BROMINATION OF 2,6-DIMETHYL-3,5-DIMETHOXYCARBONYL-4-(2'-DIFLUOROMETHOXYPHENYL)-1,4-DIHYDROPYRIDINE (FORIDONE)

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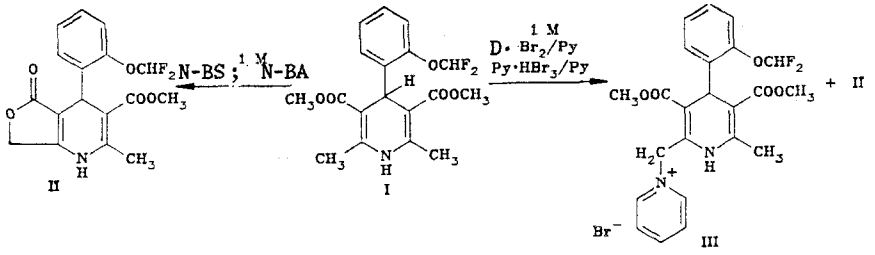
The action of mild brominating agents (pyridinium bromide-perbromide, dioxan dibromide N-bromosuccinimide, and N-bromoacetamide) on 2,6-dimethyl-3,5-dimethoxycarbonyl-4-(2'-difluoromethoxyphenyl)-1,4-dihydropyridine (Foridone) has been studied. Depending on reaction conditions, furo-, difuro-, and dibromomethyl-1,4-dihydropyridines are obtained together with certain oxidized forms.

Only a few papers [1-3] are devoted to the reaction of pyridinium bromide-perbromide with 1,4-dihydropyridines and in general the object has been the preparation of furo-1,4-dihydropyridines. In a continuation of a study of the bromination of dihydropyridine derivatives [4], we have examined the action of mild brominating agents (pyridinium bromide-perbromide, dioxan dibromide, N-bromosuccinimide, and N-bromoacetamide) on 2,6-dimethyl-3,5-dimethoxycarbonyl-4-(2'-difluoromethoxyphenyl)-1,4-dihydropyridine (Foridone, I).

In the bromination of Foridone by equimolar quantities of pyridinium bromide-perbromide ($Py \cdot HBr_3$), dioxan dibromide ($D \cdot Br_2$), N-bromosuccinimide (N-BS), or N-bromoacetamide (N-BA) we obtained the corresponding furo-1,4-dihydropyridine II, previously prepared by another route [5].



The greatest yield of the furo-1,4-dihydropyridine II (84%) was obtained using N-BS. The other brominating agents gave reduced yields in the order N-BA (68%) > $Py \cdot HBr_3$ (58%) > $D \cdot Br_2$ (47%).

When using $Py \cdot HBr_3$ and $D \cdot Br_2$ in the presence of pyridine, the previously unknown product (III), of the substitution of bromine into pyridine was isolated in the form of a salt, in addition to the lactone II.

If a double quantity of the brominating (N-BS) is used, both methyl groups (in positions 2 and 6) are brominated and subsequent cyclization with elimination of two molecules of methyl bromide leads to the difuro-1,4-dihydropyridine IV.

In the present work the bromination of Foridone in chloroform and in methanol has been studied in more detail together with the effect of the concentration of the brominating agent on the reaction. In the reaction in chloroform with a threshold excess of N-BS a mixture of products is formed in which, judging from TLC data, compounds IV and V are present. We were not successful in separating this mixture on a preparative scale.

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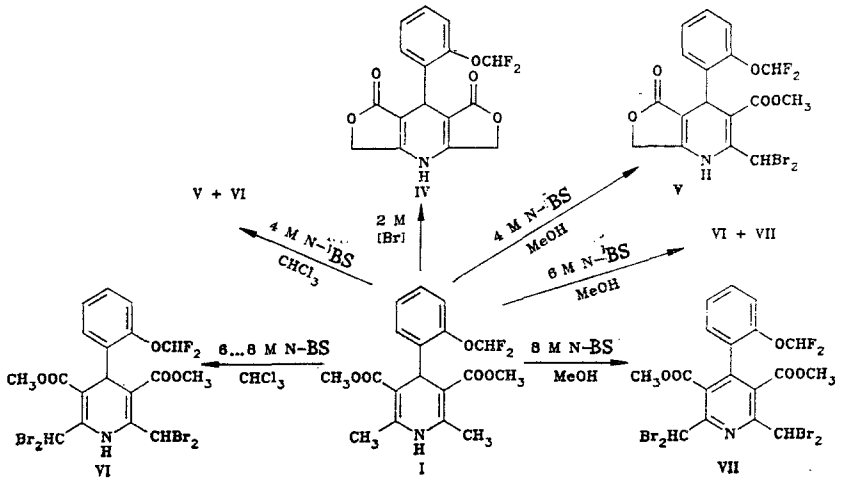


In the reaction with 4 moles of N-BS, the 1,4-dihydropyridines V and VI were isolated from the reaction mixture. On further increasing the amount of brominating agent (6-8 M), the 2,6-bis(dibromomethyl)-1,4-dihydropyridine VI is formed exclusively. It seems that under these conditions rapid substitution of two hydrogen atoms by bromine takes place in each methyl group; compound VI does not split off alkyl bromide and closure of the lactone ring does not occur.

Bromination of Foridone by N-BS in methanol with ratios of 1:1 and 1:2 gives compounds II and IV, but with a fourfold excess of N-BS the reaction differs from that in chloroform in that the furo-1,4-dihydropyridine V, containing a dibromomethyl group, is formed.

With a 1:6 ratio of the reactants a mixture is obtained which consists of the tetrabromide VI and its oxidized form VII, and with an eightfold quantity of N-BS, VII is the sole product. One can assume that the product VI is more readily oxidized in methanol than in chloroform. We have established that after 48 h solutions of compound VI ($c = 5 \cdot 10^{-5}$ mole/liter) in methanol contain 87%, and in chloroform 100%, compound VII, calculated in terms of the reduction in (disappearance of) the longwave maximum in the UV spectra.

The structures of all the compounds prepared were confirmed by UV, infrared, mass and PMR spectroscopy.

The UV spectra of compounds II-IV did not differ from those of the analogous Nifedipine derivatives [4]. In the spectrum of the brominated furo-1,4-dihydropyridine V a 9 nm shift of the longwave maximum to a longer wavelength than in compound II was observed. In compound VII the longwave absorption was absent and there was an indistinct maximum at 280 nm.

The proton NMR spectra were the most informative in establishing the structures. The protons of the dibromomethyl group gave a signal at ~8.0 ppm (compounds V and VI) and at 7.04 ppm in the oxidized product VII. Carbon-13 NMR spectra were in full agreement with the structures given below (see experimental section). The chemical shifts of the ^{13}C nucleus for compounds V-VII were close to those expected [6].

In the mass spectrum of compound V the molecular ion peak was absent. The characteristic peaks in the mass spectrum were those of the ions $[M - H_2 - Br]^+$ (426),* $[M - H_2 - HBr]^+$ (425) and $[M - Br_2]^+$ (349). The ion $[M - Br_2]^+$ broke down further with parallel splitting of the radicals $OCHF_2$ or $C_6H_4OCHF_2$ forming ions 282 (39) or 206 (100) respectively.

In the mass spectrum of compound VI, a low intensity multiplet of molecular ion peaks is observed; the configuration of the signals points to the existence of four atoms of bromine. Decomposition of the molecular ion takes place in four different ways:

1) splitting off of the substituent in position 4 (route A in the scheme below). Further breakdown of the ion $(M - C_6H_4OCHF_2)^+$ proceeds with successive separation of three bromine atoms;

*The number in parentheses is the m/z value characterizing the ion.

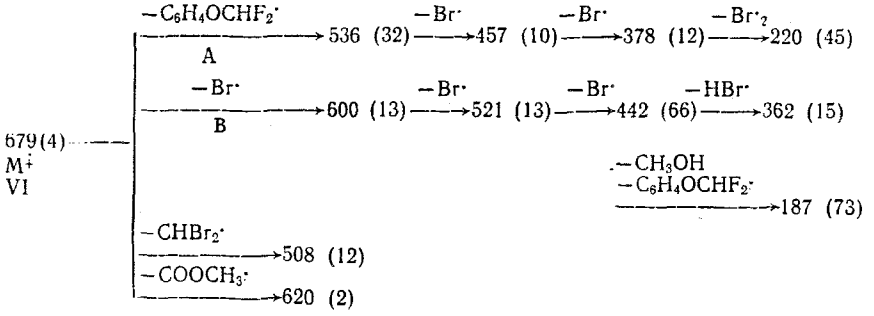
2) successive splitting off of a bromine atom and a molecule of HBr (route B);

3) splitting off of the $CHBr_2$ substituent at position 2 (6);

4) splitting off of the $COOCH_3$ radical at position 3 (5).

In the mass spectrum of compound III the molecular ion peak is absent. A peak of low intensity is observed $[MH - Br]^+$ (446) apparently formed as a result of addition of a hydrogen atom to the pyridine ring under the conditions of the experiment. Breakdown of this ion proceeds by several routes with separation of OCH_3 and $COOCH_3$ radicals together with pyridine molecules.

Scheme 1*



*Here and below, the m/z values are given calculated for the ^{79}Br isotope with the relative intensities in parentheses.

In the mass spectrum of compound VII also, a low intensity multiplet of molecular ion peaks, 677 (1.0) is observed which corresponds to the presence of four atoms of bromine. In the breakdown of the molecular ion, successive splitting off of all the bromine atoms occurs in a similar manner to the decomposition of the compound VI (scheme 1, route B) which leads to the formation of the ions 598 (42), 519 (7), 440 (100), and 361 (19) respectively.

EXPERIMENTAL

Infrared spectra were recorded on a Perkin Elmer 580B instrument as Nujol mulls, UV spectra on a Specord UV-Vis in ethanol ($c = 5 \cdot 10^{-5}$ mole/liter). A WH-90/DS spectrometer was used for the NMR spectra with $CDCl_3$ or DMSO-D_6 as solvents and TMS as internal standard at frequencies of 90 MHz (^1H) or 22.63 MHz (^{13}C). Mass spectra were run on an MS-50 spectrometer (AEI) with 70 eV ionization energy, direct introduction of the samples to the system and a ion-source temperature of 200°C. Progress of the reactions was monitored and the purity of the prepared compounds established by TLC on Silufol UV-254 plates. The results of elemental analyses for C, H, N, on compounds II-VII were in agreement with those calculated.

2-Methyl-3-methoxycarbonyl-5-oxo-4-(2'-difluoromethoxyphenyl)-1,4,5,7-tetrahydrofurol-[3,4-b]pyridine (II, $C_{17}H_{15}F_2NO_5$). A. A solution of 19.8 g (0.054 mole) 2,6-dimethyl-3,5-dimethoxycarbonyl-4-(2'-difluoromethoxyphenyl)-1,4-dihydropyridine (I) in 350 ml chloroform was cooled to 5°C and 20.2 g (0.063 mole) pyridinium bromide-perbromide and 7.1 g (0.09 mole) pyridine added. The mixture was stirred and cooled for 30 min and then heated to bp for 90 min. It was washed with 450 ml 2 N HCl and 2 × 450 ml saturated NaCl solution and dried over anhydrous calcium chloride. On standing in the cold, a precipitate was deposited which was recrystallized from 1:1 acetane–hexane to yield 10.9 g (58%) compound II, mp 201-203°C (from [5], mp = 200-202°C). R_f 0.17 (1:1:1 chloroform–hexane–ethyl acetate). IR spectrum (cm^{-1}): 1700, 1730, 1748, 3095, 3182. UV spectrum, λ_{max} nm (log ε): 210 (4.2), 229 (4.3), 346 (3.8). PMR spectrum ($CDCl_3$) (δ ppm): 2.40 (3H, s, CH_3), 3.54 (3H, s, OCH_3), 4.68 (2H, s, CH_2), 5.16 (1H, s, 4-H), 6.40 (1H, s, NH), 6.61 (1H, q, $OCHF_2$, J_{FH} = 71 Hz, J_{FH} = 77 Hz), 7.25 (4H, m, ArH). Mass spectrum, m/z (%): 351 (1) M^+, 336 $[M - CH_3]^+$ (7), 320 $[M - OCH_3]^+$ (3), 292 $[M - COOCH_3]^+$ (1), 284 $[M - OCHF_2]^+$ (2), 272 (15), 252 (5), 208 $[M - C_6H_4OCHF_2]^+$ (100), 176 (20).

The filtrate was distilled in vacuum, the oily residue treated with ether, and the product crystallized from methanol to yield 4.54 g (16%) N-[2-methyl-3,5-dimethoxycarbonyl-4-(2'-difluoromethoxyphenyl)-1,4-dihydropyridine-6-methylene]pyridinium bromide (III,

$C_{23}H_{23}BrF_2N_2O_5$), mp 212-215°C, R_f 0.12 (8:2:1 acetone–methanol–water). IR spectrum (cm^{-1}): 1653, 1695, 3060, 3155, 3360. UV spectrum (λ_{max} nm (log ε)): 208 (4.4), 219 (4.4), 364 (3.8). PMR spectrum ($CDCl_3$) (δ ppm): 2.48 (3H, s, CH_3), 3.57 (3H, s, OCH_3), 3.63 (3H, s, OCH_3), 5.35 (1H, s, 4-H), 6.30 (2H, s, N–CH_2), 6.42 (1H, t, $OCHF_2$, J_{HF} = 74 Hz), 7.10 (4H, m, ArH), 7.95 (2H, t, PyH-β), 8.40 (1H, t, PyH-γ), 9.75 (2H, d, PyH-α), 10.70 (1H, s, NH). Mass spectrum m/z (%): 446 $[MH - Br]^+$ (0.4), 415 $[446 - OCH_3]^+$ (1), 387 $[446 - COOCH_3]^+$ (2), 365 $[446 - 2H - C_5H_5N]^+$ (1), 351 $[MH - CH_2 - C_5H_5N]^+$ (7), 336 $[351 - CH_3]^+$ (4), 320 $[351 - OCH_3]^+$ (4), 292 $[351 - COOCH_3]^+$ (13), 208 $[351 - C_6H_4OCHF_2]^+$ (100), 79 $[C_5H_5N]^+$ (24).

B. A mixture of 36.7 g (0.1 mole) compound I and 17.8 g (0.1 mole) N-BS in 200 ml chloroform was stirred for 1 h and then heated at bp for 2 h. On cooling, compound II was deposited. The solid was washed with water and crystallized from a 10:4 methanol–water mixture. Yield 29.5 g (74%), mp 200-203°C.

C. To a solution of 7.34 g (0.02 mole) compound I in 80 ml chloroform was added 4.8 ml pyridine, the mixture cooled to −5°C and 11.4 g (0.046 mole) dioxan dibromide added and stirred at the same temperature for 30 min. It was then heated to bp for 30 min. The solution was washed with 300 ml 2N HCl and with 2 × 300 ml saturated NaCl solution. On standing in the cold, 3.3 g (47%) compound II was deposited, mp 200-202°C.

The filtrate was distilled and the residue treated with hexane to yield 1.58 g (15%) compound III, mp 212-214°C.

D. A mixture of 3.67 g (0.01 mole) compound I and 1.38 g (0.01 mole) N-bromoacetamide in 60 ml chloroform was stirred 30 min and then heated at bp for 3 h. It was washed with 2 × 200 ml water and on standing in the cold, compound II was deposited. Yield 2.4 g (68%), mp 201-203°C.

1,7-Dioxo-8-(2'-difluoromethoxyphenyl)-1,3,4,5,7,8-hexahydro(difuro)-[3,4-b; 3',4'-e]-pyridine (IV, $C_{16}H_{11}F_2NO_5$). A. A mixture of 7.34 g (0.02 mole) compound I and 7.12 g (0.04 mole) N-bromosuccinimide in 80 ml chloroform was stirred for 1 h and then heated at bp for a further hour. It was washed with 3 × 200 ml water and on standing in the cold, crystals were deposited. Recrystallization from 1:1 ethanol–water yielded compound IV, mp 247-250°C. R_f 0.60 (2:1 acetone–hexane). IR spectrum (cm^{-1}): 1635, 1685, 1721, 1750, 3210, 3265. UV spectrum (λ_{max} nm (log ε)): 222 (4.4), 330 (3.9). PMR spectrum ($CDCl_3$) (δ ppm): 4.75 (4H, s, CH_2), 5.05 (1H, s, 4-H), 6.71 (1H, t, CHF_2, J_{HF} = 74.5 Hz), 7.15 (4H, m, ArH), 10.20 (1H, s, NH).

B. A mixture of 3.67 g (0.01 mole) compound I and 2.76 (0.02 mole) N-bromoacetamide in 100 ml chloroform was stirred for 1 h and then heated at bp for a further hour. It was washed with 3 × 200 ml water and on standing in the cold crystals were deposited which were recrystallized from 2:1 water–methanol to yield 2.0 g (60%) compound IV, mp 247-249°C.

C. A mixture of 7.34 g (0.02 mole) compound I and 12.8 g (0.04 mole) pyridinium bromide-perbromide in 200 ml chloroform was cooled and stirred for 30 min and then heated at bp for 90 min. It was washed with 350 ml 2N HCl followed by 2 × 350 ml saturated NaCl solution and dried over anhydrous calcium chloride. Compound IV (3.5 g, 52%) was deposited on standing in the cold. mp 246-249°C.

2-Dibromomethyl-3-methoxycarbonyl-5-oxo-4-(2'-difluoromethoxyphenyl)-1,4,5,7-tetrahydrofuro[3,4-b]pyridine (V, $C_{17}H_{13}Br_2F_2NO_5$). A mixture of 7.34 g (0.02 mole) compound I and 14.24 g (0.08 mole) N-bromosuccinimide in 170 ml methanol was stirred until solution was complete and then heated at bp for 1 h and 40 ml water added. A yellow precipitate of compound V was deposited on cooling. It was recrystalized from 1:2 acetone–hexane to yield 2.6 g (26%) compound V, mp 185-187°C. R_f 0.18 (1:3:1 chloroform–hexane–ethyl acetate). IR spectrum (cm^{-1}): 1598, 1677, 1735, 3252. UV spectrum (λ_{max} nm (lg ε)): 209 (4.2), 236 (4.2), 355 (3.7). PMR spectrum ($CDCl_3$) (δ, ppm): 3.55 (3H, s, OCH_3), 4.76 (2H, s, CH_2), 5.19 (1H, s, 4-H), 6.64 (1H, q, CHF_2, J_{HF} = 71.0, J_{HF} = 77.0 Hz), 7.13 (4H, m, ArH), 7.90 (1H, s, NH), 8.09 (1H, s, CH). Carbon-13 NMR spectrum (DMSO-D_6) (δ ppm): 170.9 (CO lactone ring), 166.1 (CO), 156.7 (C_6), 144.8 (C_2), 148.5 (C_2), 135.7 (C_1'), 130.5, 128.6, 125.6, 118.0 (C phenyl), 117.1 ($OCHF_2$, t, J = 255.9 Hz), 102.3 (C_3), 100.0 (C_5), 66.0 (OCH_2), 51.8 (OCH_3), 33.4 (CH_2Br_2), 31.6 (CH). Mass spectrum (only those ions not mentioned elsewhere are identified) (m/z (%)): 348 $[M - Br - HBr]^+$ (12), 266 (51), 71 (63), 57 (36), 43 (40), 42 (35).

2,6-Bis(dibromomethyl)-3,5-dimethoxycarbonyl-4-(2'-difluoromethoxyphenyl)-1,4-dihydropyridine (VI, $C_{18}H_{15}Br_4F_2NO_5$). A mixture of 7.34 g (0.02 mole) compound I and 28.48 g (0.16

mole) N-bromosuccinimide in 200 ml chloroform was heated at bp for 1 h. The precipitate which formed* was washed with 2 × 200 ml water and dried over anhydrous calcium chloride. The solvent was removed in vacuum and the residue crystallized from 1:1 acetone–hexane to yield 6.5 g (48%) compound VI, mp 128-130°C. R_f 0.80 (1:3:1 chloroform–ethyl acetate). IR spectrum (cm^{-1}): 1645, 1695, 3060, 3370. UV spectrum (λ_{max} nm (log ε)): 209 (4.3), 244 (4.1), 363 (3.5). PMR spectrum (δ ppm): 3.66 (6H, s, OCH_3), 5.38 (1H, s, 4H), 6.53 (1H, t, CHF_2, J = 74.0 Hz), 7.20 (5H, m, Ar-H + NH), 8.04 (2H, s, CH). Carbon-13 NMR spectrum (DMSO-D_6) (δ ppm): 165.2 (CO), 143.0 ($C_{2,6}$), 101.3 ($C_{3,5}$), 147.8 (C_2'), 134.4 (C_1'), 129.4, 129.0, 125.3, 116.9 (C phenyl), 116.5 ($OCHF_2$, t, J = 256.3 Hz), 52.1 (OCH_3), 33.5 ($CHBr_2$), 33.4 (C_4). Mass spectrum (m/z (%)): 304 (41), 80 HBr^+ (100), 70 Br^+ (68), 59 $COOCH_3^+$ (57).

2,6-Bis(dibromomethyl)-3,5-dimethoxycarbonyl-4-(2'-difluoromethoxyphenyl)pyridine (VII, $C_{18}H_{13}Br_4F_2NO_5$). A mixture of 7.34 g (0.02 mole) compound I and 28.48 g (0.16 mole) N-bromosuccinimide in 230 ml methanol was heated at bp for 1 h and then 200 ml water added. On cooling, crystals were deposited which were recrystallized from 1:2 acetone–hexane to yield 8.5 g (62%) compound VII, mp 151-153°C. R_f 0.71 (1:3:1 chloroform–hexane–ethylacetate). IR spectrum (cm^{-1}): 1590, 1609, 1738. UV spectrum (λ_{max} nm (log ε)): 213 (4.4), 234 (4.2), 280 (3.6). PMR spectrum ($CDCl_3$) (δ ppm): 3.56 (6H, s, OCH_3), 6.39 (1H, t, CHF_2, J_{HF} = 73 Hz), 7.04 (2H, s, CH), 7.23 (4H, m, ArH). Carbon-13 NMR spectrum (DMSO-D_6) (δ ppm): 164.3 (CO), 155.0 ($C_{2,6}$), 125.6 ($C_{3,5}$), 125.1 (C_4), 147.9 (C_2'), 144.8 (C_1'), 131.3, 130.0, 124.6, 116.5 (C phenyl), 116.0 ($OCHF_2$, t, J = 258.5 Hz), 53.2 (OCH_3), 39.5 ($CHBr_2$). Mass spectrum (m/z (%)): 346 (87), 318 (11), 298 (16), 80 HBr^+ (55), 79 Br^+ (18), 63 (90).

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