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# SYNTHESIS AND PHARMACOLOGICAL ACTIVITY OF 4-ARYL-1,4-DIHYDROPYRIDINES WITH FLUORINATED NITROGEN-CONTAINING SUBSTITUENTS IN THE BENZENE RING

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4-Aryl-1,4-dihydropyridine derivatives of the nifedipine (Ia) type are at present considered the most effective therapeutic substances used in the treatment of cardiovascular diseases, especially hypertension and ischemic heart disease [1, 2].

The biological activity of 1,4-dihydropyridine derivatives (1,4-DHP) is associated with their ability to block voltage-dependent calcium channels in cell membranes. This class of compounds also includes agents with the opposite action, i.e. activators of calcium channels. Thus, 1,4-DHP compounds are interesting not only as pharmacological agents, but also as probes for studies of calcium channels.

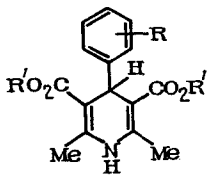
Current concepts [3] indicate that 4-aryl-1,4-dihydropyridines of the type represented by I have the conformation of a bath, with the aryl nucleus in the axial position, orthogonal with respect to the plane of the dihydropyridine nucleus (II). Optimal biological activity is achieved when substituent X is located on the same side of the C(4)-Ar bond as the hydrogen atom on C(4). Ester groups are located in the equatorial position. This requires the carbonyl ester groups to be in the cis position with respect to the substituents at C(2) and C(6).

The presence of substituent X in the ortho position promotes conformation of type II [3].

Nifedipine (compound Ia) is one of the most widely used hypotensive agents. However, the presence in the molecule of a nitro group reduces its stability on storage, especially in the presence of light. It would be interesting to replace the nitro group with nitrogen-containing fluorinated groups with similar electronic properties and dipole structure.

With this aim, we synthesized 4-aryl-1,4-dihydropyridines (Ib-h), in which the phenyl rings contained $N(CF_3)_2$, $NHSO_2CF_3$, and $N(SO_2CF_3)COOEt$.

Scheme 1




Ia-h

$R^1$=Me, R = $NO_2$ (a), 2 = $N(CF_3)2$ (b), 3 = $N(CF_3)2$ (c), 4 = $N(CF_3)2$ (d), 2 = $NHSO_2CF_3$ (e), $R^1$ = Et, R = 2 = $NHSO_2CF_3$ (f), 3 = $NHSO_2CF_3$ (g), 3 = $N(COOEt)SO_2CF_3$ (h).

Compounds Ib-d were prepared by a modification of the Hantzsch method [4] from N,N-bis(trifluoromethyl)aminobenzaldehyde, the methyl ester of acetoacetic acid, and $\beta$-aminocrotonate respectively, in methanolic solution.

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TABLE 1. 1,4-Dihydropyridines Ib-h

| Compound | Melting temperature, °C | Yield, % | Atomic formula | PMR spectrum, δ, ppm* | $^{19}$F-NMR spectrum, δ, ppm* |
|---|---|---|---|---|---|
| Ib | 157-8 | 32 | $C_{19}H_{18}F_6N_2O_4$ | 2.28 s (6H, $CH_3$), 3.50 s (6H, $CO_2CH_3$), 5.29 s (1H, CH), 5.68 s (1H, NH), 7.15-7.43 m (4H, aromatic) | -56.30 s (6F, $CF_3$) |
| Ic | 132-4 | 39 | $C_{19}H_{18}F_6N_2O_4$ | 2.28 s (6H, $CH_3$), 3.54 s (6H, $CO_2CH_3$), 4.91 s (1H, CH), 5.59 s (1H, H), 7.10-7.30 m (4H, aromatic) | -55.90 s (6F, $CF_3$) |
| Id | 124-6 | 51 | $C_{19}H_{18}F_6N_2O_4$ | 2.29 s (6H, $CH_3$), 3.52 s (6H, $CO_2CH_3$), 5.02 s (1H, CH), 5.61 s (1H, NH), 7.10-7.32 m (4H, aromatic) | -55.76 s (6F, $CF_3$) |
| Ie | 170-1 | 57 | $C_{18}H_{19}F_3N_2O_6S$ | 2.28 s, 3.60 s, 6.06 s, 7.01-7.26 m, 10.33 s (1H, $NHSO_2CF_3$) | |
| If | 210-1 | 45 | $C_{20}H_{23}F_3N_2O_6S$ | 1.13 t (6H, $CH_2CH_3$), 2.30 s (6H, $CH_3$), 4.09 q (4H, $CH_2CH_3$), 5.10 s (1H, CH), 5.73 s (1H, NH), 7.02-7.28 m (4H, aromatic), 10.62 s (1H, $NHSO_2CF_3$) | |
| Ig | 156-7 | 65 | $C_{20}H_{23}F_3N_2O_6S$ | 1.15 t, 2.26 s, 4.03 q, 4.94 s, 5.61 s, 6.90-7.25 m, 9.35 s | -75.92 s (3F, $CF_3$) |
| Ih | 125-6 | 50 | $C_{23}H_{27}N_2F_3O_8S$ | 1.14 t (6H, $CO_2CH_2CH_3$), 1.20 t (3H, $COCH_2CH_3$), 2.27 s (6H, $CH_3$), 4.01 q (4H, $CO_2CH_2CH_3$), 4.25 q (2H, $COCH_2CH_3$), 4.95 s (1H, CH), 5.60 s (1H, NH), 6.96-7.35 m (4H, aromatic) | -75.92 s (3F, $CF_3$) |

*The solvent was $CDCl_3$; standards were HMDS for PMR and $CCl_3F$ for $^{19}$F-NMR.

TABLE 2. Properties of Compounds III-VI

| Compound | Yield, % | Melting temperature, °C (boiling temperature, mm Hg) | Atomic formula | PMR spectrum, δ, ppm | $^{19}$F-NMR spectrum, δ, ppm | IR spectrum, ν, $cm^{-1}$ (KBr) |
|---|---|---|---|---|---|---|
| IIIb | 28 | 74-6(20) | $C_9H_5F_6NO$ | 7.50-8.00 m (4H, aromatic), 10.10 s (1H, CHO)* | -55.8 (6F, $CF_3$)* | 1,710(C=O) |
| IV | 63 | 102-4(18) | $C_8H_5BrF_6N_2$ | | | |
| V | 64,5 | 83-6(50) | | 7.25-7.60 m (4H,aromatic)† | -55.8 s† (6F, $CF_3$) | |
| IIIc | 36 | 86-8(20) | $C_9H_5F_6NO$ | 7.19-7.95 m (4H, aromatic), 9.99 s (1H, CHO)† | -55.7 s† (6F, $CF_3$) | 1718(C=O) |
| IIIa | 23 | 57-60(25) | $C_9H_5F_6NO$ | | | |
| VIa | 59 | 170-1 (melted [7] 170) | $C_{17}H_{20}N_2O_4$ | | | |
| VIb | 58 | 148-9 (melted [7] 149-6) | $C_{19}H_{24}N_2O_4$ | | | |
| VIc | 85 | 149-50(melted[7] 151-53) | $C_{19}H_{24}N_2O_4$ | | | |

*The solvent was $CD_3CN$.
†The solvent was $CDCl_3$.

The method for synthesizing N,N-bis(trifluoromethyl)-n-aminobenzaldehyde (IIIa, b) was as described previously [5], and its ortho and meta isomers (IIIb, c) were prepared from n-chloro-N,N-bis(trifluoromethyl)aniline [5] according to the following scheme:

Scheme 2

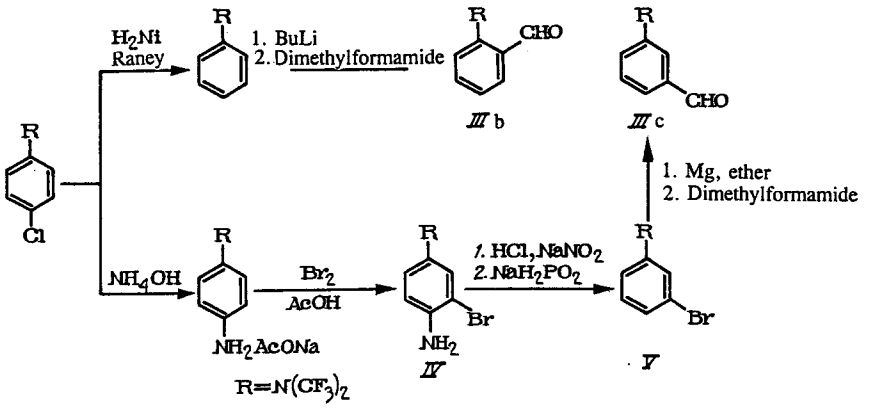

TABLE 3. Effects of Compounds Ib-h on Systemic Hemodynamics and Myocardial Contractility*

| Compound | Systolic BP | Diastolic BP | Heart rate | SV | T (isolated myocardium) |
|---|---|---|---|---|---|
| | % | | | | |
| Ib | ↓36 | ↓33 | ↓16 | ↓11 | ↓57 |
| Ic | ↓22 | ↓19 | ↑15 | ↑10 | 0 |
| Id | 0 | 0 | ↓10 | ↓5 | ↓10 |
| Ie | ↓20 | ↓18 | ↑14 | ↑12 | 0 |
| If | ↓14 | ↓21 | ↑16 | ↓9 | ↓22 |
| Ig | ↓7 | ↓10 | ↑12 | ↓10 | ↓15 |
| Ih | ↓16 | ↓12 | ↑15 | ↓22 | ↓28 |
| Nifedipine | ↓40 | ↓44 | ↓13 | ↓20 | ↓24 |

*I.v. dosage at 0.1 mg/kg.

Compounds Id-g were synthesized by reduction of nifedipine (Ia) or its analogs with an n-nitro group in the 4-phenyl ring and with ethoxycarbonyl groups in positions 3 and 5 of the hydropyridine nucleus, followed by treatment of the intermediate amino derivatives (IIa-c) of trifluoromethanesulfo acids with anhydride in a methylene chloride solution in the presence of triethylamine.

Compound Ih was prepared from Ig by treatment of Ig with a sodium methanoate solution followed by reaction of the resulting sodium salt with the ethyl ester of chlorocarbonic acid.

Melting temperatures, yields, elemental analyses, and NMR spectral data of compounds Ib, d are shown in Table 1, and yields, physicochemical properties, and elemental analyses of initial compounds IIIb, c, IV, and V are shown in Table 2.

## CHEMICAL METHODS

PMR spectra were recorded on a Gemini-200 (Varian, USA) apparatus using HMDS as the internal standard. $^{19}$F-NMR spectra were recorded on a WP-200 (Bruker, FRG) spectrometer with a working frequency for $^{19}$F of 188.28 MHz and using $CCl_3F$ as the internal standard. IR spectra were recorded in KBr tablets using a UR-20 (GDR) spectrophotometer. Product purities were monitored by thin-layer chromatography on Silufol UV-254 plates and by GLC using a Tsvet-4 chromatograph.

Experimentally determined elemental compositions agreed with calculated values.

**N,N-Bis(trifluoromethyl)aniline**. Methanolic KOH solution (1 N, 20 ml) was added to a solution of 5.27 g (0.02 mole) of n-chloro-N,N-bis(trifluoromethyl)aniline in 12 ml of methanol, along with 3.8 g of Raney nickel in 15 ml of methanol. The reaction was mixed under a hydrogen atmosphere until 470 ml of hydrogen had been absorbed. The catalyst and KCl precipitate were removed by filtration and washed with ether. Ether washings were combined with the filtrate, washed with eater, and dried with $MgSO_4$. Ether was evaporated in a fractionator and residues were redried. The yield was 3.65 g (80%). The boiling point was 118°C [6], $n_D^{20}$ was 1.3821. The PMR spectrum (acetone-$d_6$), δ, ppm, was: 7.53-7.60 m (5H, aromatic); the $^{19}$F-PMR spectrum (acetone-$d_6$), δ, ppm, was: 54.93 s (6F, $CF_3$).

**2-N,N-Bis(trifluoromethyl)aminobenzaldehyde (IIIb)**. Butyllithium (10 ml, 1.7 N) in hexane was added dropwise with mixing to a solution of 3.65 g (0.016 mole) of N,N-bis(trifluoromethyl)aniline in 15 ml of anhydrous tetrahydrofuran at −40 to −50°C; the temperature of the reaction mixture was slowly increased to 20°C and the reaction was incubated overnight. After cooling in an ice bath, 10 ml of anhydrous dimethylformamide in 10 ml of anhydrous tetrahydrofuran was added dropwise. The reaction was mixed for 30 min and treated with 40 ml of 10% HCl. The reaction mixture was extracted with ether (3 × 40 ml), and the ether extracts were pooled and washed with saturated NaCl solution. The material was dried with $MgSO_4$, the ether was evaporated with a fractionator and the residue was redried.

**2-Bromo-4-[bis(trifluoromethyl)amino]aniline (IV)**. Anhydrous AcONa (4.12 g) was added to a solution of 6.1 g (0.025 mole) of n-N,N-bis(trifluoromethyl)phenylenediamine in 12 ml of AcOH, and the reaction was mixed at 10°C, and bromine solution (4 g, 0.025 mole) in 6 ml of AcOH was added dropwise. The reaction was mixed for 2 h at 10°C and 4 h at 20°C, and was filtered. The filtrate was poured into 200 ml of water and neutralized with aqueous ammonia to pH 7. The material was extracted with ether (3 × 50 ml) and dried with $MgSO_4$. The ether was evaporated and the residue was redried *in vacuo*.

**m-Bromo-N,N-bis(trifluoromethyl)aniline (V)**. Concentrated HCl (18 ml) was added to diazo solution prepared from 5.17 g (0.016 mole) of amino compound V, 9 ml of concentrated HCl, and 1.2 g of $NaNO_2$ in 3.5 ml of water and the mixture

was poured dropwise to a cooled (ice bath) solution of 18.7 g (0.21 mole) of sodium hypophosphate in 20 ml of water. The reaction mixture was incubated overnight and then distilled with water steam. The azeotrope was extracted with ether (3 × 30 ml) and dried with $MgSO_4$; the ether was evaporated and the residue redried *in vacuo*.

**m-N,N-Bis(trifluoromethyl)aminobenzaldehyde (IIIc).** Dimethylformamide (0.8 g in 3 ml of ether) was added with mixing at 20°C to a Grignard solution prepared from 3 g (0.0097 mole) of compound V in 30 ml of anhydrous ether, and the reaction was mixed for 1 h, diluted with 50 ml of ether, and incubated overnight. The reaction was poured into 100 ml of saturated $NH_4Cl$ solution and extracted with ether (3 × 50 ml). After drying with $MgSO_4$, the ether was evaporated and the residue was redried *in vacuo*.

**n-N,N-Bis(trifluoromethyl)aminobenzaldehyde (IIIa).** Compound IIIa was prepared by a similar method, using p-iodo-N,N-bis(trifluoromethyl)aniline [5].

**2,6-Dimethyl-3,5-dicarbomethoxy-4-[N,N-bis(trifluoromethyl)aminophenyl]-1,4-dihydropyridines (Ib-d).** N,N-bis(trifluoromethyl)aminobenzaldehyde (0.005 mole) was boiled in 15 ml of methanol with an equimolar quantity of the methyl ester of β-aminocrotonic acid and the methyl ester of acetoacetic acid for 8 h. The methanol was evaporated *in vacuo*. The residue was chromatographed on a column containing silica gel 40/100, eluted with $CH_2Cl_2$, and crystallized from aqueous methanol.

**4-Aminophenyl-1,4-dihydropyridines (VIa-c).** Raney nickel (0.4 g) was added to a solution of 0.0025 mole of the appropriate 4-nitrophenyl-1,4-dihydropyridine in 100 ml of tetrahydrofuran, and hydration was conducted at 20°C with mixing under hydrogen at 1.5-2 atmospheres. After the reaction had finished (monitored by thin-layer chromatography), the catalyst was removed by filtration and the filtrate was evaporated; the resulting oil was taken up in ether and crystallized from methanol with water.

**4-Trifluoromethylsulfonylaminophenyl-1,4-dihydropyridines (Ie-g).** A solution of 0.28 g (0.001 mole) of the anhydride of trifluoromethanesulfoacid in 5 ml of anhydrous $CH_2CH_2$ was added dropwise with mixing to a solution of 0.001 mole of 4-aminophenyl-1,4-dihydropyridine (VIa-c) and 0.001 mole (0.1 g) of triethylamine in 5 ml of anhydrous $CH_2Cl_2$ at −10 to −15°C. Reactions were mixed for 30 min at −10°C, 30 min at 0°C, and 2 h at 20°C. Reactions were poured into water, the organic layer was removed and the aqueous layer was washed with $CH_2CH_2$ (2 × 10 ml). The organic extracts were pooled, washed with water (1 × 10 ml), dried with $MgSO_4$, and evaporated to dryness *in vacuo*. Residues were crystallized from benzene.

**2,6-Dimethyl-3,5-dicarboethoxy-4-[3-N-(trifluoromethylsulfonyl)-N-(carboethoxy)aminophenyl]-1,4-dihydropyridine (Ih).** Sodium methylate (1.5 N, 0.62 ml) was added dropwise to 0.45 g (0.00095 mole) of 2,6-dimethyl-3,5-dicarboethoxy-4[3-N-(trifluoromethylsulfonyl)aminophenyl]-1,4-dihydropyridine (Ig). The reaction was mixed for 5 min, methanol was evaporated *in vacuo*, and the residue was dissolved in 2 ml of anhydrous acetone. A solution of 0.11 g (0.001 mole) of the ethyl ester of chlorocarbonic acid in 1 ml of acetone was added and the reaction was mixed for 6 h at 20°C. The precipitate was collected by filtration and the filtrate was dried *in vacuo*. The resulting oil was purified by chromatography on a column containing silica gel L40/100 eluted with chloroform:ethyl acetate (1:1). The product was crystallized from aqueous ethanol.

## BIOLOGICAL METHODS

The hemodynamic effects of compounds were studied in acute experiments in Wistar rats of both sexes, weighing 250-300 g, anesthetized with sodium thiopental (50 mg/kg). Arterial blood pressure was measured electromagnetically (TR-200T apparatus, obtained from Nichon Kohden, Japan) in the carotid artery. Cardiac pump function was assessed in terms of changes in the stroke volume (SV) by tetrapolar rheography [8] (using a P 04-02 rheograph). The effects of compounds on vessels were studied by calculating total peripheral vascular resistance (TPVR) as TPVR = (mean blood pressure/minute volume) × 1333, where the minute volume was SV × heart rate.

Continuous ECG recordings were made during experiments in standard lead II (using an AB-60129 amplifier from Nichon Kohden, Japan). Synchronized recording of blood pressure, ECG, and SV was carried out using a Polygraph System 6000 recorder (from Nichon Kohden, Japan).

Compounds were dissolved in dimethylacetamide and physiological saline, and given i.v. (in the jugular vein) at doses of 0.1-1.0 mg/kg. The volume ratio of solvent and physiological saline was not greater than 1:100 and had no effect on the hemodynamic parameters measured.

The effects of experimental compounds on myocardial contractile activity were studied in experiments on isolated left ventricular papillary muscles, contracting isometrically. Muscles were stimulated electrically with square-wave impulses lasting 5 msec at voltages 10-25% over threshold, and a frequency of 1 Hz. Muscles were perfused with Tyrode solution oxygenated with carbogen (95% $O_2$, 5% $CO_2$). Contraction strength (T) was measured with a 6 MKh ZS recorder. Compounds were used at concentrations of $10^{-8}$ to $10^{-3}$ M at a ratio of solvent to Tyrode solution of 1:100. All results were analyzed by variation statistics using Student's test.

The results presented in Table 3 show that compounds I had a unique pharmacological profile. Most of these compounds had hypotensive and negative inotropic activities of differing intensities. The most active compounds were compounds Ib, c, e. Interestingly, the effects of compounds I on the cardiovascular system were accompanied by changes in heart rate in different directions. This is presumably due in some cases to the effect of compounds themselves on cardiac rhythm (reduction in heart rate) and in others to the absence of this effect (resulting in reflex tachycardia in response to reductions in blood pressure). The levels of the cardiodepressive and hypotensive effects were not always similar. Thus, compound Ic, which had pronounced vasodilator activity, had no great effect on myocardial contractility; compound Ih, with a significant negative inotropic effect (reduction in myocardial contractility by 28%) had a moderate hypotensive effect.

In addition, the pharmacodynamic profile and similarity in structure of experimental compounds and known calcium ion antagonists, i.e. nifedipine (Ia), suggests a common mechanism of action for these agents.

The most active compound was compound Ib, which contains an $N(CF_3)_2$ group in the ortho position of the benzene nucleus. This supports the suggestion that optimal biological activity requires the presence in the ortho position of a substituent which is very voluminous and not very strongly electron-accepting. Activity is also favored by the similarity of the electronic properties and dipole structure of the $N(CF_3)_2$ group and the $NO_2$ group.

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