SYNTHESIS AND PROPERTIES OF ETHYL ESTERS OF SOME 1,2-DIHYDROPYRIDINE-3,5-DICARBOXYLIC ACIDS

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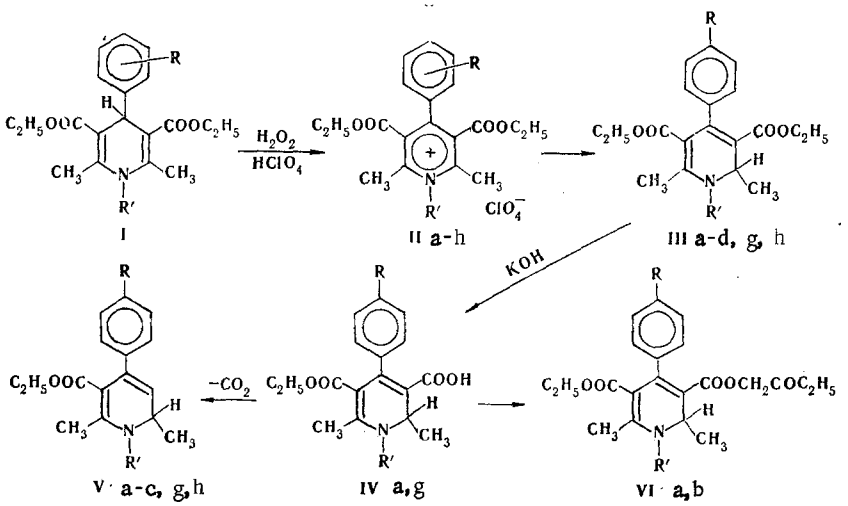
The oxidation of diethyl 1-methyl- or 1-aryl-2,6-dimethyl-4-aryl-1,4-dihydropyridine-3,5-dicarboxylates with hydrogen peroxide in the presence of perchloric acid gave the perchlorates of the corresponding pyridinium ions, the reduction of which with $NaBH_4$ is a preparative method for the synthesis of diethyl esters of 1-substituted 2,6-dimethyl-1,2-dihydropyridine-3,5-dicarboxylic acids. Derivatives of the 5-carboxylic acid of the corresponding 1,2-dihydropyridine are formed by alkaline hydrolysis of these esters.

In the series of partially hydrogenated pyridines considerably less study has been devoted to 1,2-dihydropyridines than to their 1,4 isomers. For the more detailed study of 1,2-dihydropyridines preparative methods for their synthesis must be developed. The production of 1,2 isomers has been reduced only to the reduction of pyridine derivatives or pyridinium salts [1-5]. The effect of various factors on the formation of 1,4 or 1,2 isomers in the reaction has been primarily studied, and only individual studies were of a preparative nature.

We have developed a general method for the synthesis of diethyl esters of 1-substituted 4-aryl-2,6-dimethyl-1,2-dihydropyridine-3,5-dicarboxylic acids. 1-Methyl- and 1-arylpyridinium perchlorates II, which were obtained by oxidation of the corresponding 1,4-dihydropyridines I with hydrogen peroxide in the presence of perchloric acid, which differs favorably from the previously known method [6], in which pyridinium perchlorates are formed by exchange of anions, were selected as the starting compounds. The reduction of salts II with sodium borohydride is a preparative method for the production of diethyl esters of 1-substituted 4-aryl-2,6-dimethyl-1,2-dihydropyridine-3,5-dicarboxylic acids (III), since the formation of the corresponding 1,4 isomers is not observed in the reaction.



a R=H, R′=CH_3; b R=4-CH_3, R′=CH_3; c R=4-OCH_3, R′=CH_3; d R=4-NO_2, R′=CH_3; e R=3-NO_2, R′=CH_3; f R=4-$N(CH_3)_2$, R′=CH_3; g R=H, R′=C_6H_5; h R=H, R′=$C_6H_4CH_3$-4

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TABLE 1. Characteristics of the Synthesized Compounds

Compound	mp, °C	Found, %			Empirical formula	Calc., %			Yield, %
		C	H	N		C	H	N	
IIa	195—196	54,7	5,5	3,1	$C_{26}H_{24}ClNO_8$	54,4	5,5	3,2	60
IIb	168—169	55,3	5,5	2,7	$C_{21}H_{26}ClNO_8$	55,3	5,7	3,1	65
IIc	135—136	53,9	5,3	2,5	$C_{21}H_{26}ClNO_9$	53,5	5,6	3,0	65
IId	179—181	49,3	4,8	5,6	$C_{21}H_{26}ClN_2O_{10}$	49,3	4,8	5,7	35
IIe	157—159	49,0	4,6	5,3	$C_{21}H_{26}ClN_2O_{10}$	49,3	4,8	5,7	45
IIf	170—173	54,8	5,8	5,7	$C_{22}H_{29}ClN_2O_8$	54,5	6,0	5,8	30
IIg	174—176	54,1	6,1	2,8	$C_{20}H_{26}ClNO_8$	54,1	5,9	3,2	45
IIh	214—216	55,3	6,3	3,1	$C_{21}H_{28}ClNO_8$	55,1	6,2	3,1	48
IIIa	129—130 a	69,8	7,6	3,9	$C_{20}H_{25}NO_4$	69,9	7,3	4,1	97
IIIb	116—118	70,5	7,7	3,8	$C_{21}H_{27}NO_4$	70,6	7,6	3,9	93
IIIc	107—109	67,4	7,1	3,7	$C_{21}H_{27}NO_5$	67,6	7,3	3,7	89
IIId	116—118	62,1	6,2	7,6	$C_{20}H_{24}N_2O_6$	61,8	6,2	7,2	90
IIIg	82—83	73,7	6,2	3,1	$C_{25}H_{27}NO_4$	74,1	6,7	3,5	80
IIIh	113—114	75,5	6,9	3,6	$C_{26}H_{29}NO_4$	74,4	7,0	3,3	75
IVa	114—116 b	68,1	6,6	4,8	$C_{18}H_{21}NO_4$	68,6	6,7	4,4	84
IVg	155—156 b	72,8	6,2	3,8	$C_{23}H_{23}NO_4$	73,2	6,1	3,7	70
Va	97—98	75,7	7,9	4,9	$C_{17}H_{21}NO_2$	75,3	7,8	5,2	75
Vb	108—109	75,6	8,0	5,0	$C_{18}H_{23}NO_2$	75,8	8,1	4,9	—
Vc	85	64,8	7,6	4,4	$C_{18}H_{23}NO_3$	71,7	7,7	4,6	—
Vg	77—78	79,0	7,3	4,5	$C_{22}H_{23}NO_2$	79,2	7,0	4,2	—
Vh	107—108	79,3	7,0	4,2	$C_{23}H_{25}NO_2$	79,5	7,2	4,0	—
VIa	130—131	72,1	6,5	3,5	$C_{26}H_{27}NO_5$	72,0	6,3	3,2	—
VIb	137—139	72,0	6,4	3,6	$C_{27}H_{29}NO_5$	72,5	6,5	3,1	—

[a]According to the data in [2], this compound was obtained in 70-80% yield and had mp 130°C. [b]Decomposes.

Under the influence of excess alkali on esters III only one ester grouping undergoes hydrolysis, and 2-monocarboxylic acids of 1,2-dihydropyridine (IV) are formed. These acids are readily decarboxylated even during recrystallization, and they were therefore isolated only in individual cases, and their structures were proved by the preparation of phenacyl esters VI and the structures of the decarboxylation products (V). Absorption bands of free or associated OH groups were not observed in the IR spectra of acids IV in the solid form, whereas broad absorption with maxima at 3440 and 3510 cm^{-1} is observed in the spectra of solutions in chloroform.

All of the synthesized 1,2-dihydropyridines III have a characteristic absorption maximum in the UV region at 386-388 nm, which does not depend on the character of the 4-aryl substituent. This distinguishes their UV spectra from the spectra of the corresponding 1,4-dihydro analogs (long-wave absorption at ~355 nm [2, 7]). The strong hypsochromic shift of the long-wave absorption maximum (to 339 nm) in the series of monoesters V is evidently associated with shortening of the conjugation chain. The PMR spectra confirm the 1,2-dihydro structure of the synthesized compounds (the 2-H signal is a quartet, and the 2-CH_3 signal is a doublet) and also prove the structure of monoacid IV: In the spectra of decarboxylation product V the signal of the 2-H proton is split into a quintet, while the signal of the 3-H proton is split into a doublet. However, in the case of hydrolysis of the ester group in the 5 position the 2-H signal in the spectrum of the decarboxylation product should be observed in the form of a quartet, whereas the 5-H signal should be observed as a singlet.

EXPERIMENTAL

The UV spectra of solutions of the compounds in ethanol were recorded with a Specord UV-vis spectrophotometer. The IR spectra of suspensions in Nujol or solutions in chloroform were recorded with a UR-20 spectrometer. The PMR spectra were recorded with an R-12 (60 MHz) or WH-90 (90 MHz) spectrometer with hexamethyldisiloxane as the internal standard. The physicochemical characteristics of the synthesized compounds are presented in Tables 1-3.

Pyridinium Perchlorates II. A mixture of N-substituted 1,4-dihydropyridine derivative I, a 30% solution of hydrogen peroxide, and a 57% solution of perchloric acid in a molar ratio of 1:2:1 (1:5:1 for Id,f) was refluxed in ethanol (in methanol in the case of Ig,h) for 4 h, after which it was evaporated *in vacuo*, cooled, and treated with ether. The precipitate was recrystallized from isopropyl alcohol.

TABLE 2. UV and IR Spectra of the 1,2-Dihydropyridine Derivatives and Pyridinium Salts

Compound	UV spectrum, λ_{max}, nm (log ε)	IR spectrum, cm^{-1} (absorption, %)
IIa	206 (4,47), 288 (4,08)	1735 (88), 1615 (81), 1570 (69)
IIb	206 (4,46), 220 (4,33)[a], 280 (3,88), 287 (3,85)[a], 339 (3,91)	1738 (78), 1610 (73), 1565 (49), 1522 (58)
IIc	207 (4,48), 289 (4,04), 307 (3,88)[a]	1740 (86), 1602 (80), 1568 (67), 1518 (51)
IId	207 (4,44), 280 (4,22)	1738 (79), 1605 (46), 1568 (45), 1532 (63)
IIe	208 (4,48), 258 (4,16), 281 (4,09)[a]	1735 (88), 1520 (76)
IIf	207 (4,51), 266 (4,22), 280 (4,03)[a], 437 (4,03)	1730 (72), 1610 (65), 1570 (36), 1532 (46)
IIg	206 (4,63), 293 (4,09)	1745 (87), 1728 (92), 1608 (74), 1590 (70), 1555 (57)
IIh	206 (4,66), 293 (4,09)	1742 (92), 1605 (72), 1555 (64), 1508 (57)
IIIa	202 (4,25), 220 (4,15)[a], 283 (4,11), 388 (3,87)	1690 (74), 1660 (85), 1588 (71), 1525 (65)
IIIb	203 (4,36), 222 (4,26)[a], 283 (4,25), 388 (3,92)	1675 (67)[a], 1655 (74), 1582 (58), 1520 (52)
IIIc	203 (4,36), 225 (4,29), 287 (4,30), 388 (3,90)	1690 (73), 1670 (79), 1610 (60), 1590 (58), 1520 (72)
IIId	204 (4,32), 217 (4,25)[a], 287 (4,38), 357 (3,86), 388 (3,83)[a]	1680 (90), 1598 (75), 1585 (82), 1523 (84)
IIIg	204 (4,35), 283 (4,16), 386 (3,83)	1690 (90), 1590 (78), 1572 (68)[a], 1515 (84)
IIIh	204 (4,49), 283 (4,33), 386 (4,00)	1700 (67), 1680 (78), 1592 (56), 1572 (49), 1510 (72)
IVa	205 (4,44), 221 (4,18)[a], 270 (4,07), 385 (3,76)	1682 (66), 1620 (75), 1581 (74), 1568 (74), 1512 (74)
IVg	206 (4,42), 236 (4,05)[a], 375 (3,92)	1700 (52), 1640 (73), 1588 (54), 1572 (50)[a]
Va	204 (4,30), 238 (4,19), 285 (3,91), 339 (3,83)	1676 (88), 1628 (84), 1600 (70), 1575 (66), 1545 (87)
Vb	206 (4,37), 245 (4,23), 281 (3,92), 339 (3,83)	1673 (87), 1620 (84), 1578 (62), 1538 (88), 1518 (82)
Vc	206 (4,41), 253 (4,28), 278 (4,05)[a], 339 (3,86)	1672 (85), 1626 (82), 1608 (74), 1578 (54), 1538 (87), 1515 (85)
Vg	205 (4,46), 235 (4,18), 260 (4,19), 349 (4,07)	1684 (92), 1620 (86), 1596 (82), 1574 (71), 1535 (92)
Vh	206 (4,46), 237 (4,20), 259 (4,19), 349 (4,07)	1678 (66), 1620 (55), 1600 (47), 1574 (42), 1530 (61), 1508 (62)
VIa	204 (4,53), 244 (4,35), 284 (4,08), 301 (4,09)[a], 397 (3,95)	1718 (83), 1698 (88), 1600 (88), 1520 (82)
VIb	204 (4,63), 243 (4,44), 287 (4,44), 397 (4,02)	1722 (55), 1708 (64), 1680 (63), 1602 (65), 1520 (54)

[a]Shoulder.

1,2-Dihydropyridine Derivatives III. A mixture of 0.005 mole of the pyridinium perchlorate and 0.01 mole of $NaBH_4$ in acetonitrile–methanol (10:1) was stirred for 2 h, after which the solvent was evaporated *in vacuo*, and the precipitate was treated with water. The yellow precipitate was recrystallized from ethanol.

Hydrolysis of 1,2-Dihydropyridine Esters. A mixture of 0.003 mole of ester III and 0.84 g (0.015 mole) of KOH was refluxed in 20 ml of ethanol for 6-8 h, after which the solvent was removed, and the residue was treated with 25 ml of hot water. The mixture was filtered, cooled, and acidified with dilute HCl. Recrystallization from acetonitrile gave acids IV or mixtures of the acids and V.

1,2-Dihydropyridine-5-carboxylic Acid Derivatives V. These compounds were obtained by brief heating of the acid at 160°C or by refluxing (for ~1 h) in acetonitrile. The products were crystallized from ethanol.

TABLE 3. PMR Spectra of 1,2-Dihydropyridine Derivatives and Pyridinium Salts

Compound	2-Ha	2-CH3 (d)	6- or 2,6-CH3 (s)	5- or 3,5-OCH2CH3 (t), 3-H (d)	5- or 3,5-OCH2CH3 (q)	5-OCH2CH3 (t)	5-OCH2CH3 (q)	4-Substituent[b]	1-Substituent [1-CH3 (s)]
IIa	—	—	2,77	0,81	4,05	—	—	7,10—7,34; 7,41—7,63 (m,5H)	4,11
IIb	—	—	2,77	0,91	4,06	—	—	7,10 (d, 2H); 7,27 (d, 2H)	4,17
IIc	—	—	2,74	0,91	4,07	—	—	7,15 (s, 4H); 3,75 (s, 3H)	4,08
IId	—	—	2,85	0,87	4,11	—	—	7,11 (d, 2H); 8,50 (d, 2H)	4,21
IIe	—	—	2,80	0,90	4,04	—	—	7,60 (d, 1H); 7,81 (t, 2H); 8,00 (s, 1H); 8,32 (d, 1H)	4,16
IIf	—	—	2,71	0,97	4,06	—	—	6,77 (d, 2H); 7,10 (d, 2H) 2,93 (s, 6H)	4,07
IIg	—	—	2,31	0,83	4,01	—	—	7,71 (s, 5H)	7,17—7,67 (m,5H)
IIh	—	—	2,32	0,84	4,05	—	—	7,58 (s, 5H)	7,20—7,55 (m, 4H), 2,41 (s,3H)
IIIa	4,40	1,19	2,37	0,56	3,48	0,74	3,77	7,14 (s, 5H)	3,14
IIIb	4,42	1,14	2,31	0,55	3,51	0,76	3,77	6,92 (s, 4H); 2,24 (s, 3H)	3,10
IIIc	4,44	1,14	2,32	0,61	3,56	0,80	3,79	6,68 (d, 2H); 6,99 (d, 2H); 3,71 (s,3H)	3,12
IIId	4,50	1,17	2,38	0,62	3,54	0,79	3,77	7,17 (d, 2H), 8,00 (d, 2H)	3,16
IIIg	4,81	1,39	2,15	0,61	3,69	0,74	3,75		7,16 (br s, 10H)
IIIh	4,74	1,37	2,13	0,58	3,55	0,72	3,73	7,10 (s, 5H)	7,01 (s, 4H); 2,28 (s, 3H)
IVa	4,46	1,11	2,31	—	—	0,51	3,42	7,10 (s, 5H)	3,17
IVg	4,77	1,32	2,11	—	—	0,49	3,49	7,32 (s, 5H)	7,17 (s, 5H)
Va	3,90	1,09	2,38	4,96	—	0,52	3,63	7,11 (s, 5H)	3,00
Vb	3,89	1,08	2,37	4,96	—	0,55	3,64	6,99 (s, 4H); 2,23 (s, 3H)	2,99
Vc	3,93	1,08	2,37	4,95	—	0,60	3,67	6,72 (d, 2H); 7,06 (d, 2H); 3,71 (s, 3H)	2,99
Vg	4,25	1,26	2,17	5,16	—	0,59	3,69		7,10 (s, 10H)
Vh	4,24	1,27	2,18	5,15	—	0,59	3,71	7,18 (s, 5H)	7,03 (s, 4H); 2,28 (s, 3H)
VIa	4,58	1,19	2,33	4,97 (s, CH_2), 7,26—7,48; 7,60—7,78 (m, 5H, Ph)		0,54	3,48	7,09 (s, 5H)	3,14
VIb	4,58	1,21	2,35	4,97 (s, CH_2), 7,18—7,53; 7,60—7,82 (m, 5H, Ph)		0,57	3,50	6,96 (s, 4H); 2,22 (s, 3H)	3,17

[a] A quartet for III, IV, and VI, a quintet for V. [b] For III-VI, J_{2H-2CH_3} = 6.6 Hz, for Va-c, J_{2H-3H} = 7.2 Hz, and for Vg,h, J = 6.6 Hz.

Phenacyl esters VI were prepared by the general method in [8].

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