CHLORINATION OF 2,6-DIMETHYL-3,5-DICARBOMETHOXY-4-(2'-DIFLUOROMETHOXYPHENYL)-1,4-DIHYDROPYRIDINE (PHORIDONE)

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Chlorination of 2,6-dimethyl-3,5-dicarbomethoxy-4-(2'-difluoromethoxyphenyl)-1,4-dihydropyridine gives 2,3,4,5-tetrahydropyridines with different degrees of chlorination dependent upon the quantitative ratio of reagents. The reaction proceeds without oxidation of the dihydropyridine ring.

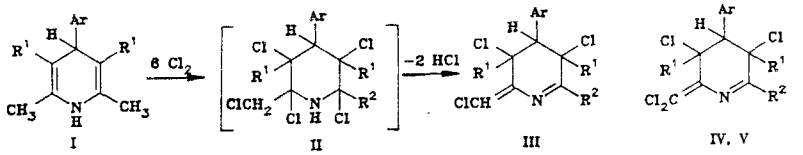
In continuation of our work on the halogenation of 1,4-dihydropyridines [1, 2] we have studied the effect of chlorine on 2,6-dimethyl-3,5-dicarbomethoxy-4-(2'-difluoromethoxyphenyl)-1,4-dihydropyridine (phoridone, I) [3]. Analogous reactions amongst 1,4-dihydropyridines are unknown.

Chlorination of phoridone was carried out in various solvents (methanol, chloroform, ethanol, acetic acid) but the most reproducible results were obtained for the reactions in chloroform or in ethanol.

Passage of a sixfold excess of chlorine through a solution of phoridone in ethanol gave a solid product containing several compounds. Purification on a silica gel column gave 2-chloromethylen-3,5-dicarbomethoxy-3,5-dichloro-4-(2'-dichloromethoxyphenyl)-6-dichloromethyl-2,3,4,5-tetrahydropyridine (III). Formation of this product can be explained in terms of chlorination of the 2,6-methyl groups together with addition of chlorine to the double bonds of the 1,4-dihydropyridine ring to form the unstable intermediate II. The reaction may then continue via the loss of two molecules of HCl to form III.

Such a reaction has not been described for 1,4-dihydropyridines. A similar addition to the double bond of the heterocycle by halogen atoms with subsequent separation of hydrogen halide is known for dihydro- [4] and tetrahydropyrimidines [5].

Increasing the amount of chlorine to 12 moles gives, in good yield, the tetrahydropyridine IV which differs from the analog III by the presence of a dichloromethylene group at position 2. Further increase of the amount of chlorine passed gives the 2,3,4,5-tetrahydropyridine (V) in which all of the hydrogen atoms in the 2-methylene and 6-methyl groups are substituted by chlorine.



I–V $R^1 = COOCH_3$, $Ar = C_6H_4OCHF_2$; II–IV $R^2 = CHCl_2$; V $R^2 = CCl_3$

The purity of the chlorination products of I was shown by HPLC. The product obtained with a sixfold excess of chlorine gave the product III together with IV as impurity. That from the reaction with a twelvefold excess showed all three tetrahydropyridines (III, IV, and V). With a thirtyfold excess, compound III was not observed in the reaction product (see Table 1).

The UV spectra of III-V showed the absence of a long wavelength absorption maximum near 360 nm characteristic of 1,4-dihydropyridines and the presence of a maximum in the region 274-292 nm. The IR spectra showed the presence of carbonyl group absorption at

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TABLE 1. Composition of the Reaction Products III-V

Compound	Composition, %, with quantity of Cl		
	6 mole	12 mole	30 mole
III	87.4	4.2	—
IV	1.0	90.5	1.0
V	0.1; 10.9; 0.6	3.5	97.7
UP*	—	0.2; 0.4; 0.3; 0.9	0.1; 1.2

*UP - unidentified product.

1750-1760 cm^{-1} (significantly higher than for 1,4-dihydropyridines) and the absence of any NH absorption.

The unsymmetrical structure of the ring is indicated by the split signals for the protons of the 3,5-carbomethoxy groups. The disappearance of the signals for the 2,6-methyl groups is attributed to chlorination of these. Absence of NH proton signals was also noted in the chlorination products.

Most informative are the ^{13}C NMR spectra (see Experimental section) which also confirmed the non-symmetrical structure of the chlorination products. The presence of one signal at very low field (157-159 ppm) and of signals at 136-138 ppm was in agreement with the presence of the C=N bond and the exocyclic $C_2{=}CCl_2$ in the molecule. The shift of the C_3 and C_5 signals to high field points to their sp^3 character, i.e., the Cl atoms in fact remain in these positions upon separation of two molecules of HCl from the intermediate II (see above).

The mass spectra of compounds III-V (see Experimental) show low intensity peaks corresponding to the presence of five, six, and seven chlorine atoms in III, IV, and V, respectively. Dissociation of M^+ for III-V takes place with elimination of $Cl^{\cdot}$, HCl, and/or Cl_2 as indicated by the change in the relative Cl isotope content and corresponding to that calculated. Further fragmentation leads to uncharacteristic, low intensity ion peaks until the appearance of an ion with m/z 187 which does not contain chlorine and is maximal in the spectra of III-V.

Thus the ^1H and ^{13}C NMR and the mass spectra fully confirm that chlorination of phoridone leads to the structures III-V. The stereochemistry of these compounds will be reported separately.

Because III-V are hydrogenated analogs of the known hypotensive compound of phoridone (riodipine) [7] their hypotensive activity was examined. When dosed internally in narcotized cats (0.01-6 mg/kg), compounds IV and V did not cause a significant effect on systemic arterial pressure.

EXPERIMENTAL

UV Spectra were recorded on a Specord UV-vis instrument in ethanol (5×10^{-5} mole/liter). IR Spectra were taken on a Perkin-Elmer 580 B instrument as Nujol suspensions. PMR Spectra were taken using a WH-90/DS spectrometer (90 MHz ^1H, 22.63 MHz ^{13}C) with TMS as internal standard. Mass spectra were recorded on an AEI MS-50 instrument with direct introduction of the sample, ionization intensity of 70 eV, and ionization chamber temperature of 200°C.

Compounds were purified by preparative column chromatography on 100/400 micron silica gel using hexane–chloroform–ethyl acetate (3:1:1) as eluent. TLC was carried out on Silufol UV-254 plates in the same eluent. HPLC analysis was performed on a Varian 8500 chromatograph with UV detection at 254 nm, Silasorb C 18 (150 × 4.6 mm) column, acetonitrile–water (70:30) mobile phase, and flow rate of 1.5 ml/min. Samples (50 µl) were 0.54 mg/ml in mobile phase.

Chlorine was obtained by method [6].

2-Chloromethylen-3,5-dicarbomethoxy-3,5-dichloro-4-(2'-difluoromethoxyphenyl)-6-dichloromethyl-2,3,4,5-tetrahydropyridine (III). Gaseous chlorine (0.12 mole) was passed through a solution of phoridone I (7.34 g, 0.02 mole) in ethanol (100 ml). The product was cooled in iced water, the solvent removed in vacuo, and the residue recrystallized from aqueous ethanol (1:1) to give III (8.70 g, 80.6%). Preparative chromatography was used to prepare

an analytically pure sample with mp 137-138°C and R_f 0.54. UV Spectrum, λ_{max} (log ε): 277 nm (3.9). IR Spectrum: 1590, 1608, 1637, 1750 cm^{-1}. PMR Spectrum ($CDCl_3$): 3.27 (3H, s, OCH_3); 3.60 (3H, s, OCH_3); 5.08 (1H, s, 4-H); 6.40 (1H, s, $CHCl_2$); 6.50 (1H, t, CHF_2, J_{HF} = 72.0 Hz); 7.45 (1H, s, =CHCl); 6.50-7.36 ppm (4H, m, C_6H_4). Mass spectrum,* m/z (I_{rel}, %); 537 (5) M^+; 502 (88) $[M - Cl]^+$; 466 (32) $[502 - HCl]^+$; 454 (23) $[M - CHCl_2]^+$; 187 (100) $C_9H_9O_2F_2^+$ (exp. 187.0587; calc. 187.0603); 126 (15); 59 (85) $COOCH_3^+$, 51 (29) CHF_2^+.

2-Dichloromethylen-3,5-dicarbomethoxy-3,5-dichloro-4-(2'-difluoromethoxyphenyl)-6-dichloromethyl-2,3,4,5-tetrahydropyridine (IV). Gaseous chlorine (0.24 mole) was passed through a solution of phoridone (7.34 g, 0.02 mole) in ethanol (100 ml) which had been cooled in ice. The product was poured into water (200 ml) and the oily precipitate separated and crystallized from acetone–hexane (1:1) to give IV (9.85 g, 85.5%). Preparative chromatography gave a sample with mp 164-165°C and R_f 0.68. UV Spectrum, λ_{max} (log ε): 289 nm (3.9). IR Spectrum: 1602, 1620, 1758 cm^{-1}. PMR Spectrum ($CDCl_3$): 3.19 (3H, s, OCH_3); 3.42 (3H, s, OCH_3); 5.03 (1H, s, 4-H); 6.46 (1H, q, CHF_2, J_{HF} = 71.0, 74.0 Hz); 6.77 (1H, s, $CHCl_2$); 6.80-7.41 ppm (4H, m, C_6H_4). ^{13}C NMR Spectrum (DMSO-d_6): 165.21 and 164.61 (COO); 159.06 (C_2); 148.98 ($C_{2'}$); 121.88 ($C_{1'}$); 116.60 ($C_{3'}$); 124.25 ($C_{5'}$); 131.48 and 129.02 ($C_{4'}$ and $C_{6'}$); 116.38 (CHF_2, $^1J_{CF}$ = 258.8); 137.30 and 136.55 (C_6 and $=CCl_2$); 68.42 ($CHCl_2$); 63.38 and 60.01 (C_3 and C_5); 53.78 and 53.67 (OCH_3); 49.31 ppm (C_H). Mass spectrum, m/z (I_{rel}, %): 571 (0.8) M^+; 536 (61) $[M - Cl]^+$; 500 (40) $[536 - HCl]^+$; 488 (12) $[M - CHCl_2]^+$; 466 (14) $[536 - Cl_2]^+$; 191 (7); 187 (100); 143 (39) $C_6H_4OCHF_2^+$; 59 (35).

2-Dichloromethylen-3,5-dicarbomethoxy-3,5-dichloro-4-(2'-difluoromethoxyphenyl)-6-trichloromethyl-2,3,4,5-tetrahydropyridine (V). Gaseous chlorine (0.3 mole) was passed through a solution of phoridone (3.67 g, 0.01 mole) in chloroform (75 ml) over 2 h. The solvent was removed in vacuo and the residue washed with ethanol to give V (4.92 g, 80.9%). Preparative chromatography gave a sample with mp 188-189°C and R_f 0.76. UV Spectrum, λ_{max} (log ε): 292 (4.1). IR Spectrum: 1610, 1760 cm^{-1}. PMR Spectrum ($CDCl_3$): 3.30 (3H, s, OCH_3); 3.38 (3H, s, OCH_3); 5.08 (1H, s, 4-H); 6.44 (1H, t, CHF_2, J_{HF} = 73.0 Hz); 6.91-7.40 ppm (4H, m, C_6H_4). ^{13}C NMR Spectrum (DMSO-d_6): 165.02 and 164.43 (COO); 157.15 (C_2); 149.35 ($C_{2'}$); 121.53 ($C_{1'}$); 116.79 ($C_{3'}$); 124.04 ($C_{5'}$); 131.51 and 130.62 ($C_{4'}$ and $C_{6'}$); 116.52 (CHF_2, $^1J_{CF}$ = 258.5 Hz); 138.06 and 136.07 ($=CCl_2$ and C_6); 94.65 (CCl_3); 63.51 and 61.92 (C_3 and C_5); 53.92 and 53.65 (OCH_3); 51.87 ppm (C_4). Mass spectrum, m/z (I_{rel}, %); 605 (>0.1) $M^{+\cdot}$; 570 (16) $[M - Cl]^+$; 569 (25) $[M - HCl]^+$; 534 (21) $[569 - Cl]^+$; 500 (13) $[570 - Cl_2]^+$; 191 (27); 187 (100); 143 (10); 59 (2).

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*Chlorine-containing ions are calculated based on the ^{35}Cl isotope.