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FORMATION OF FURO- AND DIFURO-1,4-DIHYDROPYRIDINES IN THE BROMINATION OF 2,6-DIMETHYL-3,5-DIMETHOXYCARBONYL-4-(o-NITROPHENYL)-1,4-DIHYDROPYRIDINE

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Furo- and difuro-1,4-dihydropyridines were obtained by bromination of 2,6-dimethyl-3,5-dimethoxycarbonyl-4-(o-nitrophenyl)-1,4-dihydropyridine with mild brominating agents (pyridinium bromide perbromide, N-bromosuccinimide, and dioxane dibromide).

Relatively little study has been devoted to the bromination of 1,4-dihydropyridines. The 2,6-methyl groups are brominated in the action of bromine on 4,4-disubstituted 1,4-dihydropyridines [1, 2], while 4-aryl-1,4-dihyropyridines are oxidized in this case and form unidentified substances [3-5]. It has been shown [6] that the action of a mild brominating reagent — pyridinium bromide perbromide — on 4-aryl-1,4-dihydropyridines does not lead to oxidation, and Young isolated lactones of the III type.

We have studied the action of pyridinium bromide perbromide, as well as dioxane dibromide and N-bromosuccinimide, on 2,6-dimethyl-3,5-dimethoxycarbonyl-4-(o-nitrophenyl)-1,4-dihydropyridine (I) (also known as nifedipine and fenigidin).

Bromination of the methyl group evidently occurs initially in the action of pyridinium bromide perbromide ($Py^+H\cdot Br_3^-$) on I in an equimolar ratio in solution in chloroform. The

Scheme 1

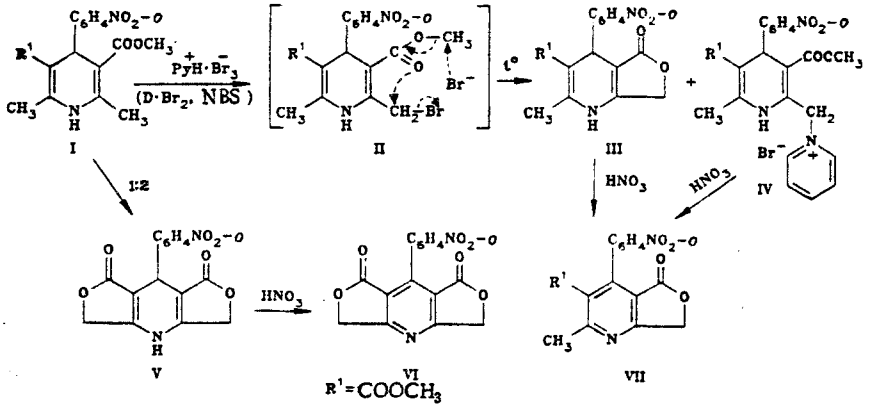

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TABLE 1. Characteristics of III-VII

Compound	T_{mp}, °C	R_f (system)*	UV spectrum, λ_{max} (log ε)	IR spectrum, cm^{-1}	PMR spectrum, ppm	Found, % C	Found, % H	Found, % N	Empirical formula	Calc., % C	Calc., % H	Calc., % N	Yield, % (method)
III	259—262 (261—263) [6]	0,01 (*1*), 0,40 (*2*)	207 (4,4), 227 (4,4), 347 (3,9)	3230, 3170, 3080, 1735, 1700, 1675, 1530	2,30 (3H, s, 2-CH_3); 3,30 (3H, s, OCH_3); 4,76 (2H, s, CH_2); 5,52 (1H, s, 4-H); 7,50 (4H, m, Ar—H); 9,74 (1H, s, N—H)	57,6	3,7	8,5	$C_{16}H_{14}N_2O_6$	58,2	4,3	8,5	47 (A), 45 (B), 54 (C)
IV	181—183	0,10 (*1*), 0,66 (*2*)	208 (4,4), 236 (4,4), 369 (3,6)	3160, 3120, 3060, 1708, 1692, 1651, 1540	2,55 (3H, s, 2-CH_3); 3,61 (6H, d, OCH_3); 5,75 (1H, s, 4-H); 6,33 (2H, s, CH_2); 7,50 (4H, m, Ar—H); 8,0 (2H, m, β-H—Py); 8,46 (1H, m, γ-H—Py); 9,63 (2H, d, α-H—Py); 10,65 (1H, s, NH)	53,0	4,5	8,1	$C_{22}H_{22}BrN_3O_6$	52,4	4,4	8,3	10 (A)
V	289—291	0,01 (*1*), 0,44 (*2*)	208 (4,3), 218 (4,4), 324 (3,7)	3330, 3210, 1760, 1730, 1685, 1615, 1530	4,93 (2H, s, CH_2); 5,56 (1H, s, 4-H); 7,70 (4H, m, Ar—H); 10,70 (1H, s, N—H)	57,4	2,9	9,4	$C_{15}H_{10}N_2O_6$	57,4	3,2	8,9	65
VI	238—241	0,25 (*1*), 0,79 (*2*)	209 (4,6), 278 (4,2)	1780, 1760, 1630, 1595, 1524	5,50 (2H, s, CH_2); 7,43, 7,80, 8,37 } (4H, m, Ar—H)	57,5	2,3	9,1	$C_{15}H_8N_2O_6$	57,7	2,6	9,0	70
VII	171—174	0,34 (*1*), 0,84 (*2*)	208 (4,5), 272 (3,9)	1770, 1735, 1600, 1570, 1530	2,77 (3H, s, 2-CH_3); 3,51 (3H, s, OCH_3); 5,30 (2H s, CH_2); 7,24, 7,70, 8,30 } (4H, m, Ar—H)	3,7	58,0	8,7	$C_{16}H_{12}N_2O_6$	58,5	3,7	8,5	68 (A), 61 (B)

*Systems for TLC: (1) chloroform—ethyl acetate—hexane (1:1:1); (2) acetic acid.

TABLE 2. Mass Spectra of III-VII*

Compound	m/z values (relative intensities, %)
III	330 (0,6) $M^{+\cdot}$, 314 (2) $[M-O]^+$, 313 (3) $[M-OH]^+$, 297 (2), 282 (100), 267 (11), 266 (31), 254 (2), 250 (4), 238 (6), 237 (7), 222 (6), 209 (6), 208 (6), 140 (6), 139 (6), 127 (6), 126 (6), 44 (22). High resolution exptl. 314,0853; $C_{16}H_{14}N_2O_6$; calc. 314,0902; Δ=0,0049; exptl. 297,0515; $C_{15}H_8N_2O_5$; 297,0511; Δ=0,0004
IV	329 (2), 313 (4), 298 (2), 296 (3), 285 (5), 282 (100), 267 (18), 266 (18), 254 (9), 251 (8), 250 (7), 238 (14), 237 (9), 224 (66), 79 (93), 78 (18), 52 (59), 51 (36), 44 (73)
V	313 (0,6) $[M-H]^+$, 267 (16), 266 (100), 265 (7), 264 (10), 238 (10), 235 (7), 209 (8). High resolution; exptl. 267,0493; $^{12}C_{14}{}^{13}CH_8NO_4$; calc. 267,0485; Δ=0,0008; exptl. 266,0440; $C_{15}H_8NO_4$; calc. 266,0452; Δ=0,0012; exptl. 238,0563; $C_{14}H_8NO_3$; exptl. 238,0504; Δ=−0,0059
VI	266 (100), 238 (9), 209 (7)
VII	297 (1), 282 (100), 267 (7), 266 (5), 250 (6), 238 (5), 222 (6). High resolution: exptl. 282,0769; $C_{16}H_{12}NO_4$; calc. 282,0766; Δ=−0,0003

*For the m/z values below 250 the peaks with intensities ≥ 5% of the maximum peak are presented.

hypothetical intermediate II readily undergoes ring opening to give lactone III, as in [6]. In addition, the bromine atom in the II molecule is replaced by pyridine to give salt IV, which can be isolated from the reaction mixture. The second methyl group of the 1,4-dihydropyridine could not be brominated by the above-metioned reagent. Only salt IV was isolated from the mixture when the reaction was carried out with a twofold excess of $Py^+H \cdot Br_3^-$. Repeated treatment of both salt IV and lactone III with $Py^+H \cdot Br_3^-$ leads to oxidation and the formation of VII. The latter was also obtained by treatment of dihydropyridines III and IV with 3 N nitric acid.

Since lactones of the III type are agonists of calcium ions and display positive ionotropic activity [7, 8], to develop a more suitable method for their preparation we studied the bromination of I with dioxane dibromide and N-bromosuccinimide.

A mixture of products, which we could not separate, was isolated in the bromination of I with dioxane dibromide in chloroform. Judging from TLC data, it may be assumed that lactone III, its oxidized form VII, and dilactone V are present in the mixture, i.e., bromination of the second methyl group also is observed. Lactone III can be isolated when the reaction is carried out in the presence of pyridine; in addition, according to TLC data, salt IV is formed, but it was not isolated in pure form.

The best results were obtained in the case of bromination with N-bromosuccinimide (NBS). Refluxing with an equimolar amount of NBS in chloroform gives lactone III in good yield. The previously unknown dilactone V was obtained when the reaction was carried out with a twofold excess of NBS.

In their general features, the character of the UV spectra of III-V is similar to that of the spectra of 4-aryl-1,4-dihydropyridines [9]. A significant hypsochromic shift of the long-wave maximum as compared with the shift of I (Δ 13 and 36 nm, respectively) is observed for lactones III and V. A long-wave absorption band is absent for oxidized products VI and VIII, but a maximum appears at ~270 nm.

Stretching vibrations of the CO group of a lactone ring are observed in the IR spectra (Table 1) at 1735-1760 cm^{-1} (III and V), while the ν_{CO} band is significantly higher (1770-1780 cm^{-1}) for the oxidized products.

In the PMR spectrum (Table 1) of salt IV the protons of the 3,5-ester methyl groups give two signals centered at 3.61 ppm (unequivalent because of the unsymmetrical character of the substituents in the 2 and 6 positions). It is interesting to note that for compounds with a 1,4-dihydropyridine structure (III and V) the signal of aromatic protons gives a multiplet at 7.50-7.70 ppm, while for the oxidized lactones the signals of these protons give three multiplets at 7.24-7.43, 7.70-7.80, and 8.30-8.37 ppm.

The mass spectrum of the m-nitro analog of VII, which was described in [10], is characterized by a molecular-ion peak with an intensity of 18%, which undergoes fragmentation with the detachment of an $\dot{O}CH_3$ or $\dot{O}H$ radical and the subsequent formation of an $[M-OH, -NO]^+$ ion with m/z 281.

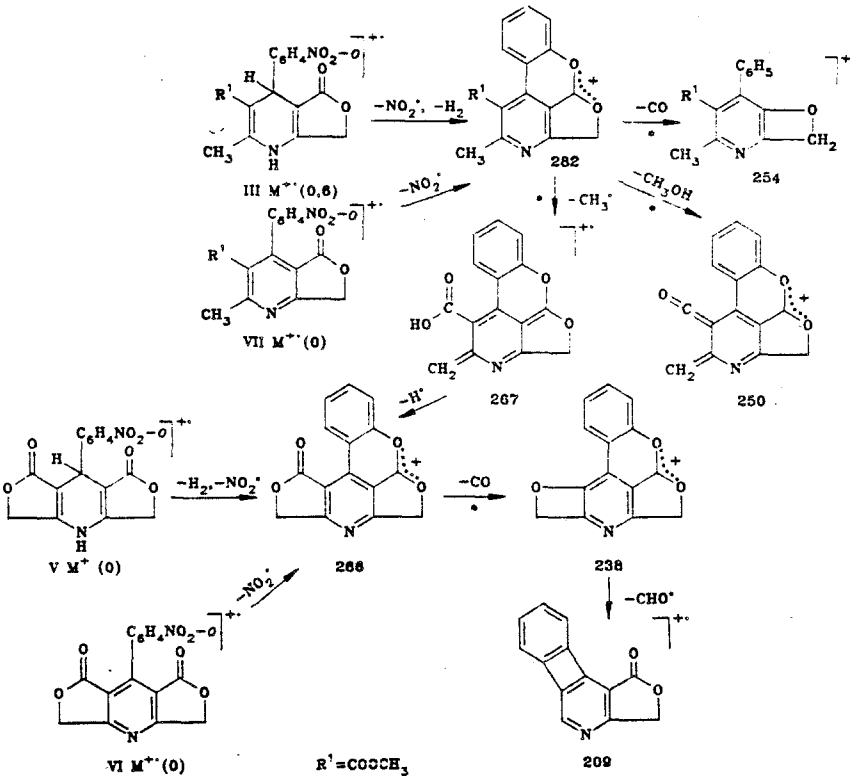
A molecular-ion peak is absent in the mass spectra of IV-VII, and a low-intensity molecular-ion peak is present only in the spectrum of III (Table 2).

The principal fragmentation process is detachment of a nitro group for pyridine compounds VII and VI, whereas for dihydropyridine compounds V and III the principal fragmentation process is the simultaneous detachment of a nitro group and a molecule of hydrogen with the formation of a pyridine ring (Scheme 2, m/z 282 and 266). The ejection of a molecule of CO takes place after the detachment of a nitro group.

The formation of ions with m/z 314, 297, and 208 also occurs simultaneously with these processes in the fragmentation of III. The formation of an $[M - OCH_3]^+$ ion is observed for the corresponding pyridine compounds VII.

In the mass spectrum of IV the greatest mass number m/z 329 is observed for the ion corresponding to the ejection of pyridine and CH_4 molecules. The subsequent ejection of a molecule of HNO_2 leads to the formation of an ion with m/z 282, which undergoes fragmentation, as shown in Scheme 2. In addition, an intense peak of an iion with m/z 79, viz., $[C_5H_5N]^{+\cdot}$, and products of its fragmentation are present in the spectrum of IV.

Scheme 2. The Processes Denoted by an Asterisk Were Confirmed by Scanning of the Metastable Ions.



It is known [11] that nifedipine (I) is a photosensitive compound and that oxidation occurs particularly readily in solutions. Lactones III and V are also relatively unstable in dilute alcohol solutions ($5 \cdot 10^{-5}$ mole/liter). When they are allowed to stand in light, the long-wave maximum in the UV spectra vanishes, and a maximum of the oxidized form appears at ~270 nm. After 6 days, lactone III undergoes 42% oxidation, as compared with 8% oxidation for dilactone V; fenigidin undergoes 81.2% oxidation after 2 h. The increase in the stability when lactone rings are introduced into the 1,4-dihydropyridine molecule is also confirmed by electrochemical oxidation. Compounds I, III, and V on a graphite disk in acetonitrile solutions give one well-expressed electrooxidation wave, the half-wave potentials of which lie at 0.80-1.12 V (0.80, 0.99, and 1.12 V, respectively).

Thus in the action on I of mild brominating agents – pyridinium bromide perbromide, N-bromosuccinimide, and dioxane dibromide – one observes bromination of the methyl group, probably with the formation of unstable compound II, which is stabilized via two competitive pathways: with the formation of a lactone ring and with replacement of the bromine atom by pyridine (when the reaction is carried out in the presence of pyridine).

EXPERIMENTAL

The mass spectra were recorded with an MS-50 spectrometer (KRATOS) at an ionizing-electron energy of 70 eV and an ionization-chamber temperature of 300°C with the use of direct introduction of the samples into the source. The elementary composition was determined at a resolution of ~50,000. The metastable transitions were determined in the first fieldless region by scanning of the accelerating voltage and combined scanning of the accelerating voltage and the voltage of the electrostatic analyzer. Electrochemical oxidation was carried out with a Brucker apparatus on a rotating graphite disk electrode (S^D = 0.47 cm^2) at a rotation rate of 2000 rpm. The potentials were measured relative to an $Ag/AgNO_3$ reference electrode (in acetonitrile). The concentration of the investigated compounds was $5 \cdot 10^{-4}$ mole/liter. A solution (0.1 mole/liter) of tetrabutylammonium perchlorate was used as the inert electrolyte. The IR spectra of suspensions of the compounds in Nujol were recorded with a Perkin–Elmer 580 B spectrometer. The UV spectra of solutions in ethanol (c $5 \cdot 10^{-5}$ mole/liter) were recorded with a Specord UV-vis spectrophotometer. The PMR spectra of

solutions in $CDCl_3$ were obtained with a WH-90/DC spectrometer with tetramethylsilane as the internal standard. Monitoring of the course of the reaction and the individuality of the synthesized compounds was accomplished by means of TLC on Silufol UV-254 plates.

2-Methyl-3-methoxycarbonyl-5-oxo-4-(o-nitrophenyl)-1,4,5,7-tetrahydrofuro[3,4-b]pyridine (III). A. A 6.23-g (1.8 mmole) sample of I was dissolved in 40 ml of anhydrous chloroform, and the solution was cooled to 0°C and treated with 2.37 g (3.0 mmole) of pyridine and 6.72 g (2.1 mmole) of pyridinium bromide perbromide. The mixture was stirred with cooling for 30 min, after which it was refluxed for 90 min. It was then washed successively with 300 ml of 2 N hydrochloric acid and twice (to 300-ml portions) of a saturated aqueous solution of NaCl and dried with anhydrous calcium chloride. Cooling to 0°C precipitated 3.3 g (55%) of lactone III, which was crystallized from acetone–hexane (1:1) to give 2.8 g (46.6%) of the product (see Table 1). The chloroform was removed by distillation to dryness, and the residue was washed with ether and crystallized from methanol to give 0.9 g (10%) of N-[2-methyl-3,5-dimethoxycarbonyl-4-(o-nitrophenyl)-1,4-dihydropyridinyl-6-methyl]pyridinium bromide (IV) (see Table 1).

B. A 6.92-g (2 mmole) sample of I was dissolved in 40 ml of anhydrous chloroform, and the solution was cooled to 0°C and treated with 3.16 g (4 mmole) of pyridine and 5.70 g (2.3 mmole) of dioxane dibromide. The mixture was stirred with cooling for 60 min, after which it was refluxed for 90 min. It was then washed successively with 300 ml of 2 N hydrochloric acid and twice (to 300-ml portions) with a saturated aqueous solution of NaCl and dried with anhydrous calcium chloride. The solvent was removed by distillation, and the residue was washed with ethanol and crystallized from acetone–hexane (1:1) to give 3.0 g (45%) of III.

C. A 3.46-g (1.0 mmole) sample of I was dissolved in 20 ml of chloroform, 1.78 g (1.0 mmole) of N-bromosuccinimide was added, and the mixture was refluxed for 30 min. The precipitate that formed when the mixture was cooled was removed by filtration to give 2.3 g (70%) of lactone III, which was crystallized from acetone–hexane (1:1) to give 1.8 g (54%) of III.

1,7-Dioxo-8-(o-nitrophenyl)-1,3,4,5,7,8-hexahydro(difuro)-[3,4,3',4'-b,e]pyridine (V). A mixture of 6.92 g (2 mmole) of I and 7.12 g (4 mmole) of N-bromosuccinimide in 40 ml of chloroform was refluxed for 30 min. Cooling of the mixture precipitated 4.1 g (65%) of dilactone V, which was crystallized from acetone–hexane (3:1) to give 1.8 g (29%) of product (see Table 1).

2-Methyl-3-methoxycarbonyl-5-oxo-4-(o-nitrophenyl)-5,7-dihydrofuro[3,4-b]pyridine (VII). A. A mixture of 0.45 g (0.9 mmole) of salt IV and 1.58 ml of 3 N nitric acid was stirred at 66-75°C for 60 min, after which it was diluted with 50 ml of water and filtered. The solid material was crystallized from methanol to give 0.2 g (68%) of product (see Table 1).

B. A mixture of 0.33 g (1.0 mmole) of lactone III and 1.75 ml of 3 N nitric acid was stirred at 60-75°C for 30 min, after which it was diluted with 50 ml of water and filtered. The solid material was crystallized from methanol to give 0.2 g (61%) of product.

1,7-Dioxo-8-(o-nitrophenyl)-1,3,5,7-tetrahydro(difuro)-[3,4,3',4'-b,e]pyridine (VI). A mixture of 0.31 g (1.0 mmole) of dilactone V and 1.75 ml of 3 N nitric acid was stirred for 2 h, after which it was diluted with 50 ml of water and filtered. The solid material was crystallized from methanol to give 0.15 g (48%) of product (see Table 1).

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