NEW DERIVATIVES OF 4-ARYL-2,6-DIMETHYL-3,5-DIACETYL-1,4- AND 1,2-DIHYDROPYRIDINES

V. K. Lusis, A. Z. Zandersons,
D. Kh. Mutsenietse, and G. Ya. Dubur

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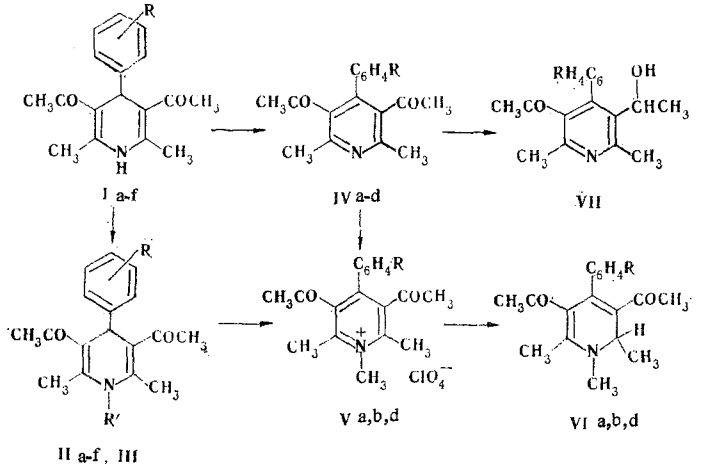
4-Aryl-1,2,6-trimethyl-3,5-diacetyl-1,4-dihydropyridines and the corresponding pyridinium salts, which upon reduction with $NaBH_4$ form 4-aryl-1,2,6-trimethyl-3,5-diacetyl-1,2-dihydropyridines, were synthesized.

Continuing our research on the synthesis of 1,2-dihydropyridine derivatives [1] we set out to develop a method for the preparation of the heretofore unknown 4-aryl-1,2,6-trimethyl-3,5-diacetyl-1,2-dihydropyridines. The synthesis of 1-unsubstituted 3,5-diacetyl derivatives of 1,2-dihydropyridine presents difficulties [2], since a tetrahydropyridine and a pyridine derivative with a reduced acetyl group are formed, in addition to the 1,2-dihydro isomer, in the catalytic hydrogenation of the corresponding pyridines. It should be noted that in the case of the reduction of 4-phenyl-2,6-dimethyl-3,5-diacetylpyridine (IVa) with sodium borohydride we also obtained methyl[3-(4-phenyl-2,6-dimethyl-5-acetylpyridyl)]carbinol (VII). For the synthesis of 3,5-diacetyl-1,2-dihydropyridine derivatives we therefore used the scheme that we previously developed [1] for the preparation of ethyl 1,2-dihydropyridine-3,5-dicarboxylates.



I a-f

IV a-d

VII

II a-f, III

V a,b,d

VI a,b,d

I—VI a R=H; I, II, IV—VI b R=4-CH_3; I, II, IV c R=4-OCH_3; I, II, IV—VI d R=4-Br; I, II e R=4-NO_2; I, II f R=2,3-$(OCH_3)_2$; II R′=CH_3; III R=C_2H_5

Since only a small number of 4-aryl derivatives of 2,6-dimethyl-3,5-diacetyl-1,4-dihydropyridines are known [3-6], we synthesized some new derivatives, viz., Ib-d,f, by the reaction of acetylacetone, an aromatic aldehyde, and ammonia and obtained Ie by condensation of 3-(4-nitrobenzylidene)pentane-2,4-dione and 4-aminopent-3-en-4-one in higher yield than in the case of the method in [5]. We obtained 1-substituted 4-aryl derivatives of 2,6-dimethyl-3,5-diacetyl-1,4-dihydropyridine (II, III) for the first time by the action of alkyl halides on 1,4-dihydropyridine anions; in contrast to 1,4-dihydropyridine-3,5-dicarboxylic acid esters [7], in which the acidic properties are expressed very weakly and sodium hydride is necessary for the formation of the anion, a solution of NaOH in acetone

Institute of Organic Synthesis, Academy of Sciences of the Latvian SSR, Riga 226006.
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TABLE 1. Characteristics of the Synthesized Substances

Compound	mp, °C	Found, %			Empirical formula	Calc., %			Yield, %
		C	H	N		C	H	N	
Ib	172—173	75,8	7,7	4,8	$C_{18}H_{21}NO_2$	76,2	7,5	4,9	73
Ic	176—177	72,6	7,2	4,2	$C_{18}H_{21}NO_3$	72,2	7,1	4,7	67
Id	190—192	58,1	5,4	3,7	$C_{17}H_{18}BrNO_2$	58,6	5,2	4,0	73
Ie	202—203[a]	65,1	6,0	8,3	$C_{17}H_{18}N_2O_4$	65,1	5,8	8,9	59
If	168—170	69,0	7,0	4,6	$C_{19}H_{23}NO_4$	69,2	7,0	4,2	63
IIa	102—103	76,1	7,5	5,0	$C_{18}H_{21}NO_2$	76,3	7,5	4,9	77[b]
IIb	139—140	76,7	8,0	4,4	$C_{19}H_{23}NO_2$	76,7	7,8	4,7	61[b]
IIc	89—91	73,1	7,6	4,2	$C_{19}H_{23}NO_3$	72,8	7,4	4,5	62
IId	104—105	60,1	5,7	3,3	$C_{18}H_{20}BrNO_2$	59,7	5,6	3,8	41
IIe	108—110	65,5	6,1	8,6	$C_{18}H_{20}N_2O_4$	65,8	6,1	8,6	55
IIf	100—102	69,5	7,3	3,8	$C_{20}H_{25}NO_4$	69,9	7,3	4,0	61
III	70—71	76,3	7,8	4,8	$C_{19}H_{23}NO_2$	76,8	7,8	4,7	45
IVb	170—172	76,3	6,5	5,1	$C_{18}H_{19}NO_2$	76,7	6,8	5,0	95
IVc	163—165	72,5	6,0	5,0	$C_{18}H_{19}NO_3$	72,7	6,4	4,7	73
IVd	210—212	59,5	4,2	4,5	$C_{17}H_{16}BrNO_2$	59,0	4,7	4,1	93
Va	195—197	56,2	5,1	4,0	$C_{18}H_{20}ClNO_6$	56,6	5,3	3,7	56
Vb	190—191	57,4	5,2	3,4	$C_{19}H_{22}ClNO_6$	57,6	5,6	3,5	62
Vd	175—177	47,0	4,0	2,8	$C_{18}H_{19}BrClNO_6$	46,9	4,2	3,0	64
VIa	130—132	76,4	7,6	5,2	$C_{18}H_{21}NO_2$	76,3	7,5	4,9	50
VIb	147—148	76,6	7,3	4,9	$C_{19}H_{23}NO_2$	76,7	7,8	4,7	52
VId	172—174	59,4	5,6	3,4	$C_{18}H_{20}BrNO_2$	59,7	5,6	3,8	56
VII	98—100	75,6	7,4	5,0	$C_{17}H_{19}NO_2$	75,8	7,1	5,2	45

[a]According to the data in [5], this compound had mp 202-203°C and was obtained in 28% yield. [b]The yields by method A (see the experimental section) were 37 and 40%, respectively; the remaining compounds were prepared by method B.

can be used for the formation of the anions. However, the use of NaH and a polar aprotic solvent promotes the production of 4-aryl-1,2,6-trimethyl-3,5-diacetyl-1,4-dihydropyridines (II) and particularly 1-ethyl derivative III in higher yields. In contrast to the synthesis of 3,5-diethoxycarbonyl-4-aryl-1,2,6-trimethylpyridinium salts [1], the oxidation of 1-methyl derivatives II with hydrogen peroxide in the presence of perchloric acid proved to be unsuitable for the preparation of 3,5-diacetylpyridinium salts V. It is possible that the low yields (20-37%) of salts V in their synthesis via the indicated scheme are due to reactions that lead to oxidation of the substituents in the pyridine ring [8]. A preparative method for the synthesis of 4-aryl-1,2,6-trimethyl-3,5-diacetylpyridinium salts is methylation of the corresponding pyridines IV with dimethyl sulfate with subsequent treatment of the resulting methylsulfates with $NaClO_4$, since pyridinium perchlorates V are readily crystallized substances. Reduction of salts V with sodium borohydrides leads to the formation of previously unknown 3,5-diacetyl-1,2,6-trimethyl-4-phenyl-1,2-dihydropyridines (VI).

The structures of the synthesized compounds were confirmed by the PMR, UV, and IR spectra. The same regularities as in the spectra of a number of their 3,5-diethoxycarbonyl analogs [7] are observed in the UV spectra of the synthesized 1,4-dihydropyridines II and III. The hypsochromic shifts of the long-wave absorption maxima in the case of If and IIf are evidently associated with the steric effect of the ortho substituent of the phenyl ring. Two characteristic absorption bands at 336 and 418 nm are observed in the UV spectra of 1,2-dihydropyridines VI. Thus the long-wave absorption band of 1,2-dihydropyridines VI is shifted bathochromically 33 nm as compared with the corresponding maximum of their 1,4-dihydro analogs I (absorption at 385 nm). The same shift is also observed on passing from the 1,4- to the 1,2-dihydropyridines in series of 3,5-diethoxycarbonyl derivatives (maxima at 355 and 388 nm, respectively [1]). The 3,5-diacetyl derivatives of 1,2-dihydropyridines (like the 1,4-dihydropyridine series) absorb at higher wavelengths (a 30-nm bathochromic shift) than their corresponding 3,5-diethoxycarbonyl analogs. According to the data in [8], this is also peculiar to 2,6-unsubstituted 1,4-dihydropyridines.

The unusually strong-field position of the signals of the methyl protons of the 3,5-$COCH_3$ groups in the PMR spectra of 1,2-dihydropyridines VI should be noted. This is probably associated with the steric effect of the substituents in the 2,4, and 6 positions, since the signals of the acetyl groups of 1-methyl-3,5-diacetyl-1,2-dihydropyridine are found in the normal position (at 2.20 and 2.34 ppm, respectively [2]).

TABLE 2. PMR, UV, and IR Spectra of I-V

Compound	PMR spectrum, [a] δ, ppm					UV spectrum, λ_{max}, nm (log ε)	IR spectrum, ν_{max}, cm^{-1} (absorption, %), at 1500-1800 and 3000-3600 cm^{-1}
	2,6-CH_3 (s, 6H)	3,5-COC**H**$_3$ (s, 6H)	4-H (s, 1H)	N—R R=H (s, 1H), R=CH_3 (s, 3H)	4-Ar		
Ia	2,20	2,35	5,05	6,29	7,20 (s, 5H)[b]	205 (4,23), 258 (4,13), 267 (4,05), 387 (3,85)[c]	1670 (84), 1630 (54), 1602 (90), 3320 (88), 3220 (56), 3240 (58), 3180 (51)
Ib	2,22 (s, 15H)		5,00	6,73	7,01 (s, 4H)	204 (4,24), 217 (4,11), 257 (4,15), 265 (4,12)[c], 385 (3,90)	1672 (92), 1630 (67), 1600 (96), 1510 (81), 3320 (95), 3242 (81), 3215 (80), 3180 (78)
Ic	2,20	2,26	4,98	5,80	6,73 (d, 2H), 7,12 (d, 2H); 3,70 (s, 3H)	204 (4,32), 226 (4,19), 258 (4,11), 269 (4,06)[c], 385 (3,91)	1670 (89), 1648 (91), 1610 (82), 1585 (66), 1570 (73), 1510 (89), 3260 (78), 3220 (79), 3190 (77), 3160 (76), 3120 (77)
Id	2,15	2,24	5,01	8,30	7,03 (d, 2H); 7,26 (d, 2H)	204 (4,25), 219 (4,16)[c], 255 (4,22), 384 (3,85)	1655 (85), 1630 (89), 1580 (77), 3270 (79), 3185 (78)
Ie	2,18	2,28	5,24	8,15	7,91 (d, 2H); 8,04 (d, 2H)	205 (4,25), 217 (4,11)[c], 257 (4,34), 387 (3,76)[d]	1632 (82), 1618 (95), 1605 (96), 1515 (92), 3330 (93), 3230 (76)
If	2,18	2,23	5,29	8,15	3,73 (s, 3H); 3,83 (s, 3H) 6,10—6,80 (m, 3H)	206 (4,38), 257 (3,95), 376 (3,70)	1670 (78), 1585 (88), 3320 (86)
IIa	2,28	2,34	5,02	3,10	7,11 (s, 5H)	205 (4,19), 264 (4,11), 282 (3,90)[c], 376 (3,87)	1661 (77), 1645 (86), 1610 (70), 1598 (72), 1540 (83)
IIb	2,30	2,35	5,12	3,09	6,94 (s, 4H), 2,21 (s, 3H)	204 (4,24), 217 (4,14)[c], 263 (4,10), 274 (4,05)[c], 375 (3,88)	1668 (60), 1648 (62), 1610 (58), 1530 (62), 1510 (59)
IIc	2,28	2,35	4,94	3,10	6,74 (d, 2H); 6,98 (d, 2H); 3,68 (s, 3H)	204 (4,17), 225 (4,07), 263 (3,94), 277 (3,92)[c], 372 (3,73)	1660 (56), 1640 (64), 1603 (56), 1530 (61), 1510 (65)

TABLE 2 (continued)

Compound	PMR spectrum, [a] δ, ppm: 2,6-CH_3 (s, 6H)	3,5-$COCH_3$ (s, 6H)	4-H (s, 1H)	N—R R=H (s, 1H), R=CH_3 (s, 3H)	4-Ar	UV spectrum, λ_{max}, nm (log ε)	IR spectrum, ν_{max}, cm^{-1} (absorption, %), at 1500-1800 and 3000-3600 cm^{-1}
II d	2,28	2,35	4,99	3,10	6,92 (d, 2H); 7,29 (d, 2H)	205 (4,22), 267 (4,15), 374 (3,85)	1655 (85), 1645 (92), 1598 (77), 1520 (90)
II e	2,29	2,36	5,10	3,12	7,22 (d, 2H); 8,00 (d, 2H)	206 (4,23), 217 (4,09)[c], 262 (4,31), 277 (4,23)[c], 375 (3,75)	1630 (78)[c], 1620 (85)[c], 1547 (7 1513 (90)
II f	2,26 (s, 6H)		5,14	3,06	3,20 (s, 3H); 3,21 (s, 3H) 6,15—6,88 (m, 3H)	206 (4,40), 261 (3,88), 279 (3,73)[c], 356 (3,78)	1710 (47), 1660 (89), 1640 (96), 161[illegible] (83), 1585 (76), 1540 (96)
III	2,28	2,35	4,94	3,60 (q, 2H), 0,82 (t, 3H)	7,10 (s, 5H)	204 (4,37), 221 (4,22), 262 (4,21), 374 (3,88)	1650 (83), 1605 (91)[c], 1598 (94), 1520 (83)
IV a	1,84	2,33	—	—	7,00—7,49 (m, 5H)	206 (4,37), 226 (4,46)[c], 240 (4,18)[c], 280 (3,86)[c]	1690 (97), 1600 (47), 1563 (55), 1543 (95)
IV b	1,83	2,43	—	—	7,09 (br s, 4H)	207 (4,36), 241 (4,18)[c], 265 (4,01)[c]	1698 (92), 1610 (41), 1543 (83), 1503 (67)
IVc	1,83	2,43	—	—	3,78 (s, 3H); 6,78 (d, 2H); 7,10 (d, 2H)	206 (4,40), 246 (4,06), 277 (4,11)	1693 (90), 1607 (64), 1573 (48), 1547 (72), 1513 (70)
IVd	1,88	2,45	—	—	7,04 (d, 2H); 7,51 (d, 2H)	208 (4,45), 228 (4,28)[c], 244 (4,25)[c]	1692 (94), 1590 (36), 1563 (44), 1543 (67)
V a	2,00	2,62	—	4,05	7,00—7,21 (m, 2H); 7,41—7,54 (m, 3H)	208 (4,41), 288 (4,08),	1700 (79), 1598 (64), 1543 (58)
V b	2,02	2,66	—	4,08	3,32 (s, 3H); 7,06 (d, 2H); 7,34 (d, 2H)	207 (4,40), 247 (4,06), 275 (4,11)	1710 (88), 1600 (79), 1553 (72), 1520 (56)
V c	2,13	2,66	—	4,16	7,10 (d, 2H); 7,54 (d, 2H)	209 (4,46), 290 (4,13)	1703 (79), 1600 (62), 1543 (49)

[a]In $CdCl_3$ in the case of I-III, and in d_6-DMSO in the case of IV-V. [b]According to [10], 2.32 ($COCH_3$), 2.35 (2,6-CH_3), and 5.33 ppm (4-H) in $CDCl_3$. [c]Shoulder. [d]According to [5], 385 nm (6750).

TABLE 3. Spectra of 4-Aryl-1,2,6-trimethyl-3,5-diacetyl-1,2-dihydropyridines

Compound	PMR spectrum, δ, ppm (in $CDCl_3$): 1-CH_3 (s, 3H)	2-H (q, 1H)	2-CH_3 (d, 3H)	3-$COCH_3$ (s, 3H)	5-$COCH_3$ (s, 3H)	6-CH_3 (s, 3H)	Ar	UV spectrum, λ_{max}, nm (log ε)	IR spectrum, ν_{max}, cm^{-1} (absorption, %), at 1500-1800 cm^{-1}
VIa	3,17	4,64	1,12	1,39	1,43	2,59	7,12—7,39 (m 5H)	204 (4,23), 238 (4,04)[a], 269 (4,07), 283 (4,03)[a], 336 (4,07), 419 (3,95)	1647 (81), 1622 (93), 1577 (73), 1553 (87), 1503 (73)
VIb	3,16	4,62	1,11	1,41	1,47	2,32	7,08 (br s, 4H); 2,37 (s, 3H)	204 (4,32), 234 (4,09), 291 (4,09), 335 (4,09), 417 (3,95)	1633 (97), 1613 (91)[a], 1603 (94), 1573 (94), 1553 (94), 1513 (92), 1500 (86)
VId	3,16	4,62	1,11	1,43	1,48	2,37	7,08 (d, 2H); 7,46 (d, 2H)	204 (4,36), 224 (4,17)[a], 277 (4,16), 337 (4,08), 419 (3,95)	1647 (73), 1607 (80), 1583 (75), 1567 (84), 1553 (80), 1507 (76)

[a]Shoulder.

EXPERIMENTAL

The IR spectra of mineral oil suspensions of the compounds were obtained with PE 580 B and Specord 75-IR spectrometers. The UV spectra of solutions in ethanol were recorded with a Specord UV-vis spectrophotometer. The PMR spectra were obtained with a WH-90 spectrometer with hexamethyldisiloxane as the internal standard. The principal characteristics of the synthesized substances are given in Tables 1-3. Except when otherwise indicated, ethanol was used to crystallize the compounds.

4-Aryl-2,6-dimethyl-3,5-diacetyl-1,4-dihydropyridines Ia-d,f were synthesized by the method in [5], except for Ie, for which the method in [4] gave a higher yield.

Alkylation of 4-Aryl-2,6-dimethyl-3,5-diacetyl-1,4-dihydropyridines Ia-f. A) A 0.01-mole sample of dihydropyridine I was dissolved in acetone, 15 mmole of ground NaOH was added, and the mixture was refluxed for 10 min. It was then cooled and treated with 25 mmole of CH_3I, and the mixture was allowed to stand for 2 h. The NaI was separated, the solvent was evaporated, and the residue was crystallized from 80% ethanol.

B) Alkylation in hexametapol was carried out by the method in [7].

4-Aryl-2,6-dimethyl-3,5-diacetylpyridines IV. These compounds were obtained by oxidation of I with sodium nitrite in glacial acetic acid at 60-70°C.

4-Aryl-1,2,6-trimethyl-3,5-diacetylpyridinium Perchlorates Va,b,d. A mixture of 0.02 mole of IV and 0.06 mole of freshly distilled $(CH_3)SO_4$ was heated on a water bath for 6 h, after which the mixture was cooled, washed with ether, and dissolved in 100 ml of water. A saturated solution of $NaClO_4$ was then added until the formation of a colorless precipitate ceased, and the precipitate was then removed by filtration and crystallized.

4-Aryl-1,2,6-trimethyl-3,5-diacetyl-1,2-dihydropyridines VIa,b,d. A 0.15-g (4 mmole) sample of $NaBH_4$ was added to 3 mmole of V and 1.5 g of Na_2CO_3 in 100 ml of ethanol and 10 ml of water, and the mixture was stirred for 20 min and filtered. The filtrate was extracted with ether (two 50-ml portions), the ether extracts were dried and evaporated, and the residue was crystallized from methanol.

Reduction of 4-Phenyl-2,6-dimethyl-3,5-diacetylpyridine (IVa). A 0.8-g (0.02 mole) sample of $NaBH_4$ was added to 1.3 g (5 mmole) of IVa in 40 ml of acetonitrile and 4 ml of methanol, and the mixture was allowed to stand overnight. Dilute (1:1) acetic acid was added to precipitate colorless VII. PMR spectrum ($CDCl_3$), δ: 1.39 (d, 3H, $CHCH_3$), 1.81 (s, 3H, 2-CH_3), 2.36 (s, 3H, 6-CH_3), 2.71 (s, 3H, $COCH_3$), 4.83 (q, 1H, $CHCH_3$), 6.92-7.10 (m, 2H, 4-Ar), and 7.24-7.40 ppm (m, 3H, 4-Ar). IR spectrum: 1682 (CO) and 3280 cm^{-1} (OH).

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