BROMINATION OF 4-ARYL-3,5-DIALKOXYCARBONYL-2,6-DIMETHYL-1,4-DIHYDROPYRIDINES

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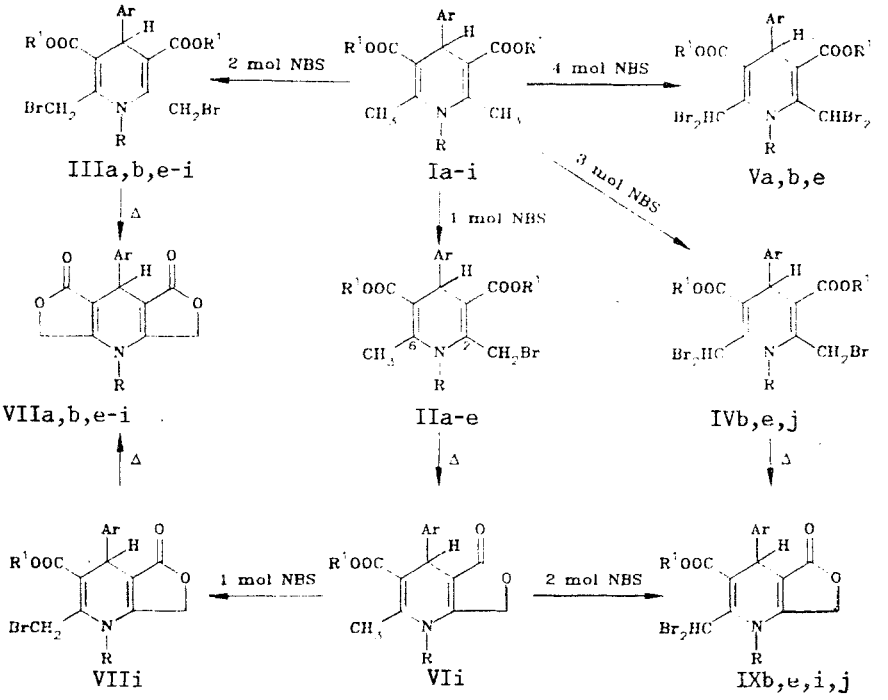
4-Aryl-3,5-dialkoxycarbonyl-2,6-dimethyl-1,4-dihydropyridines are brominated by N-bromosuccinimide in methanol at room temperature at the methyl groups at positions 2 and 6 to form mono-, di-, tri-, and tetrabromo derivatives. When the N-unsubstituted bromomethyl-1,4-dihydropyridines are heated they are easily converted to tetrahydrofuropyridines, but in the case of the analogous N-substituted-1,4-dihydropyridines cyclization does not occur. The 2,6-bis(bromomethyl)-substituted products easily replace bromine under the influence of nucleophilic reagents.

In the first publications on the bromination of methyl-substituted 3,5-dialkoxycarbonyl-1,4-dihydropyridines the intermediate 2-bromomethyl derivatives were not separated. It was only shown that when they are heated they cyclize to the 1,4,5,7-tetrahydrofuro[3,4-b]pyridines; this is a convenient way to synthesize the latter [1, 2]. Later when pyridinium bromide perbromide was used as brominating agent under mild conditions, the 2-bromomethyl-1,4-dihydropyridines [3-5], or the products of their reaction with nucleophilic reagents were separated [6-8].



I—IX a Ar = C_6H_5, R = H, $R^1 = CH_3$; b Ar = C_6H_5, R = H, $R^1 = C_2H_5$; c Ar = $C_6H_4OCHF_2$-2, R = H, $R^1 = C_3H_7$-*i*; d Ar = $C_6H_2(OCH_3)_3$-3,4,5, R = H, $R^1 = C_2H_5$; e Ar = $C_6H_4OCHF_2$-2, R = CH_3, $R^1 = CH_3$; f Ar = C_6H_4Br-4, R = C_6H_5, $R^1 = C_2H_5$; g Ar = C_6H_5, $R^1 = C_6H_4OCH_3$-4; R = H, $R^1 = C_2H_5$; h Ar = $C_6H_4NO_2$-3, R = $C_6H_4CH_2$, $R^1 = C_2H_5$; i Ar = $C_6H_4OCHF_2$-2, R = H, $R^1 = CH_3$; j Ar = $C_6H_4NO_2$-3, R = CH_3, $R^1 = CH_3$

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TABLE 1. Properties of Compounds II-V, VII, and X-XIV

Compound	Empirical formula	mp, deg C	UV spectrum, λ_{max}, nm (log ε)	IR spectrum, cm^{-1}	Yield, %
IIa	$C_{17}H_{18}BrNO_4$	121 ... 123	248 (4,1); 361 (3,6)	1642, 1681, 1701, 3318	63
IIb	$C_{19}H_{22}BrNO_4$	95 ... 96	249 (4,2); 367 (3,8)	1672, 1695, 3308	47
IIc	$C_{22}H_{26}BrF_2NO_5$	91 ... 93	246 (4,2); 372 (3,7)	1664, 1685, 3303	76
IIf	$C_{22}H_{28}BrNO_7$	139 ... 141	305 (3,6); 361 (3,7)	1628, 1646, 1692, 3330	41
IIe	$C_{19}H_{20}BrF_2NO_5$	124 ... 126	249 (4,2); 344 (3,7)	1638, 1691	61
IIh	$C_{17}H_{17}Br_2NO_4$	123 ... 125	253 (4,0); 333 (3,7)	1642, 1679, 1702, 3338	70
IIIb	$C_{19}H_{21}BrNO_4$	121 ... 123	250 (4,1); 342 (3,2)	1645, 1672, 1706, 3300	41
IIIe	$C_{19}H_{19}Br_2F_2NO_5$	111 ... 113	252 (4,1); 337 (3,7)	1642, 1699	85
IIIf	$C_{25}H_{24}Br_3NO_4$	136 ... 138	266 (4,2); 345 (3,3)	1630, 1680, 1690	80
IIIg	$C_{26}H_{27}Br_2NO_5$	124 ... 126	228 (4,4); 270 (4,2); 355 (3,3)	1635, 1690, 1700	81
IIIh	$C_{26}H_{26}Br_2N_2O_6$	149 ... 151	263 (4,3); 346 (3,7)	1635, 1690, 1700	86
IIIi	$C_{18}H_{17}Br_2F_2NO_5$	115 ... 117	248 (4,1); 332 (3,7)	1678, 1696, 3325	80
IVb	$C_{19}H_{20}Br_3NO_4$	105 ... 107	252 (4,2); 368 (3,7)	1646, 1682, 3302	39
IVe	$C_{19}H_{18}Br_3F_2NO_5$	116 ... 118	245 (4,0); 340 (3,6)	1634, 1682, 1712	19
IVj	$C_{18}H_{17}Br_3N_2O_6$	143 ... 145	251 (4,1); 347 (3,8)	1625, 1695	53
Va	$C_{17}H_{15}Br_4NO_4$	143 ... 145	236 (4,1); 355 (3,6)	1696, 3380	39
Vb	$C_{19}H_{19}Br_4NO_4$	127 ... 129	225 sh. (4,1); 320 (3,8)	1690, 3383	33
Vd	$C_{19}H_{17}Br_4F_2NO_5$	121 ... 123	241 (4,2); 338 (3,6)	1624, 1690	47
VIIi	$C_{17}H_{14}BrF_2NO_5$	105 ... 107	224 (4,2); 344 (3,7)	1635, 1727, 3076, 3222	46
Xa	$C_{17}H_{17}N_7O_4$	98 ... 100	238 (4,3); 354 (3,8)	1690, 2110, 3350	87
Xb	$C_{19}H_{21}N_7O_4$	84 ... 86	240 sh (4,1); 362 (3,7)	1648, 1685, 2115, 3360	49
Xi	$C_{18}H_{17}F_2N_7O_5$	115 ... 116	240 (4,2); 364 (3,8)	1649, 1688, 2122, 3375	22
XIi	$C_{18}H_{17}F_2I_2NO_5$	137 ... 139	285 (4,0); 368 (3,6)	1648, 1675, 1695, 3325	45
XIIf	$C_{27}H_{24}BrN_3O_4S_2$	124 ... 127	254 (4,1); 353 (3,5)	1642, 1690, 2160	79
XIIj	$C_{28}H_{27}N_3O_5S_2$	102 ... 105	232 (4,3); 257 (4,1); 353 (3,6)	1630, 1676, 1690, 2143, 2160	77
XIIh	$C_{28}H_{26}N_4O_6S_2$	147 ... 150	263 (4,2); 348 (3,7)	1650, 1680, 1698, 2150, 2158	83
XIIIf	$C_{33}H_{40}BrN_3O_6$	133 ... 137	237 (4,2); 348 (3,6)	1635, 1678, 1703	28
XIIIg	$C_{32}H_{43}N_3O_7$	105 ... 108	232 (4,3); 348 (3,8)	1648, 1700	35
XIIIh	$C_{34}H_{42}N_4O_8$	145 ... 147	242 (4,2); 261 (4,1); 346 (3,7)	1570, 1625, 1700	33
XIVk	$C_{17}H_{17}N_3O_2$	288 ... 290	220 (4,3); 334 (3,9)	1630, 1681, 3125, 3200	20
XIVℓ	$C_{18}H_{17}F_2N_3O_3$	279 ... 281	220 (4,3); 342 (3,8)	1649, 1683, 3120, 3185	15

We have shown that methyl-substituted 1,4-dihydropyridines are more conveniently brominated by milder brominating agents, and we have studied the cyclization of the bromo derivatives to mono- and dilactones [9-12].

In the present work we have studied the effect of N-bromosuccinimide on the substituted 2,6-dimethyl-1,4-dihydropyridines (I) at room temperature in methanol solution (see Table 1); under these conditions furopyridines are not formed.

Depending on the amount of brominating agent, we were able to separate in good yield the products of bromination of the methyls at positions 2 and 6, viz., compounds (II-V). For proof of the structure of the latter the PMR spectra were most informative. In addition to the signals of the methyl protons of (I) at 2.2-2.3 ppm they also contained the signals of the CH_2Br protons of (II-IV) as an AB quartet with SSCC $^2J_{(HH)}$ = 11.0 Hz at 3.9-5.2 ppm, and the signals of the $CHBr_2$ protons of (IV) and (V) as a singlet at 8.05-8.4 ppm.

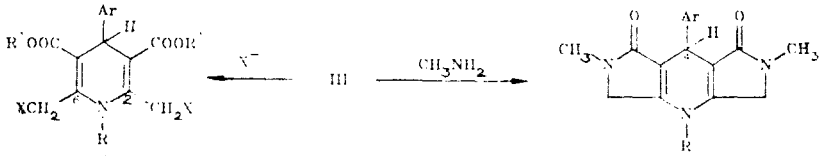
When the 1,4-dihydropyridines that are not substituted at nitrogen and contain bromomethyl groups (II-IV, VII, R = H) are heated they readily split off alkyl bromide to form the lactones (VI), (VIII), or (IX), which we have obtained previously [9, 11, 12]. In contrast the analogous 1-substituted 1,4-dihydropyridines (II-IV) (R = alkyl, aralkyl, aryl) are stable, and do not cyclize to lactone even after heating for many hours [13]. This is in agreement with the previously identified feature of the N-substituted 2,6-dimethyl-3,5-dialkoxycarbonyl-1,4-dihydropyridines [14], that is related to their stress and the significant change in reactivity. Stuart—Brigleb models show that for the

1-substituted 1,4-dihydropyridines of this series rotation of the $-CH_2Br$ group is not possible; a convergence of the reactive centers when the ring is closed is therefore improbable.

To confirm the mobility of the halogen in 2,6-bis(bromomethyl)-1,4-dihydropyridines we carried out a nucleophilic substitution of (III) with morpholine, sodium azide, potassium thiocyanate, and potassium iodide. The reactions took place under mild conditions, and substitution products (X-XIII) were formed in good yield. With 1-unsubstituted-1,4-dihydropyridines (III) the reaction must be carried out at room temperature, because the slightest heating will form dilactone (VIII).

Compounds (X-XIII) are stable crystalline materials. In the IR spectrum of the thiocyanates the thiocyanate absorption occurs around 2160 cm^{-1}; with the azides the azide absorption is around 2120 cm^{-1}. In the PMR spectra the signals of the methylenes at positions 2 and 6 form an AB quartet with $^2J_{(HH)}$ = 17.0 for (X), 14.0 for (XIII), and 13.0 Hz for (XII).

When (IIIa, b) react with methylamine, besides replacement of the halogen there is cyclization of the substitution product to form the respective dipyrrolopyridines (XIVk, *l*). An analogous reaction has been described for 2-bromomethylpyrimidines [15]. The PMR spectra of (XIVk, *l*) (see Table 2) lack the AB quartet of the 2,6-methylene protons, but show a singlet at 3.90 ppm of the pyrrole CH_2 protons; the NCH_3 proton signals form a singlet around 2.70 ppm.



Xa,b,i XIi
XII-XIII f,g,h

XIVk, *l*

X X=N_3; XI X=I; XII X=SCN; XIII X=morpholino XIV k R=H, Ar=Ph; *l* R=H, Ar=2-F_2CHO-C_6H_4

EXPERIMENTAL

IR spectra were obtained with a Perkin—Elmer 580 B instrument (suspension in Nujol); UV spectra were obtained with a Specord UV-vis instrument (in ethanol). NMR spectra were recorded with a WH-90/DS spectrometer (90 MHz), in $CDCl_3$ or DMSO-D_6, with TMS as internal standard. The course of the reaction and the individuality of the compounds synthesized was monitored by TLC on Silufol UV-254 plates.

The elemental composition of the compounds for C, H, and N agrees with the calculated values.

2-Bromomethyl-3,5-dimethoxycarbonyl-4-phenyl-6-methyl-1,4-dihydropyridine (IIa). To a solution of 10 mmoles of (Ia) in 200 ml of methanol was added 10 mmoles of N-bromosuccinimide. The mixture was stirred at room temperature for 1 h, then 120 ml of water was added. The product that separated when the mixture was kept in the cold was purified by crystallization (acetone—hexane).

2-Bromomethyl-1,4-dihydropyridines (IIb-e), starting from (Ib-e), and **compounds (IIIa, b, e-i), (IVb, e, j), and (Va, b, e)** were synthesized in analogous manner. To obtain bromides (III-V), 20, 30, and 40 mmoles, respectively, of N-bromosuccinimide were used.

Compound VIIi was obtained by the same procedure, by bromination of (VIi).

2,6-Di(azidomethyl)-3,5-diethoxycarbonyl-4-phenyl-1,4-dihydropyridine (Xb). To a solution of 2.5 mmoles of (IIIb) in 20 ml of DMFA were added 10 mmoles of sodium azide. The mixture was stirred for 5 h and poured into 100 ml of water. The product that separated (Xb) was crystallized from 1:1 methanol—water.

Compounds Xa, i were obtained similarly.

2,6-Di(iodomethyl)-3,5-dimethoxycarbonyl-4-(2'-difluoromethoxyphenyl)-1,4-dihydropyridine (XIi). A solution of 10 mmoles of (IIIi) and 20 mmoles of potassium iodide in 50 ml of acetone was stirred for 3 h. The mixture was filtered, and acetone was evaporated from the filtrate. The residue was rubbed with ether, and the resulting crystals were recrystallized from 1:1 ethanol—water to give (XIi).

1-Phenyl-2,6-di(morpholinomethyl)-3,5-diethoxycarbonyl-4-(4-bromophenyl)-1,4-dihydropyridine (XIIIf). To a solution of 6 mmoles of (IIIf) in absolute benzene was added 24 mmoles of morpholine and the mixture was left for 24 h at room temperature. The precipitated morpholine hydrobromide was filtered off. The filtrate was evaporated in vacuum, and the residue was crystallized from 1:2 ethanol—water to give (XIIIf).

Compounds (XIIIg, h) were synthesized similarly.

TABLE 2. PMR Spectra of Compounds (II-V, VII, and X-XIV)

Compound	PMR spectrum, δ, ppm							
	2-R	6-R	COOR	4-H (1H, s)	H_{Ar}	R_{Ar}	N—H (1H, s)	N—R*, X
IIa	4,57 (1H, d; 4,86 (1H, d)	2,37 (3H, s)	3,62 (3H, s); 3,66 (3H, s)	5,0	7,1...7,3 (5H, m)	—	6,04	—
IIb	4,56 (1H, d; 4,85 (1H, d)	2,36 (3H, s)	1,22 (6H, m); 4,12 (4H, m)	5,0	7,0...7,3 (5H, m)	—	6,02	—
IIc	4,43 (1H, d; 4,89 (1H, d)	2,31 (3H, s)	1,17 (12H, m); 4,8...5,12 (2H, m)	5,21	6,9...7,3 (4H, m)	6,49 (1H, t)	6,12	—
IId	4,54 (1H, d; 4,96 (1H, d)	2,37 (3H, s)	1,25 (3H, t); 1,27 (3H, t); 4,16 (4H, m)	5,0	6,51 (2H, s)	3,78 (9H, s)	6,12	—
IIe	4,76 (1H, d; 4,91 (1H, d)	2,45 (3H, s)	3,64 (3H, s); 3,70 (3H, s)	5,45	6,9...7,2 (4H, m)	6,46 (1H, t)	—	3,31 (3H, s)
IIIa	4,58 (2H, d; 4,86 (2H, d)		3,71 (6H, s)	5,03	7,1...7,3 (5H, m)	—	6,61	—
IIIb	4,60 (2H, d; 4,91 (2H, d)		1,22 (6H, t), 4,11 (4H, q)	4,99	7,1...7,3 (5H, m)	—	6,50	—
IIIe	4,60 (2H, d; 5,01 (2H, d)		3,70 (3H, s)	5,49	6,9...7,2 (4H, m)	6,45 (1H, t)	—	3,44 (3H, s)
IIIf	3,95 (2H, d; 4,68 (2H, d)		1,20 (6H, t), 4,13 (4H, m)	5,07	7,15...7,62 (9H, m)	—	—	—
IIIg	3,95 (2H, d; 4,73 (2H, d)		1,20 (6H, t); 4,13 (4H, q)	5,08	6,93...7,40 (9H, m)	3,77 (3H, s)	—	—
IIIh	4,71 (2H, d, 5,26 (2H, d)		1,22 (6H, t), 4,22 (4H, q)	5,13	6,57...8,08 (9H, m)	—	—	5,00 (2H, s)
IIIi	4,57 (2H, d; 4,82 (2H, d)		3,62 (6H, s)	5,33	6,8...7,4 (4H, m)	6,48 (1H, t)	6,52	—
IVb	4,59 (1H, d; 4,99 (1H, d)	8,06 (1H, s)	1,23 (6H, m) 4,14 (4H, m)	4,98	7,1...7,3 (5H, m)	—	6,88	—
IVe	4,60 (1H, d; 5,01 (1H, d)	8,54 (1H, s)	3,75 (6H, m)	5,51	6,9...7,2 (4H, m)	6,48 (1H, t)	—	3,75 (3H, m)
IVj	4,59 (1H, d; 5,05 (1H, d)	8,65 (1H s)	3,77 (6H, s)	5,25	7,3...7,5 7,9...8,1 (4H, m)	—	—	3,80 (3H, s)
Va	8,05 (2H, s)		3,70 (6H, s)	4,97	7,24 (5H, s)	—	7,37	—
Vb	8,04 (2H, s)		1,22 (6H, t); 4,14 (4H, q)	4,92	7,20 (5H, s_	—	7,31	—

Ve	8,40 (2H, s)		3,76 (6H, s)	5,50	6,9 ... 7,3 (4H, m)	6,47 (1H, t)	—	3,96 (3H, s)
VIIi	4,63 (4H, m)		3,47 (3H, s)	5,22	7,0 ... 7,3 (4H, m)	6,64 (1H, q)	8,19	—
Xa	4,67 (2H, d)	4,90 (2H, d)	3,60 (6H, s)	4,96	7,1 ... 7,25 (5H, m)		7,50	—
Xb	4,67 (2H, d)	4,93 (2H, d)	1,20 (6H, t); 4,08 (4H, q)	4,98	7,20 (5H, s)	—	7,47	—
Xi	4,62 (2H, d)	4,88 (2H, d)	3,58 (6H, s)	5,30	6,9 ... 7,3 (4H, m)	6,46 (1H, t)	7,58	—
XIi	4,58 (4H, d.d)		3,63 (6H, s)	5,20	7,0 ... 7,3 (4H, m)	6,49 (1H, t)	5,98	—
XIIf	3.82 (2H, d)	4,33 (2H, d)	1,15 (6H, t), 4,08 (4H, q)	5,08	7,17 ... 7,66 (9H, m)	—	—	—
XIIg	3,86 (2H, d)	4,40 (2H, d)	1,17 (6H, t), 4,11 (4H, q)	5,13	6,95 ... 7,53 (9H, m)	—		3,68 (3H, s)
XIIh	4,46 (2H, d)	5,65 (2H, d)	1,12 (6H, t); 4,17 (4H, q)	5,32	6,66 ... 8,06 (8H, m)	—	—	4,95 (2H, s) *2
XIIIf	2,86 (2H, d)	3,75 (2H, d)	1,24 (6H, t) 4,15 (4H, q)	5,11	7,13 ... 7,52 (9H, m)		—	2,15 (8H, m) *3; 3,53 (8H, m) *4
XIIIg	2,77 (2H, d)	3,64 (2H, d)	1,15 (6H, t) 4,06 (4H, q)	5,0	6,73 ... 7,51 (9H, m)	3,68 (3H, s)	—	2,06 (8H, m) *3; 3,42 (8H, m) *4
XIIIh	3,46 (2H, d)	4,26 (2H, d)	1,31 (6H, t); 4,22 (4H, q)	5.20	6,53 ... 8,11 (8H, m)	—	—	2,51 (8H, m *3; 3,64 (8H, m) *4; 5,37 (2H, s) *2
XIVk		3,92 (4H, s)	—	4,47	7,0 ... 7,2 (5H, m)	—	9,69	2,71 (6H, s)
XIVl		3,99 (4H, s)	—	4,86	6,9 ... 7,2 (4H, m)	7,30 (1H, s)	9,78	2,72 (6H, s)

*1 H_{Ar} signals shown in H_{Ar} graph.
*2 For NCH_2.
*3 For OCH_2 in (X).
*4 For NCH_2 in (X).

1-Phenyl-2,6-di(thiocyanatomethyl)-3,5-(diethoxycarbonyl)-4-(4′-bromophenyl)-1,4-dihydropyridine (XIIf). To a solution of 6 mmoles of (IIIf) in dioxane was added 15 mmoles of potassium thiocyanate in water. The mixture was heated on a water bath for 1 h. Then it was poured on ice, and the precipitate was crystallized from 1:2 ethanol—water to give (XIIf).

Compounds (XIIg, h) were synthesized similarly.

2,6-Dimethyl-1,7-dioxo-8-(2-difluoromethoxyphenyl)-1,3,4,5,7,8-hexahydro(dipyrrolo)-[3,4,3,4-b,e][pyridine (XIV*l*). To a solution of 2 mmoles of (IIIi) in 50 ml of ethanol was added 2.5 ml of 30% aqueous methylamine. The mixture was stirred for 1 h. Then 20 ml of water was added. The precipitate that separated upon cooling was crystallized from 1:1 acetone—hexane to give (XIV*l*).

Compound XIVk was synthesized similarly.

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