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SYNTHESIS AND CRYSTAL STRUCTURE OF 2,6-BIS(N-CYTISINOMETHYL)-4-PHENYL-1,4-DIHYDROPYRIDINE-3,5-DICARBOXYLIC ACID DIETHYL ESTER

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By the interaction of the diethyl ester of 2,6-bis(bromomethyl)-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylic acid with two moles of the alkaloid cytosine, the corresponding 2,6-bis(cytisinomethyl) derivative was obtained. The spatial structure of the product was demonstrated by ^{1}H NMR spectroscopy and X-ray structural analysis.

Keywords: cytisine alkaloid, 1,4-dihydropyridine, X-ray structural analysis, ^{1}H NMR spectroscopy.

Considerable importance in the years 1980-1990 was acquired by derivatives of 1,4-dihydropyridines, obtained by Hantzsch condensation, as the first representatives of highly effective vasodilators and antihypertensive agents, the calcium channel blockers (Nicardipine, Nifedipine, Felodipine, etc) [1-3]. Compounds were also discovered among the derivatives of 1,4-dihydropyridines with no less valuable pharmacological properties (antibacterial, antiviral, antidiabetic, hepatoprotecting, antiulcer, etc) [4-6], which make further searches in the 1,4-dihydropyridine series extremely urgent. Up to the present time an enormous number of symmetrical and unsymmetrical derivatives of 1,4-dihydropyridine with various functional substituents has been synthesized, and a great number of methods of obtaining them (including microwave) has been developed by further conversions and aromatization [7-11].

Scientists of the Latvian Institute of Organic Synthesis have carried out an enormous study in executing the systematic synthesis of numerous derivatives of 1,4-dihydropyridines with the aim of searching for new cardiotonic and ionotropic preparations, and clarification of structure–activity relationships [12-14].

However, in spite of the enormous number of synthesized derivatives of 1,4-dihydropyridines, no compounds combining in their structure a 1,4-dihydropyridine ring and certain physiologically active alkaloids have been described in the literature. It therefore seemed of interest to synthesize previously unknown 1,4-dihydropyridine derivatives from certain alkaloids, in particular, cytisine.

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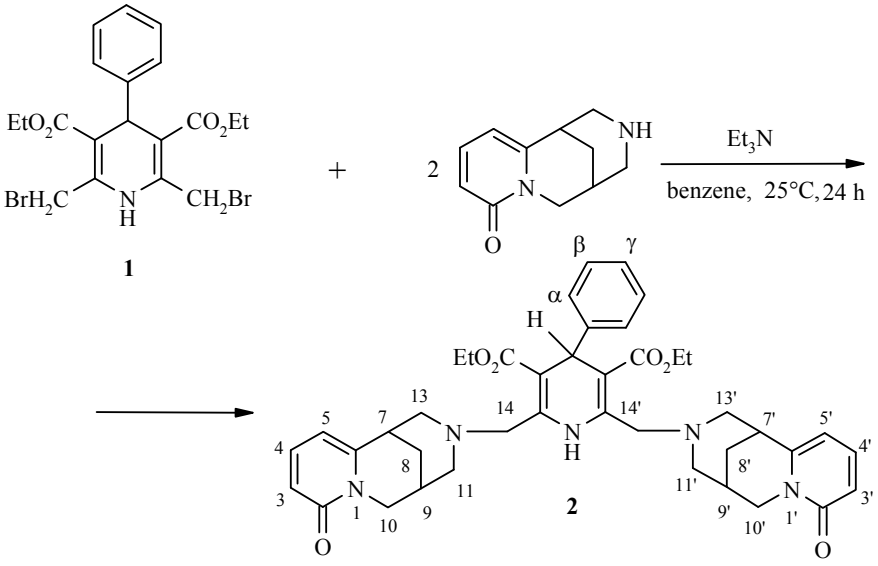
An extremely promising method of obtaining 2,6-bis(bromomethyl)-1,4-dihydropyridines, which are convenient synthons for further modification using nucleophilic substitution, was described in [13]. The diethyl ester of 2,6-bis(bromomethyl)-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylic acid (**1**), synthesized according to the procedure of [13], was selected as the starting compound for the synthesis of new alkaloid-containing 1,4-dihydropyridine derivatives.



The obtained 2,6-bis(bromomethyl)-1,4-dihydropyridine derivative **1** was used for the nucleophilic substitution of 2 equiv. of the alkaloid cytisine. Alkylation was carried out under mild conditions at room temperature in absolute benzene in the presence of a threefold excess of triethylamine, required not only to bind the hydrogen bromide formed but also to prevent possible salt formation by the initial alkaloid.

The reaction product **2** was isolated by column chromatography and was purified further by recrystallization. The disubstituted derivative **2** obtained was a white crystalline substance, readily soluble in many organic solvents, except saturated hydrocarbons.

Bands were observed in the IR spectrum of compound **2** for the stretching vibrations of the carbonyl group (1685), the amide groups of the cytisine framework (1654), and the NH bonds (3334 cm^{-1}). Mass spectrometric analysis, due to the specifics of the apparatus and the high molecular mass of compound **2** did not reveal a peak for the molecular ion, but only peaks for fragment ions. The ^1H NMR spectrum proved to be more informative. Singlet signals were displayed for NH protons and H-4 of the 1,4-dihydropyridine ring, and triplet and quartet signals for the protons of the two practically equivalent ethoxy groups. The methylene protons CH_2N in positions 2, 6 of the 1,4-dihydropyridine ring proved to be nonequivalent and were displayed as a broadened doublet at 2.94 and pairs of doublets at 3.92 ppm. An extremely interesting fact should be noted. The protons of the cytisine framework are displayed not by twin but by duplicated signals with a displacement of 0.05-0.14 ppm indicating their nonequivalence, linked probably with their different spatial orientation relative to the 1,4-dihydropyridine ring and with the shielding effect of neighboring groups.

We carried out an X-ray structural analysis of the molecule **2** with the aim of possibly determining the effect of spatial factors of the different functional electron-withdrawing ester groups, the aromatic phenyl substituent, and two bulky cytisine substituents on the general structure of the compound.

It was established that the bond lengths and valence angles in the structure of **2** were close to standard values [15].

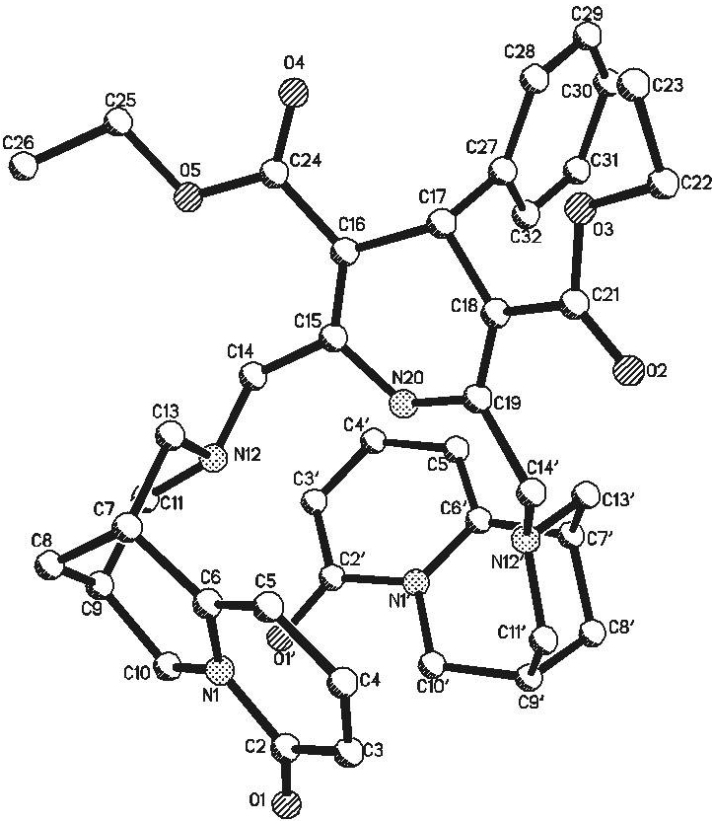


Fig. 1. Structure of the molecule of the diethyl ester of 2,6-bis(N-cytisinomethyl)-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylic acid (**2**) (hydrogen atoms are not shown).

The 1,4-dihydropyridine ring C(15)C(16)C(17)C(18)C(19)N(20) takes up the conformation of a strongly flattened *boat* ($\Delta C_2^{17} = 2.4^o$) with atoms C(17) and N(20) issuing by 0.36 and 0.15 Å respectively towards the β-side from the plane of the remaining ring atoms. The substituents at atoms C(15), C(16), C(18), and C(19) are oriented equatorially, but the phenyl ring is in an axial orientation relative to the 1,4-dihydropyridine ring. The carbon atoms in the ethoxycarbonyl groups are coplanar with a precision of ±0.009 and ±0.01 Å with the exception of the atoms of the methyl groups (C26) and C(23), which issue from the plane of the remaining atoms by 0.56 and 0.57 Å respectively. The heterocycles in the cytisine substituents take up a conformation standard for the initial cytisine. The exceptions are the valence angles at the N(12) and N(12') atoms, here this is pyramidal (sum of valence angles 331 and 334° respectively), the nitrogen atom may also take up a planar-trigonal coordination. The difference in the coordination of the nitrogen atom in the substituents mentioned above is caused by a mesomeric effect. The dihydropyridine rings in both cytisine substituents are planar. The tetrahydropyridine rings N(1)C(6)C(7)C(8)C(9)C(10) and N(1')C(6')C(7')C(8')C(9')C(10') take up the conformation of a distorted *sofa*. The piperidine rings are in the conformation of an almost ideal *chair*.

EXPERIMENTAL

The IR spectra were registered on an AVATAR-320 spectrometer. The ^{1}H NMR spectra were recorded on a Bruker DRX 500 (500 MHz) spectrometer in DMSO-d_6, internal standard was TMS. Mass spectra were obtained on a Finnigan MAT Incos 50 instrument with direct insertion of sample into the ion source (EI, 70 eV).

X-ray Structural Experiment. The parameters of the unit cell and the intensities of 7228 independent reflections were measured on a Bruker APEX-II CCD automatic diffractometer, MoKα radiation, graphite monochromator, θ/2θ scanning, 2θ ≤57°. Crystals were triclinic, clear (0.46×0.23×0.14), a = 9.272(2), b = 9.995(2), c = 10.724(2) Å, α = 97.451(1)°, β = 107.894(1)°, γ = 101.483(10)°, V = 907.26(3) Å^3, d_{calc} = 1.292 g/cm^3, Z = 1 ($C_{41}H_{47}N_5O_6$), space group $P\bar{1}$.

The structure was solved by the direct method and refined by the full-matrix least-squares method in an anisotropic approximation for the non-hydrogen atoms. The H atoms were calculated geometrically and positioned as a type of rider. In the calculations 6733 reflections with $I > 2\sigma(I)$ were used. The final divergence factors were R = 0.0367 and wR_2 = 0.0947. The structure was solved with the *SHELXS93* program and refined with the *SHELXL97* program [16]. The geometric parameters of compound **2** have been deposited in the Cambridge structural data bank (CCDC 757673).

2,6-Bis(N-cytisinomethyl)-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylic Acid Diethyl Ester (2). Triethylamine (1.27 g, 12.6 mmol) and cytisine (1.60 g, 8.4 mmol) were added to a stirred solution of 2,6-bis-(bromomethyl)-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylic acid diethyl ester (**1**) (2.05 g, 4.2 mmol) in absolute benzene (50 ml). Stirring was continued for 24 h at room temperature. The precipitate of triethylamine hydrobromide was filtered off, and washed with benzene. The combined solution was evaporated, the residue triturated in ice water to a powdery solid, which was filtered off, and dried. The light-yellow powder was dissolved in benzene (10 ml) and chromatographed in benzene on a column of silica gel. The benzene solution obtained was poured into a threefold excess of hexane, the solvent decanted, and the precipitated oily residue was recrystallized twice from hexane–benzene, 4:1. Compound **2** (2.16 g, 73%) was obtained as a white crystalline substance of mp 208-210°C. IR spectrum, ν, cm^{-1}: 3334, 2935, 1685, 1654, 1576, 1545, 1467, 1207, 1092, 797. ^{1}H NMR spectrum, δ, ppm (J, Hz): 1.10, 1.13 (6H, two t, J = 7.1, 2CH$_2$C$\underline{H}_3$); 1.76 (4H, m, H-8,8'); 2.12 (2H, m, H-9',9); 2.34 (3H, m, H-11a, H-7',7); 2.42 (3H, br. d, H-13'a,13a,11'a); 2.56 (2H, m, H-11'e,11e); 2.78 (1H, br. d, $J_{13e,13a}$ = 10.6, H-13e); 2.94 (2H, br. d, $J_{a,b}$ = 2.2, H-14); 3.08 (1H, br. d, $J_{13'e,13'a}$ = 10.3, H-13'e); 3.72 (2H, m, H-10a,10'a); 3.87 (1H, d, $J_{a,b}$ = 14.1, H-14'a); 3.96 (1H, d, $J_{a,b}$ = 14.2, H-14'b); 3.96 (4H, m, 2C$\underline{H}_2$CH$_3$); 4.14 (1H, d, $J_{10e,10a}$ = 15.7, H-10e); 4.27 (1H, d, $J_{10'e,10'a}$ = 15.55, H-10'e); 4.69 (1H, s, H-4 dihydropyridine); 5.99 (1H, d, $J_{5,4}$ = 6.9, H-5); 6.03 (1H, d, $J_{5',4'}$ = 6.9, H-5'); 6.23 (1H, d, $J_{3,4}$ = 9.0, H-3); 6.28 (1H, d, $J_{3',4'}$ = 9.0, H-3'); 6.64 (1H, s, NH); 6.98 (2H, d, $J_{\alpha,\beta}$ = 7.1, H-α arom.); 7.12 (1H, t, $J_{\gamma,\beta}$ = 7.4, H-γ arom; 7.23 (2H, t, $J_{\beta,\gamma}$ = 7.5, H-β arom); 7.30 (1H, dd, $J_{4,5}$ = 6.9, $J_{4,3}$ = 9.0, H-4); 7.42 (1H, dd, $J_{4',5'}$ = 6.85, $J_{4',3'}$ = 9.0, H-4'). Mass spectrum, m/z (I_{rel}, %): 440 (3), 327 (70), 191 (33), 189 (44), 160 (34), 147 (40), 146 (75), 134 (24), 68 (24), 58 (65), 44 (100), 42 (61), 41 (59), 39 (41). Found, %: C 70.12; H 6.03; N 10.34. $C_{41}H_{47}N_5O_6$. Calculated, %: C 69.77; H 6.71; N 9.92.

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