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EFFECT OF SUBSTITUENTS IN THE DIHYDROPYRIDINE RING ON THE REACTIVITY OF THE ESTER GROUP OF 3,5-DIALKOXYCARBONYL-1,4-DIHYDROPYRIDINES

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The reactivity of the ester group of 3,5-dialkoxycarbonyl-1,4-dihydropyridines upon reaction with nucleophilic reagents increases when substituents are absent in the ortho positions relative to the ester group and also in the case of steric disruption of the coplanarity of the β-aminovinylcarbonyl system when substituents are introduced at the nitrogen atom in 2,6-dimethyl derivatives. Mono- and dicarboxylic acids were obtained by hydrolysis of such esters. Thus use of esters of propiolic acid esters and arylamines in the Hantzsch synthesis made it possible to obtain 1-aryl-2,6-unsubstituted derivatives of 1,4-dihydropyridine.

It has been frequently noted [1-3] that esters of 1,4-dihydropyridine-3,5-dicarboxylic acids are unusually resistant to hydrolysis, on the basis of which in a review on dihydropyridines [4] it was concluded that it is impossible to hydrolyze the ester groups of these compounds without decomposition of the molecule. It must be noted that 1-unsubstituted 2,6-dimethyl derivatives of 1,4-dihydropyridines (I, R = H, $R^1 = CH_3$) have been studied in all of these cases. By way of verification of these data, it has been confirmed that esters I (R = H, $R = CH_3$) actually have low reactivities and that the acids are obtained in negligibly low yields [5]. Of these compounds, only the 4-unsubstituted compound (I, $R = R^2 = H$, $R^1 = CH_3$), from which a monocarboxylic acid can be obtained [6], proved to be somewhat more reactive. In addition, the 4-unsubstituted compound readily undergoes transesterification with primary alcohols in the presence of a basic catalyst [6]. Reports of the successful hydrolysis of esters of dihydropyridinecarboxylic acids pertain to the 1-substituted derivatives [7, 8]. Unfortunately, these reports contain no information regarding the yields, spectral characteristics [7, 8], and even the experimental conditions for the preparation of the acids [8].

We have observed [5] that the introduction of substituents at the nitrogen atom in 2,6-dimethyl derivatives I (R = alkyl, aryl) gives rise to an increase in the reactivities of the ester groups: in alkaline media they can be hydrolyzed to monocarboxylic acids in

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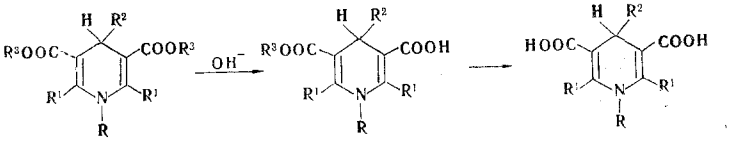
high yields. The hydrolysis of esters of 1-ethoxymethyl-1,4-dihydrocarboxylic acids was accomplished under mild conditions [9, 10].

Depending on the amounts of reagents, both mono- (II) and dicarboxylic acids (III) are formed from the esters of the 1-aryl-1,4-dihydropyridine-3,5-dicarboxylic acids (If, g) [11] investigated in the present research; 1-benzyl derivative Ih is also readily hydrolyzed.



Ia-d, f-j IIa-c, e-j IIIa,b,f,g (R^3 = H)

I—III a $R=C_6H_5$, $R^1=H$, $R^2=C_6H_5$, $R^3=C_2H_5$; b $R=C_6H_4OCH_3$-*p*, $R^1=H$, $R^2=C_6H_5$, $R^3=C_2H_5$; I, II c $R=C_6H_4OCH_3$, $R^1=H$, $R^2=C_6H_4OCH_3$-*p*, $R^3=C_2H_5$; I d $R=C_6H_5$, $R^1=H$, $R^2=C_6H_5$, $R^3=CH_3$; II e $R=C_6H_5$, $R^1=H$, $R^2=C_6H_5$, $R^3=n$-C_3H_7; I—III f $R=C_6H_5$, $R^1=CH_3$, $R^2=C_6H_5$, $R^3=C_2H_5$; g $R=C_6H_4OCH_3$-*p*, $R^1=CH_3$, $R^2=C_6H_5$, $R^3=C_2H_5$; I, II h $R=CH_2C_6H_5$, $R^1=CH_3$, $R^2=C_6H_4NO_2$-*m*, $R^3=C_2H_5$; i $R=C_6H_5$, $R^1=CH_3$, $R^2=C_6H_5$, $R^3=CH_3$; j $R=C_6H_5$, $R^1=CH_3$, $R^2=C_6H_5$, $R^3=n$-C_3H_7.

In contrast to 2,6-dimethyl derivatives, a decrease in the reactivity of the ester groups is not observed in the series of 2,6-unsubstituted I (R^1 = H). Esters I (R^1 = H), which contain both a hydrogen atom and alkyl [12] or aryl substituents in the 1 position, also form mono- and dicarboxylic acids.

Esters of 1-aryl-2,6-unsubstituted 1,4-dihydropyridine-3,5-dicarboxylic acids (Ia-c) were obtained by using compounds that contain a triple bond, viz., propiolic acid esters [13], instead of a β-dicarbonyl component; for the first time in this way we were able to demonstrate the possibility of the use of arylamines in this reaction. It is characteristic that the introduction of an aryl substituent at the nitrogen atom in 2,6-unsubstituted 1,4-dihydropyridines gives rise to a bathochromic shift of the long-wave maximum in the UV spectra as compared with 1-unsubstituted compounds [13], in contrast to the 2,6-dimethyl analogs, in which the introduction of an aryl group in the 1 position shifts the maximum hypsochromically [11].

Transesterification can be carried out with primary alcohols in the presence of sodium alkoxides with esters I of all of the groups mentioned above. Mixtures of products of hydrolysis and transesterification, the ratio of which depends on the structure of ester I and on the alcohol radical, are usually obtained when esters I are treated with potassium hydroxide in a primary alcohol with a group other than that in the ester.

The reason for the difference in the reactivities of various esters I must evidently be sought in the interaction of electronic and steric factors. It is clear that the conjugated β-aminovinylcarbonyl system in the dihydropyridines plays a definite role in decreasing the reactivity, since the oxidized compounds, viz., the corresponding 3,5-dialkoxycarbonylpyridines, are hydrolyzed without difficulty [1, 3]. Right after the completion of our research we observed a report regarding the hydrolysis of esters of 1-unsubstituted derivatives of 2,6-dimethyl-1,4-dihydropyridinecarboxylic acids that contain an electron-acceptor group in the ester radical [14]. The role of the latter evidently reduces to decreasing the electron density on the carbon atom of the carbonyl group, which leads to a decrease in the effect of conjugation. However, steric hindrance to approach of the reagent created by the substituents in the ortho positions to the ester groups also undoubtedly is operative in addition to conjugation. These substituents to a certain extent disrupt the conjugation in the β-aminovinylcarbonyl system, as evidenced by the hypsochromic shift of the long-wave maximum in the UV spectra [13, 15-17], which should lead to facilitation of hydrolysis. Nevertheless, their introduction decreases the reactivities of the ester groups, and esters of 2,6-dimethyl-4-substituted 1,4-dihydropyridine-3,5-dicarboxylic acids I (R = H, $R^1 = CH_3$, $R^2 \neq$ H) are most resistant to hydrolysis. Esters I are hydrolyzed more readily when substituents are absent either in the 2 and 6 positions or in the 4 position. Transesterification occurs even more readily with 4-unsubstituted compounds [6]. This can be explained by the fact that a decrease in the steric hindrance favors the approach to the reaction center of the more reactive but less bulky alkoxide ion. The facilitation of hydrolysis when a substituent is introduced in the 1 position is explained by the more substantial decrease in the conjugation of the ester groups with the 1,4-dihydropyridine system. The substituent (alkyl, aralkyl, or aryl) attached to the nitrogen atom in 2,6-dimethyl-1,4-dihydropyridine-

TABLE 1. 1-Aryl-4-aryl-3,5-dialkoxycarbonyl-1,4-dihydropyridines

Compound	mp, °C	UV spectrum, λ_{max}, nm (log ε)	IR spectrum at 1550-1750 cm^{-1} (absorption, %)	PMR spectrum, δ, ppm	Found, %			Empirical formula	Calculated, %			Yield, %
					C	H	N		C	H	N	
Ia	137—140	204 (4,33); 221 (4,14); 279 (4,29); 372 (3,79)	1708 (76); 1670 (51); 1605 (65)	7,17—7,60 (12H, m., arom. +2,6-H); 4,79 (1H, s, 4-H); 4,02 (4H, q, $-OCH_2CH_3$); 1,07 (6H, t, OCH_2CH_3)	73,3	6,2	3,5	$C_{23}H_{23}NO_4$	73,2	6,1	3,7	45
Ib	116—117	204 (4,26); 224 (4,02); 275 (4,17); 377 (3,72)	1708 (82); 1665 (59); 1600 (60)	6,80—7,50 (11H, m, arom. +2,6-H); 4,79 (1H, s, 4-H); 4,01 (4H, q, OCH_2CH_3); 3,77 (3H, s, OCH_3); 1,11 6H, t, OCH_2CH_3)	71,1	6,1	3,8	$C_{24}H_{25}NO_5$	70,7	6,2	3,4	49
Ic	118—121	203 (4,40); 217 (4,27); 277 (4,30); 368 (3,81)	1702 (78); 1670 (47); 1604 (68)	6,80—8,00 (10H, m, arom. +2,6-H); 4,79 (1H, s, 4-H); 4,08 (4H, q, OCH_2CH_3); 3,82 (3H, s, OCH_3); 3,74 (3H, s, OCH_3); 1,13 (6H, t, OCH_2CH_3)	68,0	5,8	3,6	$C_{25}H_{27}NO_6$	68,6	6,2	3,2	46
Id	188—190	204 (4,34); 222 (4,15); 279 (4,29); 370 (3,81)	1708 (83); 1665 (61); 1605 (68); 1590 (63)	7,00—7,60 (12H, m, arom. +2,6-H), 4,86 (1H, s, 4H); 3,55 (6H, s, OCH_3)	72,0	5,5	4,3	$C_{21}H_{19}NO_4$	72,2	5,5	4,0	76 (A), 65 (B)

TABLE 2. 1-Aryl-4-aryl-1,4-dihydropyridine-3-carboxylic and -3,5-dicarboxylic Acids

Compound	mp, °C	UV spectrum, λ_{max}, nm (log ε)	IR spectrum at 1550-1750 cm^{-1} (absorption, %)	PMR spectrum, δ, ppm	Found, %			Empirical formula	Calculated, %			Yield, %
					C	H	N		C	H	N	
IIa	220—222	206 (4,37); 222 sh (4,20); 284 (4,27); 368 (3,82)	1709 (78); 1660 (56); 1600 (68); 1580 (70)	7,00—7,60 (12H, m, arom.. +2,6-H); 4,85 (1H, s, 4-H); 4,00 (2H, q, OCH_2CH_3); 1,13 (3H, t, OCH_2CH_3)	69,9	5,3	4,1	$C_{21}H_{19}NO_4$	72,2	5,5	4,0	57
IIb	228—229	213 (4,31); 217 sh (4,27); 274 (4,08); 370 (3,81)	1715 (82); 1686 (49); 1660 (56); 1602 (60)	6,98—7,60 (11H, m, arom.. +2,6-H); 4,88 (1H, s. 4-H); 4,00 (2H, q, OCH_2CH_3); 3,80 (3H, s, OCH_3); 1,10 (3H, t, OCH_2CH_3)	69,1	5,6	4,0	$C_{22}H_{21}NO_5$	69,6	5,6	3,7	54
IIc	213—214	203 (4,28); 214 sh (4,19); 277 (4,18); 374 (3,68)	1717 (59); 1680 (45); 1662 (50); 1601 (54)	6,60—7,40 (10H, m., arom. +2,6-H); 4,62 (1H, s, 4-H); 3,88 (2H, q, OCH_2CH_3); 3,68 (3H, s, OCH_3); 3,60 (3H, s, OCH_3); 1,06 (3H, t, OCH_2CH_3)	67,2	5,7	3,8	$C_{23}H_{23}NO_6$	67,5	5,7	3,4	49
IIIa	237—238	204 (4,26); 221 sh (3,96); 282 (4,07); 368 (3,25)	1690 (81); 1595 (60); 1580 (75)	7,05—7,65 (12H, m, arom.. +2,6-H); 4,73 (1H, s, 4-H)	70,0	5,2	4,2	$C_{19}H_{15}NO_4$	71,0	4,7	4,4	60
IIIb	235—237	206 (4,29); 275 (4,23); 371 (3,70)	1696 (72); 1600 (40); 1579 (64)	6,88—7,45 (11H, m, arom.. +2,6-H); 4,75 (1H, s, 4-H); 3,70 (3H, s, OCH_3)	68,4	5,0	3,8	$C_{20}H_{17}NO_5$	68,4	4,9	4,0	58
IIc	240—244	207 (3,39); 222 sh (4,21); 282 (4,31); 372 (3,82)	1715 (79); 1665 (65); 1600 (72); 1585 (70)	6,98—7,38 (12H, m, arom.. +2,6-H); 4,85 (1H, s, 4-H); 3,89 (2H, t, $OCH_2CH_2CH_3$); 0,92—1,67 (2H, m, $OCH_2CH_2CH_3$); 0,73 (3H, t, $OCH_2CH_2CH_3$)	72,4	5,9	3,6	$C_{22}H_{21}NO_4$	72,7	5,8	3,8	31

TABLE 3. 1-Aryl(1-benzyl)-2,6-dimethyl-4-aryl-1,4-dihydropyridine-3,5-dicarboxylic Acids and Their Esters

Compound	mp, °C	UV spectrum, λ_{max}, nm (log ε)	IR spectrum at 1550-1750 cm^{-1} (absorption, %)	PMR spectrum, δ, ppm	Found, % C	Found, % H	Found, % N	Empirical formula	Calculated, % C	Calculated, % H	Calculated, % N	Yield, %
IIf	168—169	206 (4,39); 242 (4,34); 349 (3,86)	1688 (70); 1680 (69); 1640 sh (58); 1600 sh (50)	7,19—7,32 (10H, m, arom); 5,08 (1H, s, 4-H); 4,12 (2H, q, OCH_2CH_3); 2,00 (6H, s, 2,6-CH_3); 1,19 (3H, t, OCH_2CH_3)	72,8	6,3	4,0	$C_{23}H_{23}NO_4$	73,2	6,1	3,7	57
IIIf	167—169	207 (4,37); 239 (4,31); 345 (3,73)	1670 (88); 1600 (74); 1570 (84)	7,00—7,60 (10H, m, arom.); 5,05 (1H, s, 4-H); 1,98 (6H, s., 2,6-CH_3)	71,5	5,4	4,1	$C_{21}H_{19}NO_4$	72,2	5,5	4,0	60
IIg	163—164	203 (4,36); 234 (4,27); 345 (3,68)	1695 (67); 1660 (66); 1635 (56); 1576 (53)	6,99—7,37 (9H, m, arom.); 5,03 (1H, s, 4-H); 4,05 (2H, q, OCH_2CH_3); 3,78 (3H, s, OCH_3); 2,00 (6H, s, 2,6-CH_3); 1,20 (3H, t, OCH_2CH_3)	71,3	6,2	3,4	$C_{24}H_{25}NO_3$	70,7	6,2	3,4	52
IIIg	176—178	204 (4,33); 239 (4,35); 343 (3,71)	1670 (85); 1650 (79); 1565 (79)	7,00—7,30 (9H, m, arom.); 5,02 (1H, s, 4-H); 3,75 (3H, s, OCH_3); 1,95 (6H, s, 2,6-CH_3)	70,5	5,7	3,8	$C_{22}H_{21}NO_5$	69,6	5,6	3,7	56
IIh	156—157	204 (4,26); 238 (4,20); 343 (3,58)	1708 (84); 1680 (87); 1639 (77); 1579 (87)	6,90—7,60 (9H, m, arom.); 5,19 (1H, s, 4-H); 4,83 (2H, s, N—CH_2); 4,05 (2H, q, OCH_2CH_3); 2,40 (6H, s, 2,6-CH_3); 1,18 (3H, t, OCH_2CH_3)	66,8	5,8	6,8	$C_{24}H_{24}N_2O_6$	66,0	5,5	6,4	50
Ii	174—175	204 (4,35); 242 (4,32); 348 (3,70)	1695 (85); 1635 (76); 1599 sh (71); 1578 (74)	7,07—7,52 (10H, m, arom.); 4,97 (1H, s, 4-H); 3,54 (6H, s, OCH_3); 1,92 (6H, s, 2,6-CH_3)	73,0	6,2	4,3	$C_{23}H_{23}NO_4$	73,2	6,1	3,7	76 (A) 54 (B)
IIi	156—158	206 (4,32); 241 (4,14); 348 (3,60)	1704 (56); 1670 (62); 1640 (55); 1590 sh (47)	7,03—7,50 (10H, m, arom.); 5,01 (1H, s, 4-H); 3,58 (3H, s, OCH_3); 1,86 (6H, s, 2,6-CH_3)	72,3	5,8	3,5	$C_{22}H_{21}NO_4$	72,7	5,8	3,8	5
Ij	134—135	205 (4,48); 242 (4,45); 340 (3,81)	1690 (75); 1635 (60); 1580 (67)	7,11—7,57 (10H, m, arom.); 5,04 (1H, s, 4-H); 3,88 (4H, t, $OCH_2CH_2CH_3$); 1,92 (6H, s, 2,6-CH_3); 1,48 (4H, m, $OCH_2CH_2CH_3$); 0,77 (6H, t, $OCH_2CH_2CH_3$)	74,4	7,2	3,0	$C_{27}H_{31}NO_4$	74,8	7,2	3,2	23
IIj	164—165	206 (4,40); 241 (4,37); 348 (3,73)	1696 (74); 1670 (81); 1640 (75); 1592 (65)	6,95—7,60 (10H, m, arom.); 5,08 (1H, s, 4-H); 3,95 (2H, t, $OCH_2CH_2CH_3$); 1,98 (6H, s, 2,6-CH_3); 1,75—1,10 (2H, m, $OCH_2CH_2CH_3$); 0,80 (3H, t, $OCH_2CH_2CH_3$)	73,6	6,3	3,1	$C_{24}H_{25}NO_4$	73,6	6,4	3,6	38

carboxylic acid esters sterically affects the methyl groups in the 2 and 6 positions, which in turn force the 3,5-alkoxycarbonyl groups to deviate from the plane. The hypsochromic shift of the long-wave band in the UR spectra and an analysis of Stuart–Briegleb models [11, 18] (see also Table 1) constitute evidence for a decrease in conjugation as compared with the conjugation in the 1-unsubstituted analogs.

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EXPERIMENTAL

The UV spectra of solutions of the compounds in ethanol were recorded with a Specord UV-vis spectrophotometer. The IR spectra of Nujol suspensions were recorded with a UR-20 spectrometer. The PMR spectra of solutions of the compounds in d_6-DMSO (or in $CDCl_3$ in the case of Id and IIa, e, j) were recorded with Perkin-Elmer R-12A (60 MHz) and Bruker WH-DS (90 MHz) spectrometers.

Esters If, g were obtained by the method in [11], while ester Ih was obtained by the method in [19].

1-Aryl-4-aryl-3,5-diethoxycarbonyl-1,4-dihydropyridines (Ia-c). A 0.02 mole sample of the corresponding benzaldehyde, 0.04 mole of ethyl propiolate, and 0.02 mole of the arylamine were heated in the presence of 1 ml of acetic acid on a water bath for 30 min, after which the mixture was cooled, and the precipitate was crystallized from ethanol (Table 1).

Hydrolysis of 1-Aryl(benzyl)-4-aryl-1,4-dihydropyridine-3,5-dicarboxylic Acid Esters. A mixture of 0.01 mole of the corresponding diethyl ester Ia-c, f-h and 0.01 mole of potassium hydroxide was refluxed in 20 ml of ethanol for 10 h, after which the mixture was evaporated to dryness, and the residue was treated with water. The aqueous solution was acidified with dilute hydrochloric acid, and the precipitate was removed by filtration and crystallized from acetonitrile–alcohol (4:1). This procedure gave monocarboxylic acids IIa-c, f-h. A fourfold amount of potassium hydroxide was used to obtain carboxylic acids IIIa, b, f, g (Tables 2 and 3).

Transesterification of 1-Aryl-1,4-dihydropyridine-3,5-dicarboxylic Acid Esters. A. A 0.01-mole sample of diethyl ester Ia and 0.02 mole of sodium methoxide were heated in 20 ml of methanol on a water bath for 2 h. The precipitate was crystallized from methanol to give diethyl ester Id (Table 1). Dimethyl ester Ii was similarly obtained from diethyl ester If (Table 3).

B) A 0.01-mole sample of the corresponding diethyl ester Ia, f and 0.01 mole of potassium hydroxide were heated in 20 ml of methanol on a water bath for 10 h. Dimethyl ester Ig (Table 1) and dicarboxylic acid IIIa (Table 2) were obtained from diethyl ester Ic, while dimethyl ester Ii and monocarboxylic acid IIi (Table 3) were obtained from ester If.

Monocarboxylic acid IIe (Table 2) was obtained similarly from ester Ia in n-propanol, while di-n-propyl ester Ij and monocarboxylic acid IIj (Table 3) were obtained from ester If.

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CLEAVAGE OF THE N—N BOND IN 1-SUBSTITUTED INDAZOLES UNDER THE INFLUENCE OF ARYLLITHIUM COMPOUNDS

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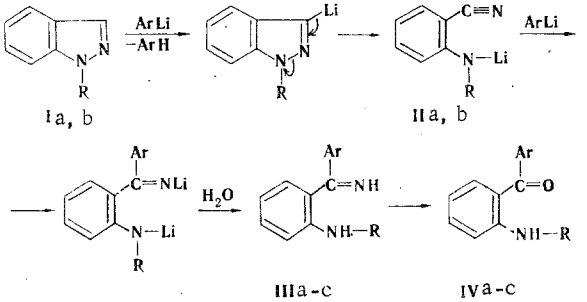
Upon reaction with aryllithium compounds (phenyllithium and m-tolyllithium) m-methyl- and 1-isopropylindazoles undergo cleavage at the N—N bond to give N-substituted 2-aminobenzophenones. The heterocyclic ring of 1-isopropyl-3-phenylindazole also undergoes cleavage at this bond under the influence of phenyllithium.

In [1] it was shown that 1-methylindazole upon metallation with butyllithium undergoes partial conversion to 1-lithiomethylindazole. Since the metallation of azoles may be accompanied by a side reaction involving the addition of the metallating agent to the C=N bond of the heterocyclic ring, it was of interest to study the reaction of 1-substituted indazoles with reagents that are less nucleophilic than butyllithium. In the reaction of 1-methyl- and 1-isopropylindazoles with aryllithium compounds we observed that a reaction does not occur under the conditions indicated in [1]; however, if the process is carried out at the boiling point of the mixture, the corresponding N-substituted 2-aminobenzophenones are formed. Our results and the data in [2, 3] make it possible to propose the following reaction scheme:



I, II a $R=CH_3$; b $R=CH(CH_3)_2$; III, IV a $R=CH_3$, $Ar=C_6H_5$; b $R=CH(CH_3)_2$, $Ar=C_6H_5$; c $R=CH(CH_3)_2$, $Ar=m\text{-}CH_3C_6H_4$

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