Synthesis of 4-Aryl-1,4-dihydro-2,6-bis(trifluoromethyl)-3,5-pyridinedicarboxylates

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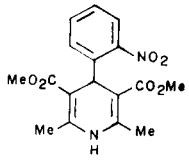
Received May 22, 1986

Treatment of 4-aryl-2,6-dihydroxy-2,6-bis(trifluoromethyl)-3,5-piperidinedicarboxylic acid esters with phosphorus oxychloride in pyridine afforded 4-aryl-1,4-dihydro-2,6-bis(trifluoromethyl)-3,5-pyridine dicarboxylic acid esters which were reported originally by Balicki and Nantka-Namirski, but were later proven to be 4-aryl-2,6-dihydroxy-2,6-bis(trifluoromethyl)-3,5-piperidine dicarboxylic acid esters.

J. Heterocyclic Chem., **23**, 1523 (1986).

Since the discovery of nifedipine, a clinically important antihypertensive and antiangina drug in 1971 [1], substituted dihydropyridines have received much attention in the search of therapeutic agents for cardiovascular ailments [2,3]. Over a dozen dihydropyridines related structurally to the prototype compound are currently under clinical evaluation. This class of compounds is known to exhibit its biological effects by the inhibition of calcium ion influx across the cell membrane through slow calcium channels [4]. 4-Aryl-1,4-dihydro-2,6-bis(trifluoromethyl)-3,5-pyridinedicarboxylates were of interest to us for their



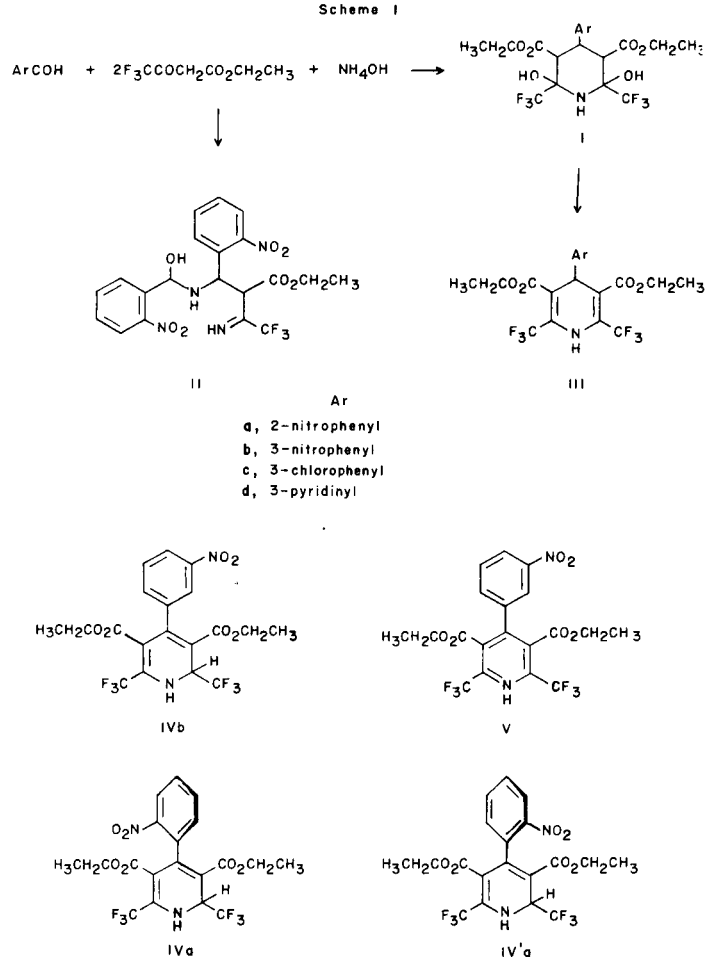
Nifedipine

potential biological activities. These compounds have trifluoromethyl groups as substitutes for the methyl groups present in the clinically important dihydropyridines.

In 1974, Balicki and Nantka-Namirski reported the synthesis of a series of 4-aryl-1,4-dihydro-2,6-bis(trifluoromethyl)-3,5-pyridinedicarboxylic acid diethyl esters III by the reaction of ethyl 4,4,4-trifluoroacetoacetate, arylaldehyde and ammonium hydroxide in ethanol by the method of Hantzsch [5]. Subsequently, Singh and Lesher [6] reinvestigated the work of Balicki and Nantka-Namirski, and found that the compounds claimed by the original workers are not the dihydropyridine derivatives III, but rather 4-aryl-2,6-dihydroxy-2,6-bis(trifluoromethyl)-3,5-piperidinedicarboxylic acid diethyl esters I. These workers then tried various dehydrating agents for the conversion of the dihydroxypiperidines I to the corresponding dihydropyridines III, but without success.

When we repeated the reaction of Balicki and Nantka-Namirski [5], we obtained compounds that had spectral and combustion analytical data which agreed with those reported by Singh and Lesher for the dihydroxypiperidine structure. It is interesting to note that immediate heating of the reaction mixture was essential for a high yield of the product. At room temperature the reaction took a different path, giving an acyclic product. Thus, when a mixture of 2-nitrobenzaldehyde, ethyl 4,4,4-trifluoroacetoacetate, and ammonium hydroxide was allowed to stir in ethanol at room temperature for 2 hours, β-[[hydroxy(2-nitrophenyl)methyl]amino]-2-nitro-α-(2,2,2-trifluoro-1-imino-

Scheme I



ethyl)benzenepropanoic acid ethyl ester (II) was obtained in a 44% yield. The structural assignment was based on the elemental analysis and spectral data (See Experimental).

We have now successfully converted I into 2,6-bis(trifluoromethyl)-1,4-dihydropyridines III. The dehydration of I was achieved in low to moderate yields simply by treating the pyridine solution of I with phosphorus oxychloride at room temperature for several hours. The ^{1}H nmr (DMSO-d_6) spectrum of 1,4-dihydro-4-(2-nitrophenyl)-2,6-bis(trifluoromethyl)-3,5-pyridinedicarboxylic acid diethyl ester (IIIa), for example, showed the resonance signal of the C_4-proton at δ 5.44 and the N_1-proton at 9.68 ppm, both as a singlet. As expected from the symmetrical nature of the molecule, signals of the protons of two ethyl groups were superimposed, and showed at δ 1.03 (6H, t) and 4.03 ppm (4H, q) for methyl and methylene protons, respectively. The aromatic protons resonated in the region of δ 7.95-7.40 ppm. The infrared spectrum of IIIa exhibited the NH stretching band at 3430 and carbonyl absorption bands at 1725 and 1710 cm^{-1}. Extention of the reaction time did not improve the yields. Rather, it caused isomerization of III to form thermodynamically more stable 1,2-dihydropyridines IV and fully oxidized pyridines V. Previously, an attempt by Singh and Lesher to obtain V by the treatment of Ib with nitric acid was unsuccessful [6]. The structure of IVb was supported by the ^{1}H nmr spectrum obtained in the DMSO-d_6 solution which was pretreated with a few drops of deuterium oxide. The resonance signal of the proton at the 2-position was shown as a quartet at δ 5.52 (J = 8 Hz) as a result of coupling with three flourines of the trifluoromethyl group. Since the molecule was no longer symmetrical, the proton of the two ethyl groups exhibited signals at δ 0.72 (3H, t) and 0.84 (3H, t) for methyl groups and 3.75 (2H, q) and 3.88 ppm (2H, q) for methine groups. The proton at the N-1 resonated δ 8.91 as a doublet. Two ethyl groups of V showed signals δ 1.07 (6H, t, $2CH_3$) and 4.06 ppm (4H, q, $2CH_2$). It is interesting to note that the dehydration reaction of Ia afforded a pair of atropisomers of 1,2-dihydro-4-(2-nitrophenyl)-2,6-bis(trifluoromethyl)-3,5-pyridinecarboxylic acid ethyl esters (IVa) which were separated by a preparative hplc in addition to IIIa. It has been shown by X-ray diffraction studies that 4-aryl-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylic acid diesters have a boat-type conformation, in which the aryl group is free to rotate unrestricted by the ester groups [7]. In the case of IVa, however, the rotational freedom of the *o*-substituted phenyl group is severly restricted due to the steric bulkiness, and the nitrophenyl group assumes a position which is perpendicular to the 1,2-dihydropyridine as shown by structure IVa and IVa'. The restricted rotational freedom and the unsymmetrical nature of the molecule made the separation of the rotational isomers possible.

4-Aryl-1,4-dihydro-2,6-bis(trifluoromethyl)3,5-pyridinedicarboxylic acid esters described in this report showed moderate *in vitro* Ca^{+2} antagonistic activity determined by the relaxation of K^+-depolarized aortic smooth muscle strips, and lowered high blood pressure when given to spontaneously hypertensive rats by oral route.

EXPERIMENTAL

Melting points were taken in capillary tubes (Thomas-Hoover melting point apparatus) and are uncorrected. The ir spectra were obtained in potassium bromide pellets using a Perkin-Elmer 21 spectrophotometer. The nmr spectra were determined on a Varian XL-300 or a Varian FT-80A spectrometer using tetramethylsilane as the internal reference. Combustion elemental analyses were performed by the Analytical Section of these Laboratories.

4-(3-Chlorophenyl)-2,6-dihydroxy-2,6-bis(trifluoromethyl)-3,5-piperidinedicarboxylic Acid Diethyl Ester (Ic).

To a solution of 3-chlorobenzaldehyde (2.8 g, 0.02 mole) and ethyl 4,4,-4-trifluoroacetoacetate (7.36 g, 0.04 mole) in ethanol (40 ml) was added ammonium hydroxide solution (approximately 58% ammonium hydroxide) (4 ml). The resulting mixture was heated under reflux for 1.5 hours. Evaporation of the reaction mixture on a rotary evaporator gave a thick oil which solidified partially on standing. The crude product was recrystallized from ethanol (95%) to give 5.1 g (50%) of the product, mp 113-115°; ir: 3440, 1720, and 1700 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 1.09 (t, 6H, $2CH_3$), 1.13 (q, 4H, $2CH_2$), 4.88 (s, 1H, H-4), 7.25-7.31 (m, 4H, aromatic H's), and 9.66 (s, 1H, NH).

Anal. Calcd. for $C_{19}H_{20}ClF_6NO_6$: C, 44.94; H, 3.97; N, 2.76. Found: C, 44.93; H, 4.01; N, 2.70.

2,6-Dihydroxy-4-(2-nitrophenyl)-2,6-bis(trifluoromethyl)-3,5-piperidinedicarboxylic acid diethyl ester (Ia) that was prepared similarly from 2-nitrobenzaldehyde, ethyl 4,4,4-trifluoroacetoacetate and ammonium hydroxide in ethanol medium and recrystallized from toluene (yield, 41%) melted at 108-111°, lit mp [5] 154-156°.

Anal. Calcd. for $C_{19}H_{20}F_6N_2O_8$: C, 44.02; H, 3.89; N, 5.41. Found: C, 43.94; H, 3.83; N, 5.40.

2,6-Dihydroxy-4-(3-pyridinyl)-2,6-bis(trifluoromethyl)-3,5-piperidinedicarboxylic acid diethyl ester (Id) that was prepared (yield, 30%) in the similar fashion and recrystallized from ether melted at 144.5-146°; lit mp 137-139° [6], 129-130° [5].

Anal. Calcd. for $C_{18}H_{20}F_6N_2O_6$: C, 45.57; H, 4.25; N, 5.91. Found: C, 45.75; H, 4.25; N, 5.91.

β-[[Hydroxy(2-nitrophenyl)methyl]amino]-2-nitro-α-(2,2,2-trifluoro-1-iminoethyl)benzenepropanoic Acid Ethyl Ester (II).

Ammonium hydroxide solution (10 ml) was added to a stirred solution of 2-nitrobenzaldehyde (7.55 g, 0.05 mole) and ethyl 4,4,4-trifluoroacetoacetate (18.40 g, 0.1 mole) in ethanol (100 ml). A mild exothermic reaction took place. A precipitate started to separate in about 10 minutes. The reaction mixture was stirred at room temperature for 2 hours, then chilled in ice. The precipitate was collected on a filter and washed with ethanol to give the product (10.6 g, 44%), mp 135-138° dec; ir: 3460 (OH), 3340 (NH), 3320 (=NH), and 1730 cm^{-1} (CO); ^{1}H nmr (DMSO-d_6): δ 1.78 (t, 3H, CH_3), 2.75 (AB_2, 1H, NH, disappeared upon deuterium oxide treatment) 3.22 (d, 1H, H-α, J = 14 Hz), 5.00 (AB_2, 1H, H-β, became doublet upon deuterium oxide treatment), 5.63 (AX_2, 1H, O-CH-N, J = 14 Hz and J = 6 Hz, became singlet upon deuterium oxide treatment), 8.00-7.50 (m, 9H, aromatic H's and OH), and 6.63 (s, 1H, HN=).

Anal. Calcd. for $C_{20}H_{19}F_3N_4O_7$: C, 49.59; H, 3.95; N, 11.57. Found: C, 49.70; H, 4.08; N, 11.54.

1,4-Dihydro-4-(3-nitrophenyl)-2,6-bis(trifluoromethyl)-3,5-pyridinedicarboxylic Acid Diethyl Ester (IIIb).

Phosphorous oxychloride (4 ml) was added slowly to a stirred ice-chilled pyridine (9 ml) solution of 2,6-dihydroxy-4(3-nitrophenyl)-2,6-(trifluoromethyl)-3,5-piperidinecarboxlic acid diethyl ester [6] (1.04 g). The temperature of the reaction mixture was gradually brought to room temperature in about 1.5 hours, and kept at the temperature for 4 hours. The reaction mixture was evaporated on a rotary evaporator to give a semi-solid which was partitioned in water and ether. The ether layer was separated, and washed with water, dried over anhydrous sodium sulfate, then evaporated on a rotary evaporator to give a thick oily residue. The residue was purified chromatographically using a silica gel column and a mixture of chloroform [8] and hexane [2] as the eluent. The titled compound (0.47 g, 49%) was finally recrystallized from toluene, mp 105-107°; ir: 3360 and 1730 cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.09 (t, 6H, $2CH_3$), 4.09 (q, 4H, $2CH_2$), 5.00 (s, 1H, H-4), 7.63-7.20 (m, 4H, aromatic H's), and 9.81 (s, 1H, NH).

Anal. Calcd. for $C_{19}H_{16}N_2O_6$: C, 47.31; H, 3.33; N, 5.81. Found: C, 47.72; H, 3.29; N, 6.06.

1,2-Dihydro-4-(3-nitrophenyl)-2,6-bis(trifluoromethyl)-3,5-pyridinedicarboxylic acid diethyl ester (IVb) was isolated in a 7% yield chromatographically as a by-product from the reaction above for the preparation of IIIb then purified by recrystallization from toluene, mp 94-98°.

Anal. Calcd. for $C_{18}H_{16}N_2O_6$: C, 47.31; H, 3.33; N, 5.81. Found: C, 47.59; H, 3.28; N, 6.10.

1,4-Dihydro-4-(3-pyridinyl)-2,6-bis(trifluoromethyl)-3,5-pyridinedicarboxylic acid diethyl ester IIId was prepared similarly from Id (1.186 g, 2.5 mmoles), pyridine (10 ml) and phosphorus oxychloride (5 ml), and purified by a fractional recrystallization from ether, yield 0.15 g, (14%), mp 130-132°; ir: 3264 (NH) and 1720 (CO) cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.09 (t, 6H, $2CH_3$), 4.09 (q, 4H, $2CH_2$), 4.91 (s, 1H, H-4), and 7.31-8.60 (m, 4H, aromatic H's).

Anal. Calcd. for $C_{18}H_{16}F_6N_2O_4$: C, 49.32; H, 3.68; N, 6.39. Found: C, 49.11; H, 3.58; N, 6.21.

4-(3-Chlorophenyl)-1,4-dihydro-2,6-bis(trifluoromethyl)-3,5-pyridinedicarboxylic acid diethyl ester (IIIc) was prepared in the similar fashion from Ic (2.54 g, 5 mmoles), pyridine (20 ml), and phosphorus oxychloride (10 ml). Evaporation of the ether extract on a rotary evaporator afforded an oily residue, from which a solid material (the unreacted starting material) deposited on standing at room temperature for several days. The solid was removed by suction filtration, and chilling of the concentrated viscous filtrate in ice caused solidification. The solid material was recrystallized from hexane to give the titled product (0.24 g, 10%), mp 61-63°. An additional amount (0.28 g, 12%) was obtained by a column chromatographic purification of the residue that was obtained by evaporation of the mother liquor; ir: 3440 (NH) and 1720 cm^{-1} (CO); ^1H nmr (DMSO-d_6): δ 1.09 (t, 6H, $2CH_3$), 4.13 (q, 4H, $2CH_2$), 4.88 (s, 1H, H-4), 7.25-7.31 (m, 4H, aromatic H's), and 9.66 (s, 1H, NH).

Anal. Calcd. for $C_{19}H_{16}F_6ClNO_4$: C, 48.37; H, 3.42; N, 2.97. Found: C, 48.37; H, 3.30; N, 3.04.

1,4-Dihydro-4-(2-nitrophenyl)-2,6-bis(trifluoromethyl)-3,5-pyridinedicarboxylic acid diethyl ester (IIIa) was prepared similarly from Ia (2.23 g, 5 mmoles), pyridine (20 ml), and phosphorus oxychloride (10 ml). The crude product obtained as a thick oil was purified by elution from a silica column with a mixture of chloroform [8] and hexane [2]. The compound that eluted first was recrystallized from hexane, giving the titled product (0.7 g, 29%), mp 105-107°.

Anal. Calcd. for $C_{19}H_{16}F_6N_2O_6$: C, 47.31; H, 3.33; N, 5.81. Found: C, 47.58; H, 3.59; N, 5.83.

1,2-Dihydro-4-(2-nitrophenyl)-2,6-bis(trifluoromethyl)-3,5-pyridinedicarboxylic Acid Diethyl Esters (IVa and IVa').

These compounds were obtained as a mixture from the chromatographic purification of the crude reaction product in the above reaction. The mixture was then separated into two fractions by a preparative hlpc. Both compounds were recrystallized from hexane. The compound that was eluted first melted at 129-130.5°, and amounted to 0.15 g (6%); ms: (CI) m/z, 483 (M + H), 437; ir: 3290 (NH) and 1690 cm^{-1} (CO); ^1H nmr (DMSO-d_6): δ 0.76 (t, 3H, CH_3), 0.86 (t, 3H, CH_3), 3.74 (q, 2H, CH_2), 3.86 (q, 2H, CH_2), 5.44 (q, 1H, H-2, J = 4 Hz), 7.16-8.30 (m, 4H, aromatic H's), and 9.08 (d, 1H, NH).

Anal. Calcd. for $C_{19}H_{16}F_6N_2O_6$: C, 47.31; H, 3.33; N, 5.81. Found: C, 46.95; H, 3.37; N, 5.70.

The second compound obtained from the hplc purification melted at 103-106°, and amounted to 0.15 g (6%); ms: (CI) m/z, 483 (M + H), 437; ir: 3290 (NH) and 1690 cm^{-1} (CO); ^1H nmr (DMSO-d_6): δ 0.72 (t, 3H, CH_3), 0.86 (t, 3H, CH_3), 3.80 (q, 4H, $2CH_2$), 5.42 (q, 1H, H-2, J = 8 Hz), 7.28-8.24 (m, 4H, aromatic H's), and 8.96 (d, 1H, NH).

Anal. Calcd. for $C_{19}H_{16}F_6N_2O_6$: C, 47.31; H, 3.33; N, 5.81. Found: C, 47.12; H, 3.40; N, 5.79.

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