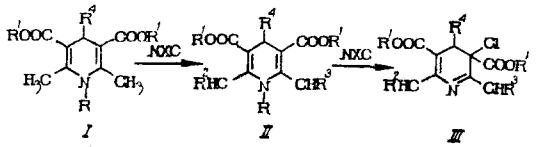
EFFECT OF 1,4-DIHYDROPYRIDINE DERIVATIVES ON THE CARDIOVASCULAR SYSTEM

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

UDC 615.225.2:547.822.1]:015.4:612.1].07

Almost no vasoselectivity was exhibited by the first cardiovascular preparations of the 1,4-dihydropyridine series. Alterations in their structure resulted in the synthesis of calcium channel blockers such as intrendipine [1], nimodipine [2], and nicardipine [3] which primarily act upon peripheral vessels. Recent searches for compounds exhibiting pronounced selectivity resulted in the synthesis of 1,4-dihydropyridines which contain halide methyl groups in position 2 [4-7]. Some of these compounds exhibit a high degree of selectivity [6] or more extended activity [7]. There are data that show that halide derivatives of intrendipine exhibit less negative inotropic action, although in some cases their vasodilatory action is even greater than in nitrendipine [8].

In our search for new cardiovascular agents with greater selective action we synthesized a number of foridone derivatives [9] in which one or two hydrogen atoms of the 2,6-methyl groups have been replaced by bromine. Bromination was accomplished by the use of N-bromosuccinimide in MeOH at room temperature by method [10]. Mono-, di- and tetrabromo derivatives of foridone (II) were obtained dependent upon the ratio of reagents (see Table 1).



II: R=H (a-c,e-g), Me (d); R^1=Me (a-f), i=Pr (g); R^2= =Br_2 (a, d), H_2 (b,e), HBr (c,f,g); R^3=Br_2 (a,d), HBr (b,c, e-g); R^4=$C_6H_4OCHF_2$-o

The synthesized compounds II are light-colored crystalline substances. Their structure was verified by IR-, UV-, and NMR-spectra. The physicochemical properties of some compounds have been described earlier [11]

TABLE 1. Effect of Compounds II and III on Hemodynamic Parameters in Experiments on Anesthetized Cats

Compound	Dose, mg/kg (v/v)	Heart rate, %	Arterial pressure, %	Pressure, %	dP/dt_{max}	Carotid artery blood flow
IIa	0,01	—20	+1	—25	—1,4	—1,9
	1,0	—38	0	—34	—8	—15
IIb	0,01	—5	—26	—34	—34	—21
	0,1	—37	—33	—55	—46	—47
IIc	0,01	+6	+13	—10	+14	+15
	0,1	+10	—16	—25	—25	—6
IId	0,01	0	0	—5	—3	—2
	1,0	—1,0	8	—21	—25	—11
IIe	0,01	+15	+6	+34	+28	+28
	1,0	+13	+15	0	+35	+73
IIf	0,01	0	+2,3	—5	—7	—20
	1,0	0	—2,9	—36	—7	—6
IIg	0,01	—3	0	+5	+20	+11
	1,0	0	0	0	—10	+3
III	0,01	—53,4	0	—54,8	0	—29,4
	0,1	—38,1	0	—18,3	0	+28,6
	1,0	—56,0	0	—64,0	0	—19,0
Foridone	0,001	—17	—26	+21	—7	+33

Institute of Organic Synthesis, Latvian Academy of Sciences, Riga. Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 25, No. 10, pp. 27-29, October, 1991. Original article submitted December 20, 1990.

 0091-150X/91/2510-0696$12.50

When the tetrabromo derivative IIa is chlorinated by N-chlorosuccinimide (NCS), the result, regardless of the quantity of NSC (2-8 moles), is the product emanating from the addition of chlorine to the double bond of the 1,4-dihydropyridine ring (III) (P^1 = Me; R^2 = R^3 = Br_2) which constitutes 3,4-dihydropyridine. The UV-spectrum of III lacks a long wave absorption maximum which is characteristic of the 1,4-dihydropyridines. The IR-spectrum of compound III lacks NH group absorption. The splitting of OCH_3 group proton signals in the PMR spectrum also are indicative of the molecule's asymmetry.

The pharmacological investigation of these compounds was made by comparing them to the antihypertensive and coronary dilator preparation foridone [9].

The experimental data demonstrate that all of the synthesized substances except compound IIb are essentially void of any hypotensive effect. For example, compound IIa, in which four hydrogen atoms in the 2,6-methyl groups were replaced by bromine, did not alter systemic arterial pressure (AP) even at a dose of ul mg/kg, whereas foridone lowers AP by 26% at doses as low as 0.001 mg/kg. The compound IIb in which only one hydrogen atom was replaced by bromine, lowers AP by 26% and 33% at doses of 0.01 and 0.1 mg/kg respectively. Compound IIb is further marked by the fact it lowers pressure (P) in the left ventricle to a greater extent than do the other examined substances, and decreases dP/dt_{max} which is indicative of its negative inotropic action. In addition, this compound significantly lowers (by 47% at a dose of 0.1 mg/kg) blood flow in the carotid artery. In addition, compounds IIa and IIb induce bradycardia. Compounds IId and IIi, containing an N-methyl group, have almost no effect on heart rate (HR) and to a lesser extent exhibit a negative inotropic effect. Compound IId essentially is the same as IIa with respect to effects on the carotid arteries. Qualitative changes were observed in the N-methyl analog of IIb. Compound IIe induces a rise in HR and AP as well as a significant increase in dP/dt_{max}. As in the case of foridone, this compound clearly increases carotid blood flow. Compound IIe increases left ventricle pressure by 34% at a dose of 0.01 mg/kg, but this effect was no longer observed when the dose was raised to 1 mg/kg.

The properties of 3,4-dihydropyridine III were practically the same as those of IIa. Compound III likewise does not exhibit hypotensive activity. It lowers left ventricle pressure to a somewhat greater degree and does not alter dP/dt_{max}.

Therefore, the characteristics that have been described for the halide derivatives of intrendipine [8] have not been established for 2,6-bromo derivatives of foridone and its analogs. The introduction of bromine does not increase the vasoselectivity of foridone and its analogs, but does induce a decrease in the hypotensive effect. This may also be accompanied by a pronounced negative inotropic action and an adverse effect on cerebral circulation. N-Methylation of the synthesized bromo derivatives can result not only in the disappearance of negative chromotropic properties, but also in the appearance of other qualitative property changes such as a cardiotonic effect. The latter might be associated with the alteration of calcium ion passage through the potential-dependent sarcolemma channels of cardiomyocytes, i.e., the appearance of a certain agonist activity. Another possibility is the inhibiting effect that compound IIe has on phosphodiesterase of cyclic AMP which is peculiar to many cardiotonic agents [12]. The same type of action is also observed in several 1,4-dihydropyridines such as nicardipine [13] as well as foridone [14]. A future study will deal with the mechanism underlying the action of this series of compounds, particularly that of compound IIe. The synthesis of 1,4-dihydropyridines in this connection might also lead to the identification of new, more powerful cardiotonics and cerebral arterial dilators.

EXPERIMENTAL (CHEMICAL)

IR spectra were recorded on a Perkin—Elmer (England) instrument in the form of a suspension in nyol. UV spectra were measured on a Specord UV-VIS (Germany) instrument in ethanol ($5 \cdot 10^{-5}$ mole). PMR spectra were recorded on a WH 90/DS (Germany) instrument (90 MHz) in a $CDCl_3$ solution. Tetramethylsilane was the standard. Reaction progress and purity were controlled by TLC on Silufol UV-254 plates in a $CHCl_3$—hexane— ethylacetate (1:3:1) system.

The found values for the element analyses corresponded to the calculated ones.

2-Bromomethyl-3,5-dimethoxycarbonyl-4-(2'-difluoromethoxyphenyl)-5-methyl-1,4-dihydropyridine (IIb). A 3.56 g (0.02 mole) portion of NBS at 0°C was added to a solution of 7.34 g

(0.02 mole) of compound I (R=H; R^1=Me) in 160 ml of MeOH, and stirred for 15 min. After the addition of 40 ml of water, the resultant precipitate was crystallized from 50% aq. ethanol to produce light-yellow crystals, compound IIb. Yield was 4.6 g (52%). mp 114-116°C, R_f 0.44. UV spectrum λ_{max} (log ε): 243 (4.17), 366 nm (3.72). IR spectrum, λ_{max}, cm^{-1}: 1625, 1650, 1694, 3105, 3330. PMR spectrum, δ, ppm: 2.32 (3H, s, 6-CH_3), 3.54 (3H, s, OCH_3), 3.60 (3H, s, OCH_3), 4.53 and 4780 (2H, q, CH_2Br), 5.28 (1H, s, 4-H), 6.11 (1H, s, NH), 6.45 (1H, t, CHF_2); 6.9-7.4 (4H, m, ArH).

2,6-Dibromomethyl-3,5-di(isopropoxycarbonyl-4-(2'-difluoromethoxyphenyl)-1,4-dihydropyridine (IIg). A 3.56 g (0.02 mole) portion of NBS was added to a solution of 4.23 g (0.01 mole) of compound I (R=H; R^1= i-Pr) in 100 ml of MeOH, and stirred for 15 min at room temperature. The precipitate was crystallized from 50% aq. ethanol. The resultant product was light-yellow crystals. Compound IIg. Yield was 2.8 g (74%) mp 90-91°. R_f 0.52. UV spectrum, λ_{max} (log ε): 251 (4.13), 372 nm (3.67). IR spectrum, ν_{max}, cm^{-1} 1647, 1673, 3280 cm. PMR spectrum, δ, ppm: 1.17 (12H, m, CH_3), 4.49 and 4.91 (4H, q, CH_2Br), 4.96 (2H, q, CH), 5.24 (1H, s, 4-H), 6.51 (1H, t, CHF_2), 6.52 (1H, s, NH), 6.9-7.4 (4H, m, ArH).

2,6-Bis(dibromomethyl)-3,5-dimethoxycarbonyl-3-chloro-4-(2'-difluoromethoxyphenyl)-3,4-dihydropyridine (III). A 2.67 g (0.02 mole) of NCS was added to a solution of 3.42 g (0.005 mole) of compound IIa in 200 ml of ethanol, The mixture was stirred for 1 h at room temperature, then boiled for 15 min after which 100 ml of water was added. The resultant precipitate was crystallized from a 1:1 MeOH–water mixture to yield 1.1 g (30.5%) of III. mp 139-142°C. R_f 0.80. UV spectrum, λ_{max} (log ε): 269 (4.06). IR spectrum, ν_{max}, cm^{-1}: 1710, 1751. PMR spectrum, δ, ppm: 3.62 (3H, s, OCH_3), 3.65 (3H, s, OCH_3), 5.12 (1H, s, 4-H), 6.48 (1H, t, CHF_2), 6.68 (1H, s, CH), 7.4-7.0 (4H, m, ArH), 7.75 (1H, s, CH).

EXPERIMENTAL (PHARMACOLOGICAL)

These compounds were tested pharmacologically in experiments on chloral-anesthetized (90 mg/kg) cats of both sexes weighing 2.5-3.0 kg. Systematic arterial pressure was recorded in the femoral artery with a MPU-0.5 (Nikon Kohden, Japan) electromanometer. A catheter was introduced into the left ventricle of the heart to determine left ventricular pressure, dP/dt_{max} and heart rate. Carotid arterial blood flow was measured with an electromagnetic fluometer (MFV-1200, Nikon Kohden). All data were recorded with the use of a RM 6000 polygraph (Nikon Kohden).

The tested substances were dissolved in a 50% solution of dimethylacetamide and administered iv.

LITERATURE CITED

1. H. Meyer, F. Bossert, E. Wehinger, et al., Arzneim. Forsch., 31, 407 (1981).
2. S. Kazda and B. Garthoff, Arzneim. Forsch., 32, 331 (1982).
3. B. J. Alps, C. Calder, A. Wilson, et al., Arzneim. Forsch., 33, 1638 (1983).
4. A. Baxter, J. Dixon, F. Mcinally, and A. Tinner, European Patent No. 225175, Chem. Abstr., 108, No. 75226 (1988).
5. A. Baxter, J. Dixon, K. Gould, and A. Tinner, European Patent No. 174131, Chem. Abstr., 105, No. 114914 (1986).
6. A. Baxter, European Patent No. 169009, Chem. Abstr., 105, No. 97318 (1986).
7. A. Baxter, European Patent No. 125903, Chem. Abstr., 102, No. 203874 (1985).
8. U. Fricke, W. Klaus, and B. Stein, Naunyn.-Schmiedeberg's Arch. Pharmacol., 338, 449 (1988).
9. R. O. Vitolinya and A. A. Kimenis, Khim.-Farm. Zh., No. 7, 889 (1989).
10. B. S. Chekavichus, A. É. Sausin'sh, I. P. Skrastin'sh, and G. Ya. Dubur, Khim. Geter. Soedin, No. 10, 1422 (1989).
11. I. P. Skrastin'sh, V. V. Kastron, B. S. Chekavichus, et al., Khim. Geter. Soedin, No. 10, 1422 (1989).
12. H. Landsmann and H. Löwe, Die, Pharmazie., 41, 41, 169 (1986).
13. K. Nishikori, T. Takenaka, and H. Maeno, Jpn. J. Pharmacol., 31, 701 (1981).
14. A. V. Selina, R. Ya. Mezhapuke, B. Z. Simkhovich, et al., Éksp. Klin. Farmakol., No. 14, 98 (1985).