1-α-L-arabinopyranosyl-4-methyl-5-nitro-chloro-7-azaindoline (XIV). We boiled 1.12 g of 4-methyl-5-nitro-6-chloro-7-azaindoline [4] and 0.79 g of L-arabinose in a mixture of 0.5 ml of acetic acid, 5 ml of water, and 15 ml of ethanol for 18 h. The precipitate, 0.68 g XIII, was filtered out, 10 ml of acetone were added to the mother liquor, the resultant precipitate of 0.11 g of L-arabinose was filtered out, the filtrate was evaporated until dry, dissolved in 5 ml of chloroform and chromatographed on five sheets in system C. Zone R_f = 0.33 was removed, eluted with acetone, evaporated, vacuum-dried, and 0.89 g of XIV were obtained in the form of yellow foam.

1-α-L-2',3',4'-tri-O-acetylarabinopyranosyl-4-methyl-5-nitro-6-chloro-7-azaindoline (XV). From 0.76 g of XIV, 18 ml of pyridine, and 12 ml of acetic anhydride we obtained 1.01 g of XV, in a manner similar to that used to obtain IV.

1-α-L-2',3',4'-tri-O-acetylarabinopyranosyl-4-methyl-5-nitro-6-chloro-7-azaindole (XVI). From 0.5 g of XV and 5.0 g of manganese dioxide we obtained 0.34 g of XVI in a manner similar to that used to obtain VII. R_f = 0.34 was used in system B.

1-α-L-arabinopyranosyl-4-methyl-5-nitro-6-chloro-7-azaindole (XVII). From 0.24 g of XVI we obtained 0.16 g of the arabinoside XVII in the form of a light yellow foam as described for obtaining X. R_f = 0.44 was used in system C.

LITERATURE CITED

1. Ya. V. Dobrynin, T. G. Nikolaeva, V. I. Mukhanov, et al., Khim. Farm. Zh., No. 5, 33-38 (1978).
2. Z. P. Sof'ina, Sh. N. Platonova, N. A. Lesnaya, et al., Khim. Farm. Zh., No. 6, 93-95.
3. M. N, Preobrazhensakaya, Usp. Khim., 36, 1760-1798 (1967).
4. D. M. Krasnokutskaya and L. N. Yakhontov, Khim. Geterotsikl. Soedin., No. 3, 380-384 (1977).
5. A. P. Terent'ev, M. N. Preobrazhenskaya, and T. M. Sorokina, Zh. Obshch. Khim., 29, 2875 (1959).
6. J. Attenburrow, A. B. Cameron, J. H. Chapman, et al., J. Chem. Soc., 1094-1111 (1952).
7. A. P. Terent'ev, M. N. Preobrazhenskaya, A. S. Bobkov, et al., Zh. Obshch. Khim., 2541-2551 (1959).

SYNTHESIS AND PHARMACOLOGIC ACTIVITY OF 4-FURYL-1,4-DIHYDROPYRIDINES

V. V. Kastron, G. Ya. Dubur, R. O. Vitolin', and A. A. Kimenis

UDC 615.31:547.822.1'722.5'722.1

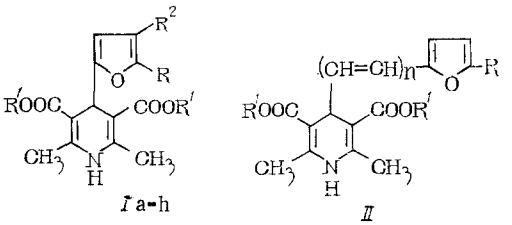
Several previously described 1,4-dihydropyridines having furyl- and α-nitrofuryl groups at position 4 possess antibacterial and antineoplastic properties [1], hypotensive, and coronary dilating activity [2, 3]. For the purpose of seeking out new cardiovascular drugs, new derivatives of 4-furyl-1,4-dihydropyridine (If-h) and 1,4-dihydropyridines (Ia-d, II) were synthesized in which the furan ring has been separated from the dihydropyridine ring by one or two vinyl groups.

Compounds If-h, whose furan rings have a CF_3 group, have been obtained by condensation of acetoacetate ester, ammonia, and the respective aldehyde. The remaining 1,4-dihydropyridines (Ia-d, II) are obtained by condensation of β-aminocrotonic acid esters, acetoacetic acid esters, and the respective aldehydes (Table 1). Carrying out condensation with ammonia under these conditions is undesirable because of the instability of the aldehydes in an alkaline medium. (See formula on next page.)

The IR spectra of I and II are similar to the spectra of 4-aryl-1,4-dihydropyridines [4]. Insertion of a nitro group in the furan ring increases and a vinyl group at position 4 decreases the oscillation frequency of the ester carbonyl.

Institute of Organic Synthesis, Academy of Sciences of the Latvian SSR, Riga. Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 13, No. 6, pp. 57-62, June, 1979. Original article submitted December 18, 1978.

0091-150X/79/1306-0611$07.50



I a-h

II

$R = CF_3, NO_2, H$; $R^2 = H, COOH$

$R' = CH_3, C_2H_5$; $n = 1, 2$

An unsubstituted 4-(2-furyl) group causes a considerable hypsochromic shift in the maximum long-wave absorption band in the UV spectra in comparison to position-4 unsubstituted 1,4-dihydropyridine (from 373 to 350 nm). This shift was greater than in the case of a 4-phenyl group (359 nm); even though the bulk of the furyl group is smaller, its steric influence is no greater than that of a phenyl group. Hence, the assertion [5, 6] that the hypsochromic shift in the long-wave maximum is caused by a steric factor of the substituent at position 4 needs to be corrected.

A 4-(5-nitro-2-furyl) group in comparison to an unsubstituted 4-(2-furyl) group causes a considerable hypsochromic shift (by 20 nm) in contrast to m- or p-nitrophenyl groups. If the furyl is connected to the dihydropyridine by way of a vinyl or divinyl bridge, than insertion of a nitro group causes a marked bathochromic shift (by 10 and 32 nm, respectively). This indicates that an extremely important reaction is taking place between formally isolated structural elements of the molecule.

In their solid form the I and II 1,4-dihydropyridines are stable. In dilute solutions 1,4-dihydropyridines containing vinyl bridges at position 4 oxidize readily. In light in an ethanol solution, at a concentration of $5 \cdot 10^{-5}$ or $5 \cdot 10^{-4}$ M, the maximum characteristic of the dihydropyridine structure disappears from the IR spectra of IIa, e, and g in as little as 4 h. Oxidation proceeds considerably more slowly in the dark; at a concentration of $5 \cdot 10^{-5}$ M the character of the UV spectrum is altered only after 12 days, at a higher concentration ($5 \cdot 10^{-4}$ μ) the UV spectrum does not change.

When the biological activity of synthesized compounds I and II was studied, it was learned that they display a hypotensive effect which, however, does not exceed that of the better known 4-furyl-1,4-dihydropyridines (Ia, b, and d) (Table 2). Insertion of a CF_3 group into the furan ring reduces the hypotensive activity to one-tenth (compounds If-h); insertion of the same group at the o-position of the 4-phenyl markedly increases hypotensive activity [2]. Separation of the furan ring from the dihydropyridine ring by means of a vinyl bridge has no appreciable effect; the activity of compounds IIa-d exists on the same level as Ia, b, and d and the hypotensive activity of compounds IIf-h is somewhat reduced by the introduction of a second vinyl link.

In the doses studied, the compounds had no appreciable effect on the rate or depth of respiration. Only during the course of reduced arterial pressure was some increase in respiration observed, apparently reflex in nature. The compounds investigated proved to have no appreciable effect on the EKG.

The compounds studied display comparatively low acute toxicity (see Table 2), the most toxic, If-h, containing a CF_3 group in the furan ring; the compounds' toxicity was reduced by insertion of a vinyl bridge at position 4 of the dihydropyridine bridge.

EXPERIMENTAL CHEMISTRY

The IR spectra were taken on apparatus VR-20° as a suspension in nujol and hexachlorobutadiene; the UV-spectra were taken on a Specord UV-vis apparatus in ethanol (approximately $5 \cdot 10^{-5}$ M).

Verification of the progress of the reaction and the identity of the synthesized compounds was achieved by means of thin-layer chromatography on Silufol UV-254 sheets in the following systems: 1) chloroform—ethylacetate—hexane (1:1:3); 2) chloroform—ethylacetate—hexane (1:1:1); 3) hexane—acetone (1:1).

TABLE 1. I and II 1,4-Dihydropyridines

Compound	R	R^1	R^2	Melting point, °C	Found, %			Empirical formula	Calculated, %			UV spectra, λ_{max}, nm (log ε)	IR spectra, cm^{-1} (absorption, %)	R_f of the system	Yield, %
					C	H	N		C	H	N				
I a	H	Et	H	163—4 165—6[2]	64,2	6,8	4,4	$C_{17}H_{21}NO_5$	63,9	6,6	4,4	229 (4,3) 350 (4,0)	1650 (84) 1706 (77) 3358 (82)	0,68 (2)	69,2
I b	H	Me	H	188—9 191—2 (2]	62,4	5,8	4,9	$C_{15}H_{17}NO_5$	61,6	5,8	4,8	230 (4,3) 350 (3,9)	1655 (88) 1702 (86) 3358 (86)	0,2 (1)	80,0
I c	NO_2	Et	H	164—5 173—4 [1]	56,6	5,8	7,5	$C_{17}H_{20}N_2O_7$	56,0	5,5	7,7	232 (4,4) 330 (4,3)	1661 (76) 1710 (63) 3255 (40) 3360 (67)	0,17 (1)	64,0
I d	NO_2	Me	H	177—8 181—2 [7]	53,8	4,9	8,6	$C_{15}H_{16}N_2O_7$	53,5	4,8	8,3	232 (4,4) 330 (4,3)	1578 (53) 1659 (82) 1715 (80) 3365 (82)	0,53 (1) 0,31 (2)	51,8
I e	H	Me Et	H	150—2	63,0	6,5	4,3	$C_{16}H_{19}NO_5$	62,9	6,3	4,6	232 (4,5) 350 (4,0)	1631 (85) shoulder 1652 (90) 1711 (86) 3355 (86)	0,72 (1) 0,40 (2)	43,5
I f	CF_3	Et	H	109—10	55,3	5,3	3,9	$C_{18}H_{21}N_3NO_5$	55,9	5,4	3,6	230 (4,3) 352 (3,8)	1618 (44) 1668 (82) 1705 (64) 3368 (73)	0,75 (3)	46,4
I g	CF_3	Et	COOH	152—3	52,3	5,1	3,3	$C_{19}H_{22}F_3NO_7$	52,7	5,1	3,2	232 (4,3) 350 (3,9)	1620 (70) 1660 (85) 1684 (85) 1710 (79) 3361 (85) 3446 (65) 3500 (65)	0,57 (3)	45,0
I h	CF_3	Me	COOH	237—8	48,0	3,9	3,3	$C_{16}H_{15}F_3NO_7$	47,4	4,0	3,4	232 (4,2) 350 (3,8)	1623 (66) 1663 (86) 1682 (81) 1742 (78) 3352 (75)	0,16 (1)	45,0
II a (n=1)	H	Et	H	151—2	66,7	6,7	4,3	$C_{19}H_{23}NO_5$	66,1	6,7	4,0	233 (4,3) 252 (4,1) shoulder 359 (3,5) 212 (3,72)* 234 (3,69) 300 (3,92)	1653 (60) 1696 (50) 3358 (54)	0,31 (1)	55,0
II b (n=1)	H	Me	H	180—1	64,7	6,0	4,5	$C_{17}H_{19}NO_5$	64,3	6,0	4,4	237 (5,0) 256 (4,2) shoulder 359 (3,7)	1652 (86) 1698 (82) 3358 (86)	0,69 (2)	54,9
II c (n=1)	NO_2	Et	H	152—3	57,9	5,7	7,8	$C_{19}H_{22}N_2O_7$	58,4	5,7	7,2	232 (4,3) 370 (4,1)	1472 (84) 1522 (53) 1570 (44) 1650 (74) 1700 (60) 3348 (74)	0,17 (1)	56,5
												232 (4,4)	1360 (75)	0,84 (2)	57,1

TABLE 1. (Continued)

Compound	R	R^1	R^2	Melting point, °C	Found, %			Empirical formula	Calculated, %			UV spectra, λ_{max}, nm (log ε)	IR spectra, cm^{-1} (absorption, %)	R_f of the system	Yield, %
					C	H	N		C	H	N				
IId (n=1)	NO_2	Me	H	218—9	56,2	4,8	7,6	$C_{17}H_{18}N_2O_7$	56,3	5,0	7,7	368 (4,2)	1571 (52) 1621 (67) 1651 (75) 1706 (82) 3378 (84)		
IIe (n=2)	O_2	E	H	192—3	61,4	5,6	6,3	$C_{21}H_{23}N_2O_7$	61,4	5,6	6,7	236 (4,1) 273 (4,1) 401 (4,2)	1350 (93) 1480 (86) 1570 (80) 1650 (68)	0,13 (1)	60,2
IIf (n=2)	O_2	Me	H	200—1	59,2	5,2	7,1	$C_{19}H_{20}N_2O_7$	58,8	5,2	7,2	209 (4,49)* 241 (3,75) 280 (3,68) 330 (3,64) 237 (4,1) 272 (4,0) 401 (4,1)	1705 (74) 3351 (83) 1555 (42) 1652 (79) 1683 (78) 3351 (84)	0,69 (2)	67,0
IIg (n=2)	H	Et	H	135—6	67,1	6,9	4,1	$C_{21}H_{25}NO_5$	67,1	6,9	4,1	204 (4,1) 237 (4,1) 311 (4,23) 369 (3,5) knee 202 (3,97)* 235 (3,78) 235 (3,78) knee 276 (4,01) 300 (4,03)	1652 (82) 1695 (76) 3360 (80)	0,44 (2)	44,3
IIh n=2	H	Me	H	166—7	65,1	6,80	4,16	$C_{19}H_{21}NO_5$	65,7	7,2	4,0	205 (4,4) 237 (4,4) 310 (4,5) 369 (3,9) knee (c $2,5\cdot10^{-5}$M) 204 (4,17)* 233 (4,01) shoulder 278 (4,30) 302 (4,33)	1666 (72) 1685 (80) 3359 (82)	0,41 (2)	46,8

*UV spectrum of the solution after being kept in the light for 4 h.

Note. Systems described in the experimental section.

TABLE 2. Effect of the Compounds Under Investigation on Arterial Pressure (ED_{30}) and Isolated Rat Intestine (EC_{50}) and Acute Toxicity (LD_{50})

Compound	ED_{30}, mg/kg	EC_{50}, g/ml	LD_{50}, mg/kg
Ia	0,12 (0,1—0,13)	$3 \cdot 10^{-6}$	>7500
Ib	0,51 (0,29—0,73)	$4 \cdot 10^{-9}$	2900 (2301—3654)
Ic	0,27 (0,17—0,37)	10^{-7}	4400 (3098—6248)
Id	4,2 (3,5—4,9)	$2 \cdot 10^{-8}$	>1000
Ie	5,7 (4,6—6,8)	10^{-7}	340 (234—493)
If	7,8 (4,4—11,2)	$2 \cdot 10^{-10}$	—
IIa	0,43 (0,32—0,54)	$3 \cdot 10^{-9}$	>5000
IIb	0,44	$3 \cdot 10^{-9}$	>5000
IIc	0,45 (0,15—0,75)	$4 \cdot 10^{-7}$	>9000
IId	0,51 (0,38—0,64)	$5 \cdot 10^{-7}$	>9000
IIe	0,57 (0,22÷0,92)	$3 \cdot 10^{-10}$	>9000
IIf	—	10^{-5}	>2500
IIg	2,9 (1,2—4,6)	$3 \cdot 10^{-7}$	>9000
IIh	0,89 (2,28—1,5)	$2 \cdot 10^{-5}$	>3000

2,6-Dimethyl-3,5-diethoxycarbonyl-4-(2'-furyl)-1,4-dihydropyridine (Ia). A mixture of 2.12 g (0.02 moles) of freshly distilled furfurol, 2.60 g (0.02 moles) of ethyl acetate, and 2.58 g (0.02 moles) of ethyl β-aminocrotonate was boiled in 10 ml of ethanol for 2 h. Crystallization was from an ethanol—water mixture (1:1) (see Table 1).

Ic-e were obtained from the respective aldehydes and esters in a similar manner (see Table 1).

2,6-Dimethyl-3,5-diethoxycarbonyl-4-(5'-trifluoromethyl-2'-furyl)-1,4-dihydropyridine (Ie). A mixture of 1.64 g (0.01 moles) of 5-trifluoromethyl-2-furylaldehyde, 2.60 g (0.02 moles) of ethyl acetate, and 2 ml of a 25% aqueous solution of ammonia was boiled in 10 ml of ethanol for 3 h. The mixture was decanted into 100 ml of water, and acidified to pH 1.0 with hydrochloric acid. The precipitate was filtered out, and crystallization was from an ethanol—water mixture (1:1) (see Table 1).

Compounds Ig and h were obtained in a similar manner (see Table 1).

2,6-Dimethyl-3,5-diethoxycarbonyl-4-(α-furyl-2'-ethylene)-1,4-dihydropyridine (IIa). A mixture of 1.22 g (0.01 moles) of furyl-acrolein, 1.29 g (0.01 moles) of ethyl β-aminocrotonate, and 1.30 g (0.01 moles) of ethyl acetate was boiled in 10 ml of ethanol for 4 h. The mixture was decanted into water and extracted with chloroform (20 ml, 3×). The chloroform extract was dried with anhydrous sodium sulfate, and the chloroform was distilled off in a vacuum. The oily residue was rubbed over with hexane, and crystallization was from ethanol with activated charcoal treatment. Yellow crystals of IIa were obtained (see Table 1).

Compounds IIb-h are obtained in a similar manner (see Table 1).

EXPERIMENTAL PHARMACOLOGY

In acute experiments on chlorolose-anesthetized (90 mg/kg, intraperitoneally) cats, arterial pressure, respiration, and the EKG were recorded. All of the recordings were made on a Narco Bio-Systems physiograph. The mean effective dose (ED_{30}) which reduced arterial pressure by 30% compared to the initial pressure ($P = 0.05$) was determined. The compounds under investigation were administered intravenously through a cannula tied into the femoral vein. The substances were dissolved in a 50% solution of dimethylacetamide. In each test the effect of the solvent on the hemodynamics of the experimental animal was checked.

The tests on isolated rat small intestine were conducted in accordance with the generally accepted methodology. We studied the effects of the substances on muscle tonus and intestinal contractions induced by acetylcholine. The mean effective concentration (EC_{50}) of the substances which decreased the effect of acetylcholine by 50% was determined by means of a graph.

The substances' acute toxicity was investigated by intraperitoneal administration to randomly bred white mice. The LD_{50} was determined by the Litchfield and Wilkinson method.

The results of these studies are shown in Table 2.

LITERATURE CITED

1. R. Balicki and P. Nantka-Namirski, Pol. J. Pharmacol., 26, 647 (1974).
2. B. Loev, M. Goodman, K. Snader, et al., J. Med. Chem., 17, 956 (1974).
3. E. Hoefer, G. Fries, E. Jassmann, et al., Pat. 122,524 (GDR), Chem. Abstr., 87, 23073 (1977).
4. U. Eisner and J. Kuthan, Chem. Rev., 72, 1 (1972).
5. D. Hofmann, E. M. Kosower, and K. Wallenfels, J. Am. Chem. Soc., 83, 3314 (1961).
6. W. Traber and P. Karrer, Helv. Chim. Acta, 41, 2066 (1958).
7. P. J. Brignell, U. Eisner, and P. L. Farrell, J. Chem. Soc., B., 1083 (1966).