1-ARYL- AND 1-BENZYL-3,5-DIETHOXYCARBONYL-1,4-DIHYDROPYRIDINES

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The possibility has been studied of using anilines in the Hantzsch synthesis. It has been shown that, with the exception of those containing strong electron-accepting substituents, they take part in this reaction with the formation of 1-aryl-1,4-dihydropyridines. The reaction largely depends on the nature of the substituents in the aniline and in the benzaldehyde and is promoted by electron-accepting substituents in the aldehyde and electron-donating substituents in the amine. The mechanism of the reaction is discussed. A number of 1-benzyl-1,4-dihydropyridines have been synthesized. The UV, IR, and PMR spectra and the electro-oxidation of the compounds obtained have been studied.

In spite of a broad investigation of the Hantzsch synthesis of dihydropyridines [1], the possibilities and limits to the use of primary amines in this reaction in place of ammonia have not been fully discovered. The method using aliphatic amines does not usually give good results [1] and sometimes a modified method using alkylamine salts and performing the reaction in the presence of pyridine is more suitable [2], but the most promising method for obtaining 1-alkyl derivatives is the N-alkylation of 1,4-dihydropyridines (1,4-DHPs) [3, 4]. Although the first two 1-aryl-3,5-dialkoxycarbonyl-1,4-DHPs were synthesized by the use of arylamines as early as 1896 [5], hitherto only isolated compounds of this series have been obtained [6-8].

We have used Bossert's method [2] to obtain a series of 1-benzyl-3,5-diethoxycarbonyl-1,4-DHPs (I). Compounds (I) were obtained in higher yields by the N-benzylation using Bossert's method of 1,4-DHPs unsubstituted in position 1 [4].

A systematic study of the possibility of using arylamines in the Hantzsch synthesis that we have performed has shown that anilines, with the exception of those containing strong electron-accepting substituents, take part in this reaction with the formation of esters of 1-aryl-1,4-DHP-3,5-dicarboxylic acids (II).

$$R^2-CHO$$

I R = CH₂C₆H₅; II R = C₆H₄R'
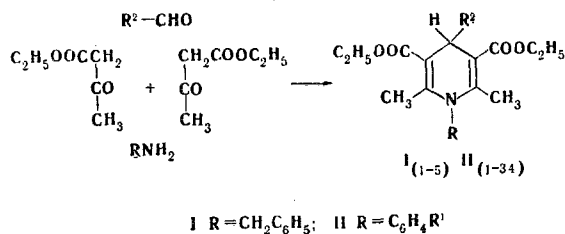
The formation of 1-aryl-1,4-DHPs (II) depends decisively on the nature of the substituents in the aniline and benzaldehyde molecules. The reaction is promoted by electron-accepting substituents in the aldehyde component and by electron-donating substituents in the amine component, and in such a case the yields reach 90% (Table 2).

If the molecule of the aniline contains electron-accepting substituents (Br, Cl), a 1,4-DHP is formed only when the benzaldehyde molecule contains electron-accepting groups (NO₂, Br). If, however, R^2 is hydrogen or an electron-donating group (p-OCH₃), no 1,4-DHPs are obtained or they are obtained in very low yield, but other products are formed in small amounts — 4-anilino-3-ethoxycarbonyl-1,2,6-triphenyl-1,2,5,6-tetrahydropyridines (III) and anils of 3-aryl-2,4-diethoxycarbonyl-5-hydroxy-5-methylcyclohexan-1-ones (IV).

TABLE 1. 1-Benzyl-3,5-diethoxycarbonyl-1,4-DHPs (1)

| Compound	R²	Reaction time, h	mp, °C	UV spectrum, λ_{max}, nm (log ϵ)	IR spectrum, 1700–1550 cm⁻¹ (absorption, %)	Found, %			Empirical formula	Calculated, %			Yield, %
						C	H	N		C	H	N	
I-1	CH_3	1	108—109	207 (4,19); 234 (4,21); 275ᵃ (4,06); 348 (3,79)	1695 (83); 1631 (72); 1574 (68)	70,6	7,7	4,2	$C_{21}H_{27}NO_4$	70,6	7,6	3,9	13
I-2	C_6H_5	1,5	157—158	207 (4,38); 246 (4,29); 345 (3,79)	1697 (82); 1674 (81); 1639 (73); 1576 (79)	74,4	7,0	3,5	$C_{26}H_{29}NO_4$	74,4	7,0	3,3	13; 42ᵇ
I-3	$4\text{-}C_6H_4Br$	4	165—167	202 (4,33); 245 (4,11); 349 (3,56)	1682 (81); 1640 (54); 1580 (70)	62,5	5,7	2,8	$C_{26}H_{28}BrNO_4$ᶜ	62,7	5,7	2,8	57
I-4	$4\text{-}C_6H_4N(CH_3)_2$	4	163—165	205 (4,36); 225 (4,30); 248ᵃ (4,20); 348 (3,81)	1684 (73); 1636 (48); 1580 (61)	72,3	7,6	6,0	$C_{28}H_{34}N_2O_4$	72,7	7,4	6,1	11
I-5	$4\text{-}C_6H_4OCH_3$	4	134—135	206 (4,42); 254 (4,30); 350 (3,76)	1680 (75); 1633 (59); 1576 (64)	71,8	7,1	3,2	$C_{27}H_{31}NO_5$	72,1	7,0	3,1	9; 47ᵇ

ᵃShoulder. ᵇAlkylation yield by Bossert's method [4]. ᶜFound: Hal 15.7%. Calculated: Hal 16.0%.

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When strong electron-donating substituents are present both in the benzaldehyde [p-OH, p-N(CH₃)₂] and in the aniline (p-OCH₃, p-OC₂H₅), the only products capable of being isolated in the Hantzsch reaction are the corresponding benzylideneanilines.

III, IV, VI a $R^1 = p\text{-Br}$, $R^2 = H$; b $R^1 = p\text{-Cl}$, $R^2 = H$
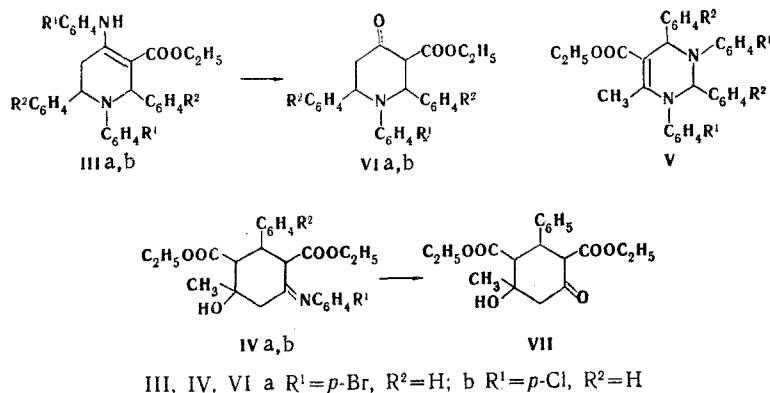
A mechanism that is generally accepted for the formation of 1,4-DHPs in the Hantzsch synthesis is one in which an α,β-unsaturated ketone and an enamine are first formed, followed by their addition to one another, cyclization to tetrahydropyridines, and the splitting out of water [1]. On the basis of our results, it appeared likely that the formation of l-aryl-1,4-DHPs (II) can also take place by another route. Benzylideneanilines are formed very easily and under the conditions of the Hantzsch reaction they frequently precipitate. It is known that they readily add compounds with active methylene groups [9], including acetoacetic ester [10, 11]. Consequently, it is possible that the nucleophilic addition of one molecule of acetoacetic ester to the benzylideneaniline first takes place with the formation of an ester of α-acetyl-β-anilino-β-phenylpropionic acid (VIII).

VIII a $R^1 = R^2 = H$; b $R^1 = H$, $R^2 = p\text{-Br}$
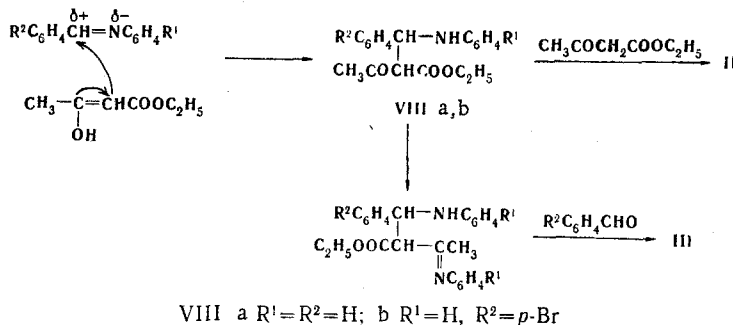
The addition product (VIII) may then react in two ways — either with a second molecule of acetoacetic ester to form a 1-aryl-1,4-DHP (II) or with aniline and benzaldehyde, as a result of which a tetrahydropyridine (III) is obtained. The possibility of the formation of compounds (VIII) and their subsequent transformation must depend to a large extent on the nature of the substituents in the benzylideneaniline molecule. Thus, when electron-donating substituents are present both in the aldehyde and in the amine components, the positive charge on the carbon atom of the benzylideneaniline is greatly diminished and the addition of acetoacetic ester does not take place, so that no 1,4-DHPs are formed.

Electron-accepting substituents in the benzylidene radical increase the positive charge on the carbon atom and promote the addition of acetoacetic ester. It is known that β-amino-β-phenyl ketones can split out amines; this reaction is also promoted by electron-accepting substituents in the β-phenyl radical [9]. It is possible that the splitting out of an amine from a β-amino ketone (VIII) is the following stage of the reaction and then the addition of a second molecule of acetoacetic ester and the closure of the 1,4-DHP ring by the amine takes place. If the aniline contains electron-accepting substituents and the aldehyde contains electron-donating substituents or hydrogen, the benzylideneaniline and the β-amino ketone (VIII) have a low reactivity and the addition of acetoacetic ester and the splitting out of amines are impeded. To a small degree, obviously, the reaction of the β-amino ketone (VIII) with the benzaldehyde and the aniline takes place with the formation of the tetrahydropyridine (III).

TABLE 2. 1-Aryl-3,5-diethoxycarbonyl-1,4-DHPs (II, $R^2 = C_6H_4R^3$)

Compound	R^1	R^3	Reaction time, h	mp, °C	UV spectrum λ_{max}, nm (log ε)
1	2	3	4	5	6
II-1	H	H	10	154—157[a]	206 (4,34); 242 (4,33); 349 (3,79)
II-2	4-CH₃	H	7	128—131[b]	206 (4,33); 243 (4,32); 348 (3,75)
II-3	H	4-NO₂	6	152—153	204 (4,30); 239 (4,18); 277 (4,02); 360[c] (3,60)
II-4	H	3-NO₂	10	144—145	204 (4,27); 248 (4,24); 347 (3,46)
II-5	H	2-NO₂	10	176—177	207 (4,35); 241 (4,28); 294 (4,05); 332—364 (3,72)
II-6	H	4-Br	6	132—133	206 (4,34); 242 (4,37); 352 (3,76)
II-7	H	4-N(CH₃)₂	10	163—165	205 (4,56); 248 (4,43); 347 (3,88)
II-8	4-OCH₃	H	8	147—149	203 (4,35); 243 (4,26); 351 (3,64)
II-9	4-OCH₃	4-NO₂	8	134—136	205 (4,44); 264 (4,22); 238[c] (4,37); 358[c] (3,48)
II-10	4-OCH₃	3-NO₂	6	134—135	203 (4,42); 242 (4,43); 350 (3,72)
II-11	4-OCH₃	2-NO₂	6	151—152	203 (4,59); 229 (4,46); 290[c] (4,11); 324—372 (3,79)
II-12	4-OCH₃	4-Br	7	125—126	204 (4,52); 244 (4,44); 350 (3,97)
II-13	4-OCH₃	4-OCH₃	6	110—112	202 (4,68); 226 (4,48); 252[c] (4,33); 347 (4,06)
II-14	4-OC₂H₅	H	8	112—113	204 (4,58); 244 (4,52); 352 (3,92);
II-15	4-OC₂H₅	4-NO₂	5,5	170—172	202 (4,49); 236 (4,38); 268[c] (4,20); 361 (3,48)
II-16	4-OC₂H₅	3-NO₂	6	124—126	202 (4,53); 241 (4,53); 350 (3,79)
II-17	4-OC₂H₅	2-NO₂	6	140—141	202 (4,64); 234 (4,52); 291[c] (4,12); 329—365 (3,81)
II-18	4-OC₂H₅	4-Br	7	166—168	204 (4,44); 246 (4,35); 354 (3,67)
II-19	4-OC₂H₅	4-OCH₃	12	124—125	202 (4,42); 228 (4,28); 257[c] (4,13); 348 (3,86)
II-20	3-OCH₃	4-NO₂	6	114—115	202 (4,55); 222 (4,40); 235[c] (4,39); 279 (4,25); 356[c] (3,88)
II-21	3-OCH₃	3-NO₂	10	137—138	205 (4,27); 223 [c](4,18); 242 (4,22); 269 [c](3,92); 354 (3,64)
II-22	3-Cl	4-NO₂	8	182—183	207 (4,38); 239 (4,30); 284 (4,18); 366[c] (3,56)
II-23	3-Cl	4-Br	8	166—167	202 (4,58); 215[c] (4,46); 241 (4,43); 350 (3,72)
II-24	3-Cl	4-OCH₃	8	150—153	202 (4,59); 221 (4,46); 276[c] (3,95); 348 (3,75)
II-25	4-Br	4-NO₂	9	193—195	204 (4,64); 240 (4,58); 282 (4,33); 360[c] (3,60)
II-26	4-Br	3-NO₂	10	170—171	205 (4,38); 241 (4,39); 350 (3,68)
II-27	4-Br	4-Br	10	178—179	203 (4,63); 240 (4,61); 273[c] (4,18); 342 (3,86)
II-28	4-Br	4-OCH₃	10	144—145	202 (4,52); 227 (4,46); 279[c] (4,02); 349 (3,81)
II-29	4-N(CH₃)₂	H	3	143—144	203 (4,60); 241[c] (4,34); 268 (4,62); 352 (3,90)
II-30	4-N(CH₃)₂	4-NO₂[d]	3	186—189	203 (4,46); 272 (4,50); 452 (3,67)
II-31	4-N(CH₃)₂	3-NO₂[e]	3	134—136	203 (4,54); 240[c] (4,41); 268 (4,60); 365 (3,90)
II-32	4-N(CH₃)₂	2-NO₂	3	151—152	206 (4,40); 268 (4,40); 317[c] (3,94); 370[c] (3,58)
II-33	4-N(CH₃)₂	4-Br	3	145—146	203 (4,66); 268 (4,62); 382 (4,16);
II-34	4-N(CH₃)₂	4-Cl	3	138—139	204 (4,66); 268 (4,68); 375 (4,15)

[a]According to the literature [5], mp 150-160°C. [b]According to the
[e]Orange substance.

IR spectrum, 1700-1550 cm⁻¹ (absorption, %)	Found, %				Empirical formula	Calculated, %				Yield, %
	C	H	N	Hal		C	H	N	Hal	
7	8	9	10	11	12	13	14	15	16	17
1685 (71); 1633 (54); 1574 (61)										13
1684 (66); 1634 (49); 1578 (52)										16
1698 (76); 1680 (76); 1645 (46); 1589 (67)	66,1	5,6	6,5	—	$C_{25}H_{26}N_2O_6$	66,7	5,8	6,2	—	40
1698 (91); 1642 (66); 1578 (70)	66,1	5,8	6,2	—	$C_{25}H_{26}N_2O_6$	66,7	5,8	6,2	—	78
1695 (74); 1665 (33); 1580 (46)	66,9	5,9	6,0	—	$C_{25}H_{26}N_2O_6$	66,7	5,8	6,2	—	46
1697 (65); 1644 (48); 1585 (52)	62,6	5,6	2,8	16,1	$C_{25}H_{26}BrNO_4$	62,0	5,4	2,9	16,5	40
1690 (76); 1639 (57); 1615 (67); 1586 (70)	72,3	7,2	6,2	—	$C_{27}H_{32}N_2O_4$	72,2	7,3	6,1	—	47
1693 (75); 1659 (36); 1589 (84)	72,1	6,8	3,1	—	$C_{26}H_{29}NO_5$	71,7	6,7	3,2	—	18
1698 (74); 1645 (40); 1610 (23); 1580 (52)	65,1	5,8	5,6	—	$C_{26}H_{28}N_2O_7$	65,0	5,9	5,8	—	70
1700 (66); 1648 (42); 1584 (56)	65,1	5,9	5,8	—	$C_{26}H_{28}N_2O_7$	65,0	5,9	5,8	—	81
1698 (76); 1640 (40); 1610 (32); 1575 (50)	64,9	6,1	5,8	—	$C_{26}H_{28}N_2O_7$	65,0	5,9	5,8	—	49
1697 (59); 1642 (30); 1585 (41)	60,4	5,5	2,9	15,8	$C_{26}H_{28}BrNO_5$	60,7	5,5	2,7	15,5	47
1690 (63); 1644 (39); 1610 (38); 1588 (55)	69,7	6,7	3,6	—	$C_{27}H_{31}NO_6$	69,7	6,7	3,0	—	30
1696 (69); 1655 (36); 1588 (44)	71,7	6,9	2,9	—	$C_{27}H_{31}NO_5$	72,1	6,9	3,1	—	32
1700 (73); 1659 (56); 1608 (39); 1589 (58)	65,5	6,1	5,5	—	$C_{27}H_{30}N_2O_7$	65,6	6,1	5,6	—	81
1698 (78); 1646 (36); 1586 (45)	65,3	6,2	5,7	—	$C_{27}H_{30}N_2O_7$	65,6	6,1	5,7	—	92
1699 (76); 1651 (50); 1610 (40); 1586 (45)	65,2	6,0	5,5	—	$C_{27}H_{30}N_2O_7$	65,6	6,1	5,7	—	45
1699 (64); 1665 (36); 1590 (38)	61,4	5,7	2,6	15,6	$C_{27}H_{30}BrNO_5$	61,4	5,7	2,7	15,1	35
1696 (68); 1646 (36); 1610 (41); 1586 (45)	70,4	6,5	3,0	—	$C_{28}H_{33}NO_6$	70,1	6,9	2,9	—	38
1699 (86); 1642 (51); 1607 (65); 1583 (63)	65,2	6,0	6,3	—	$C_{26}H_{28}N_2O_7$	65,0	5,8	5,8	—	29
1697 (84); 1642 (55); 1605 (68); 1582 (67)	65,0	5,9	6,3	—	$C_{26}H_{28}N_2O_7$	65,0	5,8	5,8	—	90
1693 (77); 1645 (40); 1585 (58)	62,1	5,0	5,8	7,8	$C_{25}H_{25}ClN_2O_6$	62,0	5,2	5,8	7,3	33
1698 (73); 1648 (43); 1585 (66)	57,8	4,8	2,8	—	$C_{25}H_{25}BrClNO_4$	57,9	4,9	2,7	—	4
1690 (94); 1643 (65); 1605 (53)	66,9	5,9	3,1	7,8	$C_{26}H_{28}ClNO_5$	66,4	6,0	3,0	7,5	8
1691 (78); 1645 (45); 1582 (57)	57,1	4,3	5,2	15,8	$C_{25}H_{25}BrN_2O_6$	56,7	4,7	5,3	15,1	31
1690 (73); 1645 (44); 1585 (42)	57,2	4,7	5,0	—	$C_{25}H_{25}BrN_2O_6$	56,7	4,7	5,3	—	44
1698 (78); 1645 (54); 1582 (57)	53,4	4,6	2,3	—	$C_{25}H_{25}Br_2NO_4$	53,4	4,7	2,5	—	39
1690 (90); 1645 (46); 1588 (63)	60,6	5,5	3,1	16,2	$C_{26}H_{28}BrNO_5$	60,7	5,5	2,9	15,5	4
1685 (79); 1638 (75); 1612 (53); 1580 (74); 1530 (73)	72,1	7,2	6,0	—	$C_{27}H_{32}N_2O_4$	72,2	7,2	6,2	—	58
1698 (81); 1649 (69); 1610 (68); 1580 (75); 1530 (81)	65,5	6,1	8,4	—	$C_{27}H_{31}N_3O_6$	65,7	6,3	8,5	—	89
1695 (76); 1640 (71); 1615ᶜ (54); 1580 (70); 1532 (83)	65,7	6,4	8,6	—	$C_{27}H_{31}N_3O_6$	65,7	6,3	8,5	—	77
1700 (66); 1650 (48); 1620ᶜ (43); 1580 (46); 1535 (70)	65,4	6,5	8,9	—	$C_{27}H_{31}N_3O_6$	65,7	6,3	8,5	—	42
1695 (65); 1645 (52); 1620 (56); 1585 (54); 1525 (63)	61,3	5,8	5,5	16,0	$C_{27}H_{31}BrN_2O_4$	61,5	5,9	5,3	15,1	76
1695 (74); 1642 (62); 1620 (63); 1585 (63); 1530 (70)	67,2	6,3	6,0	7,3	$C_{27}H_{31}ClN_2O_4$	67,1	6,5	5,8	7,3	84

literature [5], mp 133°C. ᶜShoulder. ᵈRed substance.

TABLE 3. Peak and Half-Wave Potentials (E_p and $E_{1/2}$) of the Electro-Oxidation of 1-Aryl- and 1-Benzyl-3,4-diethoxycarbonyl-1,4-DHPs

Compound	E_p, V	$E_{1/2}$, V	Compound	E_n, V	$E_{1/2}$, V
I-1	1,05	0,97	II-1	1,22	1,17
I-2	1,18	1,12	II-2	1,18	1,09
I-3	1,17	1,11	II-8	1,20	1,12
I-5	1,12	1,04	II-14	1,20	1,11
I-6[a]	1,22	1,17			

[a] $R^2 = C_6H_4NO_2$-p [19].

TABLE 4. PMR Spectra of Some of the 1,4-DHPs Synthesized

Com-pound	Chemical shifts, δ, ppm					
	4-H	2,6-CH_3	3,5-O-CH_2CH_3	3,5-O-CH_2CH_3	aromatic protons	other radicals
I-2	5,16	2,42	1,22	4,16	6,90—7,60	5,02 (N—CH_2)
II-1	5,12	2,02	1,21	4,15	7,20—7,70	
II-2	5,08	2,01	1,19	4,10	7,20—7,36	2,40 (CH_3)
II-8	5,11	2,04	1,20	4,04	7,11—7,35	3,87 (O—CH_3)
II-29	5,07	2,02	1,16	4,06	6,52—7,52	2,90 [N(CH_3)$_2$]
II-30	5,02	1,89	1,04	3,95	6,40—8,20	2,75 [N(CH_3)$_2$]
II-31	5,09	2,05	1,17	4,06	6,51—8,67	2,72 [N(CH_3)$_2$]
II-32	5,63	1,97	1,13	4,00	6,60—7,90	3,01 [N(CH_3)$_2$]

[a] The spectra of compounds I-2, II-1, II-2, II-8, and II-32 were taken in DMSO-d_6, and those of II-29, II-30, and II-31 in $CDCl_3$.

We have obtained the addition products (VIIIa, b) from the corresponding benzylidene-anilines and acetoacetic ester and from them we have obtained both 1-aryl-1,4-DHPs (II) and tetrahydropyridines (III), which is evidence in favor of the mechanism that we have suggested, although under the conditions of the Hentzsch synthesis the formation of compounds (VIII) in the reaction mixture has not been demonstrated, possibly because they are fairly unstable and undergo rapid further transformation.

In the UV spectra of 1-benzyl- and 1-aryl-1,4-DHP (I, II) (Tables 1 and 2), compared with the spectra of the 1-unsubstituted compounds, the long-wave maximum shifts hypsochromically, in the majority of cases by 5-12 nm. This indicates that the 1-substituent, as shown previously in the 1-alkyl series [4], by acting on the 2,6-methyl groups, sterically hinders the conjugation of the 3,5-CO groups with the π-electron system of the ring. Exceptions are formed by the 1-p-dimethylaminophenyl-1,4-DHPs having electron-accepting substituents in the 4-phenyl radical (II-30—II-34), in the UV spectra of which a bathochromic shift, and this a fairly considerable one (about 25 cm), is observed. In the case of 1-p-dimethylaminophenyl-4-p-nitrophenyl-1,4-DHP (II-30), this band is even shifted to 452 nm. Its wavelength changes little in different solvents. The IR and PMR spectra of the compounds do not differ appreciably. The impression is created that because of the presence of a strong acceptor in the 4-phenyl radical and a strong donor in the 1-phenyl radical the chain of conjugation is greatly lengthened through the inclusion in it, thanks to the hyperconjugation effect, of the CH group in position 4 of the 1,4-DHP ring, which is the reason for the considerable shift in the UV spectrum. With the same 1-substituent in the 1,4-DHPs (I) and (II), the wavelength is found to depend on the nature of the substituent in the 4-phenyl radical: electron-accepting substituents shift the maximum bathochromically, and electron-donating substituents shift it hypsochromically, as has also been observed for the 1-unsubstituted 1,2-DHPs [12].

The IR spectra of compounds (I) and (II) (Tables 1 and 2) do not differ from those of the 1-alkyl-1,4-DHPs [3]. In the 1700-1550 cm^{-1} region there are three characteristic vibrational bands. The strongest is the highest-frequency band, while in the case of 1,4-DHPs unsubstituted in position 1 the band at ~1650 cm^{-1} is stronger.

The electrochemical oxidation of the 1-benzyl- and 1-aryl-1,4-DHPs (I and II) at a rotating platinum microanode in acetonitrile solution has shown that these compounds are oxidized with greater difficulty than the 1-unsubstituted 1,4-DHPs [13], the oxidation potential rising by 0.10-0.14 V (Table 3). This is probably due to the steric hindrance of the approach of the molecule to the electrode.

The 4-anilinotetrahydropyridines (III) have repeatedly been obtained previously [7, 11, 14] but they have frequently been ascribed the structure of tetrahydropyrimidines (V) [7, 11], even though the structure of 4-phenyliminopiperidines had been established for them previously on the basis of their chemical properties [14]. It has been shown by a study of IR and PMR spectra [15] that they exist not in the form of the imine but in the form of the enamine (III). The 4-anilino-1,2,5,6-tetrahydropyridines (IIIa, b) have a characteristic UV spectrum with maxima at ~ 265 and ~ 315 nm. The marked fall in the frequency of vibration of the ester carbonyl and the presence of a ν_{NH} band in the IR spectrum, and also the considerable shift of the signal of the NH proton in the PMR spectrum show that these compounds exist in the enamine form with a hydrogen between the C=O and N-H groups.

The 4-anilinotetrahydropyridines (III) were hydrolyzed to the piperidones (VI), in the IR spectra of which the bands of ketonic and nonconjugated ester carbonyls are observed.

The formation of the cyclohexanone anils (IV) has also been observed previously [8, 16]. We synthesized the anils (IVa and b) and confirmed their structure by IR and PMR spectroscopy. The acid hydrolysis of the anils (IV) gave the known 2,4-diethoxycarbonyl-5-hydroxy-5-methyl-3-phenylcyclohexanone (VII) [8, 17].

EXPERIMENTAL

UV spectra were taken on a Specord UV-vis instrument in ethanol, IR spectra on a UR-20 instrument in Nujol, and PMR spectra on a Perkin-Elmer R-12 A (60 MHz) instrument.

4-Aryl-1,benzyl-3,5-diethoxycarbonyl-2,6-dimethyl-1,4-dihydropyridines (I). A mixture of 0.025 mole of a substituted benzaldehyde, 0.05 mole of acetoacetic ester, and 0.03 mole of benzylamine hydrochloride in 20 ml of pyridine was heated at 100°C for 4-5 h. The solution was poured into water containing ice, leading to the precipitation of an oil. The aqueous layer was poured off, the oil was dissolved in ether, and the ethereal extract was dried with sodium sulfate and concentrated. The residue was diluted with ethanol and in the cold crystals deposited which were recrystallized from ethanol (Table 1).

Compounds (I-2) and (I-5) were also obtained by alkylating the corresponding 1-unsubstituted 1,4-DHPs by treating them with sodium hydride and benzyl chloride at 100°C for 4 h [4].

1-Aryl-4-aryl-3,5-diethoxy-2,6-dimethyl-1,4-dihydropyridines (II). A mixture of 0.03 mole of the appropriate benzaldehyde, 0.06 mole of acetoacetic ester, and 0.03 mole of an arylamine in 10 ml of ethanol was boiled for 4-10 h. Then it was cooled and diluted with ethanol, and the precipitate was crystallized from ethanol (Table 2).

4-Amino-3-ethoxycarbonyl-1,2,6-triphenyl-1,2,5,6-tetrahydropyridines (III) and 3-Aryl-2,4-diethoxycarbonyl-5-hydroxy-5-methylcyclohexan-1-one Anils (IV). A. A mixture of 3.2 g (0.03 mole) of benzaldehyde, 7.8 g (0.06 mole) of acetoacetic ester, and 5.2 g (0.03 mole) of p-bromoaniline in 10 ml of methanol was boiled for 6 h. Then it was cooled, and the precipitate was separated off and crystallized from ethyl acetate, giving 0.6 g (5.3%) of a white substance (IIIa), mp 222-223°C (according to the literature [14], mp 221-223°C). UV spectrum λ_{max}, nm (log ε); 265 (4.37), 313 (4.36). IR spectrum, cm^{-1}: 1650 (C=O), 3260 (N-H). PMR spectrum (in CDCl$_3$), ppm: 10.3 (1 H, s, NH); 6.1-7.3 (18 H, m, arom.); 5.18 (1 H, m, J = 3.2 Hz, 6-H); 4.51 (2 H, q, J = 6 Hz, OCH$_2$CH$_3$); 2.86 (2 H, d, J = 3.2 Hz, 5-CH$_2$); 1.53 (3 H, t, J = 6 Hz, OCH$_2$CH$_3$).

B. The amounts of reactants given in the preceding experiments were heated without a solvent at 100°C for 8 h. Then the mixture was diluted with ethanol and left in the refrigerator. The precipitate was filtered off and was crystallized from ethanol, giving 0.8 g (5.2%) of a white substance (IVa), mp 173-174°C. UV spectrum, λ_{max}, nm (log ε): 205 (4.43), 320 (4.41). IR spectrum, cm^{-1}: 1730 (C=O), 3520 (O-H), PMR spectrum (in DMSO-d$_6$), ppm: 10.8 (1 H, s, OH); 7.18-7.24 (9 H, m, arom.); 4.20 (2 H, d, 6-CH$_2$); 4.00 (2 H, q, 2-OCH$_2$CH$_3$); 3.8 (2 H, q, 4-OCH$_2$CH$_3$); 1.22 (3 H, s, 5-CH$_3$); 1.08 (3 H, t, 2-OCH$_2$CH$_3$); 0.78 (3 H, t, 4-OCH$_2$CH$_3$). Found: C 59.4; H 5.8; Br 16.2; N 2.9%. C$_{25}$H$_{28}$BrNO$_5$. Calculated: C 59.8; H 5.6; Br 15.7; N 2.8%.

C. A mixture of 6.37 g (0.05 mole) of p-chloroaniline, 13.0 g (0.1 mole) of acetoacetic ester, and 5.3 g (0.05 mole) of benzaldehyde in 10 ml of methanol was boiled for 7 h. After cooling, an oil together with a solid precipitate deposited. The oil was dissolved in 20 ml of methanol, and the precipitate was filtered off and crystallized from ethyl acetate, giving 0.7 g (5%) of substance (IIIb), mp 220-221°C (according to the literature [11], mp 205°C; structure shown incorrectly). UV spectrum, λ_{max}, nm (log ε): 264 (4.42), 314 (4.34). IR spectrum, cm^{-1}; 1652 (C=O), 3259 (N-H). PMR spectrum (in CDCl$_3$), ppm: 10.6 (1 H, s, NH); 6.1-7.1 (18 H, m, arom.); 5.11 (1 H, t, J = 3.2 Hz, 6-H); 4.43 (2 H, q, J = 6.5 Hz, OCH$_2$CH$_3$); 2.77 (2 H, d, J = 3.2 Hz, 5-CH$_2$); 1.48 (3 H, t, J = 6.5 Hz, OCH$_2$CH$_3$). Found: C 70.6; H 5.2; Cl 13.3; N 5.5%. C$_{32}$H$_{28}$Cl$_2$N$_2$O$_2$. Calculated: C 70.7; H 5.2; Cl 13.1; N 5.2%.

The methanolic solution after the separation of the precipitate was evaporated to small volume. After prolonged standing (5 months) a viscous oil formed. It was covered with the minimum amount of ethanol, which led to the separation of a solid substance; this was crystallized from ethyl acetate and absolute ethanol, giving 0.25 g (2%) of a white substance (IVb) with mp 170-173°C. UV spectrum, λ_{max}, nm (log ε): 204 (4.44), 317 (4.39). IR spectrum, cm^{-1}: 1732 (C=O;, 3519 (O-H) Found: C 64.7; H 6.0; Cl 8.7; N 2.7%. C$_{25}$H$_{28}$ClNO$_5$. Calculated: C 65.6; H 6.2; Cl 7.7; N 3.1%.

D. A solution of 2.4 g (0.01 mole) of ethyl β-(p-chloroanilino)crotonate, 1.06 g (0.01 mole) of benzaldehyde, and 1.3 g (0.01 mole) of acetoacetic ester in 5 ml of ethanol was boiled for 8 h. This gave 0.3 g (5.5%) of the tetrahydropyridine (IIIb).

Hydrolysis of the 4-Anilino-3-ethoxycarbonyl-1,2,6-triphenyl-1,2,5,6-tetrohydropyridines (III). To 0.15 g of (IIIb) in 2.5 ml of acetone was added 0.3 ml of 10% HCl, and the mixture was boiled for 3 min. After cooling, 0.6 ml of water was added. The white substance (VIb) was obtained with mp 127-129°C (from ethanol). IR spectrum, cm^{-1}: 1712 (C-O), 1744 cm^{-1} (C=O). Found: C 72.5; H 5.6; N 3.6%. C$_{26}$H$_{24}$ClNO$_3$. Calculated: C 72.0; H 5.6; N 3.2%. From compound (IIIa), (IVa) was obtained similarly with mp 126-128°C (from ethanol). IR spectrum, cm^{-1}: 1712 (C=O), 1747 cm^{-1} (C=O). Found: C 65.1; H 4.7; N 3.1%. C$_{26}$H$_{24}$BrNO$_3$. Calculated: C 65.3; H 5.1; N 2.9%.

Hydrolysis of the Cyclohexanone Anil (IVb). Compound (IVb) was hydrolyzed by boiling in 3% HCl for 15 min, which gave compound (VII) with mp 149-151°C (from aqueous ethanol) (according to the literature [8], mp 156-157°C).

Esters of α-Acetyl-β-anilino-β-phenylpropionic Acids (VIII). A. Ethyl α-acetyl-β-anilino-β-phenylpropionate was obtained from benzilideneaniline and acetoacetic ester: mp 96-97°C (from a mixture of benzene and petroleum ether) (according to the literature [18], mp 103-104°C).

B. A solution of 1.3 g (5 mmole) of p-bromobenzylideneaniline in 10 ml of hot ethanol was treated with 0.65 g (5 mmole) of acetoacetic ester and the mixture was left at room temperature for 4 days and was then filtered. The white substance was crystallized from a mixture of benzene and hexane giving 0.25 g (13%) of compound (VIII) (R^1=H, R^2=p-Br) with mp 98-101°C. Found: C 58.1; H 5.1; N 3.7%. C$_{19}$H$_{20}$BrNO$_3$. Calculated: C 58.5; H 5.2; N 3.6%.

Reactions of the Esters (VIII). A. A mixture of 1.55 g (5 mmole) of compound (VIII; R^1 = R^2 = H) and 0.65 g (5 mmole) of acetoacetic ester in 10 ml of ethanol was boiled for 6 h, and then the reaction mixture was diluted with ethanol. The yield of the 1,4-DHP (II-1) (R^1 = H, R^2 = C$_6$H$_5$) was 1 g (50%).

B. A solution of 1.3 g (3.3 mmole) of compound (VIII; R^1 = H, R^2 = p-Br) in 3 ml of ethanol was treated with 0.43 g (3.3 mmole) of acetoacetic ester and the mixture was boiled for 4 h, giving 0.4 g (25%) of the 1,4-DHP (R^1 = H, R^2 = C_6H_4Br-p).

C. A mixture of 1.3 g (4 mmole) of compound (VIII; R^1 = R^2 = H), 0.42 g (4 mmole) of benzaldehyde, 0.37 g (4 mmole) of aniline, and 0.2 g (2 mmole) of malonic acid in 10 ml of ethanol was boiled for 1 h. The yield of compound (III; R^1 = R^2 = H) was 0.4 g (20%). Yellowish crystals with mp 170-172°C (from ethanol) (according to the literature [14], mp 174-175°C). UV spectrum, λ_{max}, nm (log ε): 252 (4.43), 307 (4.31).

Reactions of Benzylideneanilines with Acetoacetic Ester. A. A mixture of 0.91 g (5 mmole) of benzylideneaniline and 1.3 g (10 mmole) of acetoacetic ester in 20 ml of ethanol was boiled for 4 h. On cooling the 1,4-DHP (II; R^1 = H, R^2 = C_6H_5) deposited. Yield 40% (from ethanol).

B. A mixture of 1.28 g (5 mmole) of m-nitrobenzylidene-p-methoxyaniline and 1.3 g (10 mmole) of acetoacetic ester in 20 ml of solvent was boiled for 3 h. On cooling, the 1,4-DHP (II; R^1 = OCH_3-p, R^2 = OCH_3-p, R^2 = $C_6H_4NO_2$-m) deposited. Yield: in ethanol, 80%; in dioxane, 45%; in chloroform, 60% (crystallized from ethanol).

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