-1876-82. N-PAB was synthesized by method [15] as modified by us. In the process of synthesizing the derivative, the toxic and expensive solvent acetonitrile was replaced by rectified ethyl alcohol. We established the optimal time and temperature conditions of the reaction as well as the consumption rate of the alkylating agent which enabled us to increase the yield by 16%. N-PAB was obtained in the following manner: a 1-g portion of ajmaline was dissolved in 8 ml of rectified ethyl alcohol which was mixed upon heating with 0.7 g (0.5 ml) of n-propyl bromide. The reaction proceeded at 70°C for 9.5 h. The resultant residue was filtered and recrystallized from methanol, followed by precipitation by diethyl ether. The yield of the pharmacopeia-standard product was 78%. The resultant product was a white crystalline powder, mp 281-283°C. Found, %: C 61.12, H 7.56, Br 17.18, N 5.97. $C_{23}H_{33}Br_2O_2$. Calculated, %: C 61.17, H 7.40, Br 17.78, N 6.23. UV spectrum, alcohol, γ_{max}, nm (log ε): 245 (3.81), 290 (3.33). IR spectrum, γ_{max}, cm^{-1}: 760 (C—H), 1200 (C—O), 1300 (C—N), 1610 (aromatic ring), 3300 (OH), TLC (Silufol UV-254, Czechoslovakia). R_f 0.66 ± 0.02 ($CHCl_3$—acetone—diethylamine, 5:4:1).

Leningrad Pharmaceutical Chemical Institute. N. P. Ogarev Mordovian University, Saransk. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 21, No. 5, pp. 559-561, May, 1987. Original article submitted February 20, 1986.

0091-150X/87/2105-0331$12.50