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# SYNTHESIS AND THREE-DIMENSIONAL STRUCTURE OF 3,5-DICHLORO-3,4,5,6-TETRAHYDROPYRIDINES

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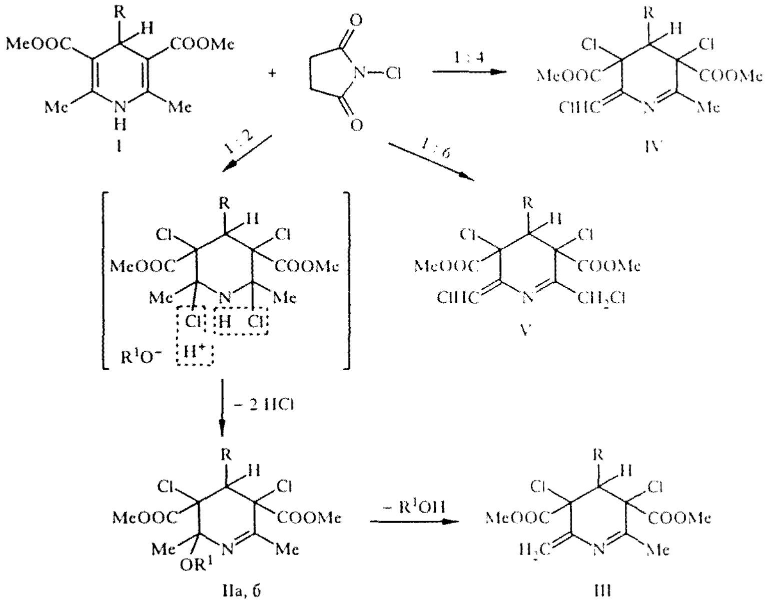
*The reaction of N-chlorosuccinimide with 2,6-dimethyl-3,5-dimethoxycarbonyl-4-(2-difluoromethoxyphenyl)-1,4-dihydropyridine (phoridone) has been studied. Depending on the amount of chlorinating agent, 3,4,5,6-tetrahydropyridines with different degrees of chlorination were obtained. The three-dimensional structure of 3,5-dimethoxycarbonyl-4-(2-difluoromethoxyphenyl)-2-methyl-6-chloromethylene-3,5-dichloro-3,4,5,6-tetrahydropyridine has been studied.*

The reaction of N-chlorosuccinimide with 1,4-dihydropyridines was unknown prior to our work [1]. Continuing these studies, we investigated the reaction of 2,6-dimethyl-3,5-dimethoxycarbonyl-4-(2-difluoromethoxyphenyl)-1,4-dihydropyridine (I, phoridone, riodipine) [2] with N-chlorosuccinimide in methanol or ethanol solution. The reaction was carried out at room temperature with a two, four- and sixfold excess of N-chlorosuccinimide. The reaction of the twofold excess of N-chlorosuccinimide gave 2,6-dimethyl-3,5-dimethoxycarbonyl-3,5-dichloro-4-(2-difluoromethoxyphenyl)-6-methoxy-3,4,5,6-tetrahydropyridine (IIa) in good yield from the reaction mixture. It may be assumed that after the addition of chlorine at the double bond of the 1,4-dihydropyridine ring, the formation of an unstable intermediate is associated with a splitting-off of hydrogen chloride and the addition of a molecule of the solvent. When the reaction is conducted in ethanol, addition of an ethoxy group of the solvent and formation of compound IIb are observed. In addition to tetrahydropyridine II, the product of the splitting-off of the solvent molecule, compound III, was isolated from the reaction mixture.



I-V R = $C_6H_4OCHF_2$-*o*, IIa $R^1$ = Me, IIb $R^1$ = Et

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TABLE 1. 3,4,5,6-Tetrahydropyridines II-V

| Compound | Empirical formula | mp, °C | UV spectrum, $\lambda_{max}$ (log c) | IR spectrum, cm$^{-1}$ | Yield, % |
|---|---|---|---|---|---|
| IIa | $C_{19}H_{21}Cl_2F_2NO_6$ | 81...83 | 207 (4,07) | 1670, 1738 | 32 |
| IIb | $C_{20}H_{23}Cl_2F_2NO_6$ | 79...81 | 207 (4,08) | 1665, 1738, 1757 | 46 |
| III | $C_{18}H_{23}Cl_2F_2NO_5$ | 80...83 | 208 (4,28), 290 sh. (3,40) | 1610, 1633, 1747 | 44 |
| IV | $C_{18}H_{16}Cl_3F_2NO_5$ | 141...144 | 208 (4,13), 249 (3,96), 303 sh. (3,38) | 1625, 1750 | 43 |
| V | $C_{18}H_{15}Cl_4F_2NO_5$ | 137...138 | 207 (4,14), 252 (3,94), 306 (3,38) | 1627, 1751 | 11 |

TABLE 2. Parameters of $^1$H NMR Spectra of Compounds II-V

| Compound | $H_{2\text{-}R}$ | $H_{6\text{-}R}$ | $H_4$ | $COOCH_3$ | $OCHF_2$ (J, Hz | $H_{Ar}$ | $H_R{}^1$ |
|---|---|---|---|---|---|---|---|
| IIa | 2,26 | 1,68 | 5,72 | 3,36, 3,77 | 6,45(74) | 6,8...7,4 | 3,42 ($CH_3$) |
| IIb | 2,25 | 1,72 | 5,90 | 3,44, 3,80 | 6,47(74) | 6,0...7,4 | 1,24 ($CH_3$),<br>3,40 ($CH_2$) |
| III | 2,37 | 5,80, 6,04 ($^2J_{HH}$ = 0) | 5,02 | 3,19, 3,52 | 6,47(73) | 7,0...7,2 | — |
| IV | 2,48 | 7,11 | 5,10 | 3,20, 3,56 | 6,52(72) | 6,7...7,3 | — |
| V | 4,54 | 7,36 | 5,10 | 3,22, 3,52 | 6,50(78) | 6,7...7,4 | — |

In the reaction of I with a fourfold excess of N-chlorosuccinimide, besides the addition of chlorine at the double bonds of the dihydropyridine ring, chlorination of the methyl group in the 6 position and formation of compound IV were observed. When the amount of chlorinating agent was raised to a sixfold excess, the methyl group in the 2 position was also chlorinated, and 3,4,5,6-tetrahydropyridine V was formed.

In the UV spectra, chlorination products II-V lack the long-wavelength peak characteristic of 1,4-dihydropyridines. The IR spectra lack the absorption band of the NH group, and absorption of the ester group is observed in the range 1738-1751 cm$^{-1}$, which is considerably higher than in the initial 1,4-dihydropyridine (Table 1).

The structure of the reaction product was also confirmed by $^1$H and $^{13}$C NMR spectra (Tables 2 and 3). The marked difference between the chemical shifts of the 3- and 5-$COOCH_3$ groups in the $^1$H NMR spectra (see Table 2) of compounds II-V is evidently due to the anisotropy of the phenyl group in the 4 position. Hence, the $COOCH_3$ groups are asymmetrically oriented with respect to the 4-aryl substituent. The $^1$H NMR spectra of compounds II-IV show signals of only one 2-$CH_3$ group, added to the double bond. In the $^{13}$C NMR spectra of compounds III-V, the chemical shifts for the $C_{(6)}$ and $C_{(6R)}$ atoms of these compounds indicate (see Tables 2 and 3) the formation of an exocyclic double bond. The $C_{(3)}$ and $C_{(5)}$ atoms absorb in the 65-60 ppm range in the $^{13}$C NMR spectra, indicating the addition of two chlorine atoms in these positions of the heterocycle. In addition, the $^1$H NMR spectra of compounds II-V lack the signals of the group NH proton.

To prove the chemical structure and determine the three-dimensional structure of the chlorination products, compound IV was subjected to x-ray diffraction analysis. A model of the molecule is shown in Fig. 1. During the experiment, variations in the unit cell parameters of the crystal were noted that were small but exceeded the experimental error. Apparently, x-rays cause an intramolecular rearrangement to occur in the crystal, owing to the migration of the chlorine atom from the $C_{(7)}$ to the $C_{(8)}$ carbon. Figure 1 shows both positions of chlorine with a population density of about 50% each. The variations of the cell parameters and also, to some extent, the observed statistical disorder of the fluorine atoms led to appreciable errors in the determination of the bond lengths and valence angles; this complicates their accurate interpretation.

The heterocycle has a half-chain conformation with a protrusion of the $C_{(4)}$ atom of 0.491(5) Å from the middle plane of the remaining ring atoms. The ester groups in positions 3 and 5 of the heterocycle in 40.6(6)° and 49.1(5)°, respectively, the $C_{(3)}-C_{(29)}$ and $C_{(5)}-C_{(28)}$ bonds have a mutual cis orientation. The phenyl ring is in an axial position perpendicular (86.4°) to the plane of the heterocycle.

TABLE 3. $^{13}C$ NMR Spectra of Compounds III-V

| Compound | $C_{(2)}$ | $C_{(3)}$ | $C_{(4)}$ | $C_{(5)}$ | $C_{(6)}$ | 2-R | 3,5-R | 6-R | $OCHF_2$ | $C_6H_4$ |
|---|---|---|---|---|---|---|---|---|---|---|
| III | 158,84 | 64,81 | 48,28 | 61,72 | 143,95 | 23,57 | 166,20 and 166,05 (CO),<br>53,11 and 53,10 ($OCH_3$) | 120,39 | 116,49 | 123,50($C\alpha$), 149,43($C_o$),<br>130,71($C_o$), 116,26(Cm),<br>124,14($C_m$), 129,42($C_p$) |
| IV | 161,49 | 64,89 | 48,50 | 62,06 | 137,49 | 24,02 | 164,75 and 165,76 (CO),<br>53,46 and 53,24 ($OCH_3$) | 124,36 | 116,36 | 123,10($C\alpha$), 149,35($C_o$),<br>130,91($C_o$), 116,36(Cm),<br>124,20($C_m$), 129,03($C_p$) |
| V | 159,41 | 63,73 | 48,69 | 61,95 | 137,52 | 44,45 | 165,61 and 165,48 (CO),<br>53,67 and 53,54 ($OCH_3$) | 124,44 | 116,38 | 122,85($C\alpha$), 149,38($C_o$),<br>131,18($C_o$), 116,46(C m),<br>124,25($C_m$), 128,73($C_p$) |

TABLE 4. Major Bond Lengths in the Structure of Compound IV

| Bond | $\delta$ | Bond | $\delta$ |
|---|---|---|---|
| $C_{(7)}$—$Cl_{(27)}$ | 1,84(2) | $C_{(19)}$—$O_{(24)}$ | 1,38(1) |
| $C_{(8)}$—$Cl'_{(27)}$ | 1,68(3) | $C_{(3)}$—$C_{(2)}$ | 1,58(2) |
| $C_{(5)}$—$Cl_{(28)}$ | 1,82(1) | $C_{(8)}$—$C_{(2)}$ | 1,47(3) |
| $C_{(3)}$—$Cl_{(29)}$ | 1,82(1) | $C_{(4)}$—$C_{(3)}$ | 1,53(2) |
| $C_{(13)}$—$F'_{(25)}$ | 1,65(4) | $C_{(14)}$—$C_{(3)}$ | 1,49(2) |
| $C_{(13)}$—$F_{(26)}$ | 1,15(2) | $C_{(5)}$—$C_{(4)}$ | 1,59(2) |
| $C_{(13)}$—$F'_{(26)}$ | 1,10(5) | $C_{(18)}$—$C_{(4)}$ | 1,53(1) |
| $C_{(2)}$—$N_{(1)}$ | 1,33(2) | $C_{(6)}$—$C_{(5)}$ | 1,42(2) |
| $C_{(6)}$—$N_{(1)}$ | 1,34(2) | $C_{(9)}$—$C_{(5)}$ | 1,56(2) |
| $C_{(9)}$—$O_{(10)}$ | 1,15(2) | $C_{(7)}$—$C_{(6)}$ | 1,34(2) |
| $C_{(9)}$—$O_{(11)}$ | 1,31(2) | $C_{(14)}$—$O_{(16)}$ | 1,31(2) |
| $C_{(12)}$—$O_{(11)}$ | 1,40(3) | $C_{(17)}$—$O_{(16)}$ | 1,52(3) |
| $C_{(14)}$—$O_{(15)}$ | 1,21(2) | $C_{(13)}$—$O_{(24)}$ | 1,34(2) |

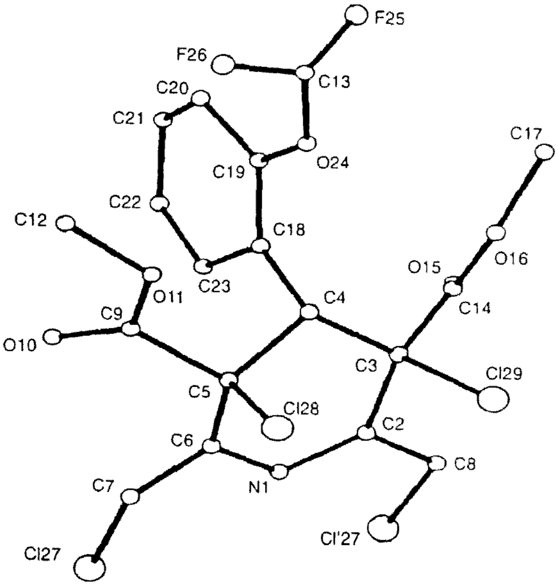

Fig. 1. Molecular structure of compound IV.

Our further work will be aimed at studying the details of the mechanism of the observed rearrangement.

## EXPERIMENTAL

The IR spectra were taken with a Perkin–Elmer 580 instrument in the form of a suspension in Nujol, and the UV spectra were taken with a Hitachi 557 instrument in ethanol ($5 \cdot 10^{-5}$ mmole/liter). The NMR spectra were taken with WH-90/DS and WH-360 instruments at frequencies of 90 MHz and 360 MHz ($^1H$) and 22.63 MHz and 90.5 MHz ($^{13}C$), with TMS as the internal standard. The purity of the compounds obtained and the course of the reactions were monitored by TLC on Silufol UV-254 plates in a 1:1:1 hexane–chloroform–ethyl acetate system.

The data of the ultimate analysis for C, H, and N are consistent with the calculated data.

TABLE 5. Major Valence Angles of Compound IV

| Angle | $\omega$ | Angle | $\omega$ |
|---|---|---|---|
| $Cl_{(27)}-C_{(7)}-C_{(6)}$ | 121,5(13) | $O_{(15)}-C_{(14)}-O_{(16)}$ | 123,6(13) |
| $Cl'_{(27)}-C_{(8)}-C_{(2)}$ | 114,3(16) | $O_{(15)}-C_{(14)}-O_{(3)}$ | 125,7(13) |
| $Cl_{(28)}-C_{(5)}-C_{(4)}$ | 108,0(8) | $O_{(16)}-C_{(14)}-C_{(3)}$ | 110,5(11) |
| $Cl_{(28)}-C_{(5)}-C_{(6)}$ | 109,1(10) | $C_{(14)}-O_{(16)}-C_{(17)}$ | 122,0(14) |
| $Cl_{(28)}-C_{(5)}-C_{(9)}$ | 105,9(09) | $C_{(13)}-O_{(24)}-C_{(19)}$ | 129,7(11) |
| $Cl_{(29)}-C_{(3)}-C_{(2)}$ | 102,9(08) | $O_{(24)}-C_{(19)}-C_{(18)}$ | 115,3(05) |
| $Cl_{(29)}-C_{(3)}-C_{(4)}$ | 111,7(07) | $O_{(24)}-C_{(19)}-C_{(20)}$ | 121,9(07) |
| $Cl_{(29)}-C_{(3)}-C_{(14)}$ | 106,1(08) | $C_{(2)}-C_{(3)}-C_{(4)}$ | 113,9(09) |
| $F'_{(25)}-C_{(13)}-F_{(26)}$ | 100,4(22) | $C_{(2)}-C_{(3)}-C_{(14)}$ | 111,9(09) |
| $F'_{(25)}-C_{(13)}-O_{(24)}$ | 154,0(21) | $C_{(3)}-C_{(2)}-C_{(8)}$ | 118,9(14) |
| $F_{(26)}-C_{(13)}-O_{(24)}$ | 137,0(20) | $C_{(3)}-C_{(4)}-C_{(5)}$ | 112,1(07) |
| $F'_{(26)}-C_{(13)}-O_{(24)}$ | 103,7(26) | $C_{(3)}-C_{(4)}-C_{(18)}$ | 108,4(10) |
| $N_{(1)}-C_{(2)}-C_{(3)}$ | 119,3(10) | $C_{(4)}-C_{(3)}-C_{(14)}$ | 109,9(09) |
| $N_{(1)}-C_{(2)}-C_{(8)}$ | 121,8(13) | $C_{(4)}-C_{(5)}-C_{(6)}$ | 112,7(12) |
| $C_{(2)}-N_{(1)}-C_{(6)}$ | 124,1(09) | $C_{(4)}-C_{(5)}-C_{(9)}$ | 105,9(10) |
| $N_{(1)}-C_{(6)}-C_{(5)}$ | 125,1(14) | $C_{(5)}-C_{(4)}-C_{(18)}$ | 111,7(10) |
| $N_{(1)}-C_{(6)}-C_{(7)}$ | 114,2(13) | $C_{(4)}-C_{(18)}-C_{(19)}$ | 119,5(05) |
| $O_{(10)}-C_{(9)}-O_{(11)}$ | 125,3(15) | $C_{(4)}-C_{(18)}-C_{(23)}$ | 122,9(05) |
| $O_{(10)}-C_{(9)}-O_{(5)}$ | 123,8(15) | $C_{(5)}-C_{(6)}-C_{(7)}$ | 119,6(15) |
| $O_{(11)}-C_{(9)}-O_{(11)}$ | 110,9(12) | $C_{(6)}-C_{(5)}-C_{(9)}$ | 114,9(13) |
| $C_{(9)}-O_{(11)}-C_{(12)}$ | 110,7(14) | | |

TABLE 6. Coordinate of Nonhydrogen Atoms ($\times 10^4$) of the Molecule of Compound IV

| Atom | $x$ | $y$ | $z$ |
|---|---|---|---|
| $Cl_{(27)}$ | -612(7) | -5039(9) | 3577(8) |
| $Cl'_{(27)}$ | -555(6) | -4925(10) | 513(7) |
| $Cl_{(28)}$ | 255(2) | 371(5) | 3204(0) |
| $Cl_{(29)}$ | 260(2) | 379(5) | 921(1) |
| $F_{(25)}$ | 2245(9) | 317(18) | 1471(15) |
| $F'_{(25)}$ | -1891(8) | 5041(13) | 1275(10) |
| $F_{(26)}$ | -2904(6) | 4943(11) | 2236(10) |
| $F'_{(26)}$ | -2561(16) | 4228(32) | 2920(21) |
| $N_{(1)}$ | -534(3) | -2813(5) | 2072(12) |
| $O_{(10)}$ | -1673(8) | -777(15) | 4228(11) |
| $O_{(11)}$ | -1290(6) | 1542(13) | 3873(8) |
| $O_{(15)}$ | -1684(7) | -853(16) | -57(10) |
| $O_{(16)}$ | -1254(7) | 1496(12) | 231(8) |
| $O_{(24)}$ | -2044(3) | 2870(5) | 2047(13) |
| $C_{(2)}$ | -585(8) | -2156(14) | 1244(10) |
| $C_{(3)}$ | -741(7) | -378(12) | 1180(8) |
| $C_{(4)}$ | -1091(3) | 317(7) | 2064(11) |
| $C_{(5)}$ | -737(8) | -468(17) | 2968(11) |
| $C_{(6)}$ | -650(9) | -2078(17) | 2872(11) |
| $C_{(7)}$ | -535(19) | -2944(19) | 3627(12) |
| $C_{(8)}$ | -475(20) | -3030(28) | 384(16) |
| $C_{(9)}$ | -1300(8) | 51(19) | 3781(11) |
| $C_{(12)}$ | -1840(20) | 2009(29) | 4552(17) |
| $C_{(13)}$ | -2298(13) | 4302(23) | 2219(29) |
| $C_{(14)}$ | -1263(7) | 24(15) | 374(10) |
| $C_{(17)}$ | -1821(19) | 2258(33) | -463(16) |
| $C_{(18)}$ | -2014(3) | 200(6) | 2022(12) |
| $C_{(19)}$ | -2478(4) | 1524(7) | 2027(14) |
| $C_{(20)}$ | -3325(4) | 1493(11) | 2147(19) |
| $C_{(21)}$ | -3699(4) | 93(9) | 2042(18) |
| $C_{(22)}$ | -3269(4) | -1248(9) | 2056(15) |
| $C_{(23)}$ | -2427(4) | -1180(7) | 2101(14) |

2-6-Dimethyl-3,5-dimethoxycarbonyl-3,5-dichloro-4-(2-difluoromethoxyphenyl)-6-methoxy-3,4,5,6-tetrahydropyridine (IIa). To a solution of 3.67 g (0.01 mole) of compound I in 100 ml of methanol is added 2.67 g (0.02 mole) of N-chlorosuccinimide, and the mixture is stirred for 2 h at room temperature. Fifty ml of water is added, and the precipitate of compound IIa is filtered off and crystallized from 50% aqueous methanol. The filtrate is kept in a refrigerator for two days, and the precipitated compound III is filtered off and crystallized from methanol.

In the same manner, we obtained compound IIb by conducting the reaction in ethanol, compound IV (with 4 moles of N-chlorosuccinimide), and compound V (with 6 moles of N-chlorosuccinimide) (see Table 1).

X-ray diffraction analysis. Single crystals of the composition $C_{18}H_{16}O_5NF_2Cl_3$ are rhombic: $a$ = 16.482(3), b = 8.759(2), c = 14.444(2) Å, V = 2085.2 Å$^3$, M = 470.7, $d_{calc}$ = 1.50 g/cm$^3$, $\mu$(MoK$\alpha$) = 2.6 mm$^{-1}$, space group $Pna2_1$, Z = 4. The intensities of 2467 independent reflections were measured with a Syntex $P2_1$ diffractometer ($\theta/2\theta$ scanning, MoK$\alpha$ radiation, graphite monochromator, $2\theta_{max}$ = 50°). A total of 1882 reflections with $I > 2\sigma(I)$ were used in the calculations. The structure was identified by the direct method using the SHELX86 program [4] and was refined by the method of least squares in the anisotropic approximation using the SHELX76 program [3]. The final R factor was 0.068. The coordinates of the nonhydrogen atoms, bond lengths and valence angles are listed in Tables 4-6.

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