indole hydrochloride was removed by filtration and washed with ether. The hydrochloride was dissolved in a small amount of cold water and neutralized with pyridine, after which the precipitated base was removed by filtration, washed on the filter with cold water, dried over P_2O_5, and crystallized from benzene. For complete removal of the crystallization benzene, the substance was heated at 100°C in vacuo for 3 h. The principal characteristics of the compounds obtained are presented in Table 1.

As compared with the 1-oxo derivatives, lower melting points and high solubilities in ordinary organic solvents are characteristic for XIII-XVIII.

LITERATURE CITED

1. N. N. Suvorov, Zh. D. Ovchinnikova, and Yu. N. Sheinker, Zh. Obshch. Khim., 31, 2333 (1961).
2. R. S. Pandit and S. Seshadri, Indian J. Chem., 12, 943 (1974).
3. P. Nantka-Namirski and Z. Ozdowska, Acta, Pol. Pharm., 32, 273 (1975).
4. H. King and E. Stiller, J. Chem. Soc., No. 2, 466 (1937).
5. N. A. Kogan and M. I. Vlasova, Khim. Geterotsikl. Soedin., No. 12, 1654 (1973).
6. V. A. Monge, V. Huarte, J. A. Palop, M. T. Martinez, and A. E. Fernandez, An. Quim., 73(2), 278 (1977); Chem. Abstr., 87, 152107 (1977).
7. R. Staunton and A. Topham, J. Chem. Soc., No. 6, 1889 (1953).
8. M. I. Vlasova and N. A. Kogan, Khim. Geterosikl. Soedin., No. 6, 754 (1974).
9. M. A. Rekhter, V. I. Gorgos, L. M. Zorin, and G. I. Zhungietu, USSR Inventor's Certificate No. 696016; Byull. Izobret., No. 41, 91 (1979).
10. G. I. Zhungietu, V. I. Gorgos, M. A. Rekhter, and A. I. Korpan', Izv. Akad. Nauk Moldavsk. SSR, Ser. Biol. Khim. Nauk, No. 3, 61 (1980).
11. G. I. Zhungietu, L. M. Zorin, and M. A. Rekhter, Izv. Akad. Nauk Moldavsk. SSR, Ser. Biol. Khim. Nauk, No. 2, 57 (1981).
12. A. N. Kost, M. A. Yurovskaya, and Nguyen Minh Thao, Khim. Geterotsikl. Soedin., No. 5, 659 (1975).

SYNTHESIS AND PROPERTIES OF 1-SUBSTITUTED DERIVATIVES OF DIETHYL 4-ARYL-1,4-DIHYDRCPYRIDINE-3,5-DICARBOXYLIC ACID ESTERS

V. K. Lusis and G. Ya. Dubur

UDC 547.822:547.827

1-Unsubstituted 4-aryl-3,5-diethoxycarbonyl-1,4-dihydropyridines in the presence of NaH form anions that react with alkyl halides, acid chlorides, and halo acid esters to form the corresponding 1-substituted derivatives of 1,4-dihydropyridine. Hydrolysis of one or both ethoxycarbonyl groups in the 3 and 5 positions, as well as hydrolysis of ethyl 4-phenyl-3,5-diethoxycarbonyl-1,4-dihydropyridinyl-1-acetate, occur upon reaction with alkali, but 1,3,5-triethoxycarbonyl-4-phenyl-1,4-dihydropyridine gives the corresponding unsubstituted 1,4-dihydropyridine.

Only a few reactions involving substitution at the nitrogen atom in series of 1,4-dihydropyridine derivatives are known: there are individual examples of acylation [1, 2] and more detailed studies of the alkylation of esters of 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylic acids [3, 4] and 2,6-dimethyl-3,5-dicyano-1,4-dihydropyridines [5, 6]. In the present research we accomplished the synthesis of 1-substituted derivatives of 4-aryl-3,5-diethoxycarbonyl-1,4-dihydropyridine (unsubstituted in the 2 and 6 positions) and studied their reactivities.

1-Unsubstituted 1,4-dihydropyridines I and II were obtained by the reaction of an aromatic aldehyde with propiolic acid ester (with the use of stoichiometric ratios of the reagents, in contrast to the method in [7]) in the presence of ammonium acetate.

Institute of Organic Synthesis, Academy of Sciences of the Latvian SSR, Riga 226006.

Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 8, pp. 1067-1071, August, 1982. Original article submitted January 7, 1981.

0009-3122/82/1808-0813$07.50

TABLE 1. Physicochemical Characteristics of the Synthesized Dihydropyridines

Compound	mp, °C	PMR spectrum, ppm						IR spectrum in the 1500-1800 cm^{-1} region (absorption, %)	UV spectrum, λ_{max} nm (log ε)	Found, %			Empirical formula	Calc., %			Yield, %
		1-R	2,6-H	3,5-$COOC_2H_5$[a] CH_3 (t)	3,5-$COOC_2H_5$[a] CH_2 (q)	4-H (s)	4-Ar			C	H	N		C	H	N	
I	123—125	9,07 (t, H)	7,17 (d)	1,03	3,90	4,63	7,10 (s)	1698 (80), 1670 (71), 1612 (50), 1505 (79)	268[b] (3,20), 207 (4,23), 227 (4,11), 366 (3,92)	67,6	6,5	4,8	$C_{17}H_{19}NO_4$	67,8	6,4	4,7	79
II	125—126	9,24 (t, H)	7,23 (d)	1,06	3,96	4,65	3,65 (s CH_3), 7,13 (d, Ph), 6,76 (d, Ph)	1702 (81), 1662 (80), 1608 (67), 1502 (87)	364 (3,97), 282 (3,53), 206 (4,21), 221 (4,30), 240b (3,92)	65,7	6,1	4,5	$C_{18}H_{21}NO_5$	65,2	6,4	4,2	70
IIIa	143—145	3,20 (s, CH_3)	7,23 (s)	1,03	3,91	4,60	7,10 (s)	1700 (84), 1670[b] (70), 1576 (82)	207 (4,27), 230 (4,15), 376 (3,95)	68,2	6,6	4,5	$C_{18}H_{21}NO_4$	68,6	6,7	4,4	96
IIIb	95—97	3,63 (sept., H), 1,32 (d, CH_3)	7,15 (s)	1,12	3,99	4,82	7,22 (s)	1695 (91), 1658 (51), 1578 (90)	207 (4,25), 229 (4,15), 238[b] (4,12), 370 (3,99)	69,5	7,1	4,3	$C_{20}H_{25}NO_4$	70,0	7,3	4,1	79
IIIc	125—127	7,55 (s, Ph)	7,93 (s)	1,05	3,95	4,75	7,23 (s)	1718 (80), 1698 (85), 1665 (73), 1618 (64)	206 (4,56), 229[b] (4,20), 283 (4,22), 323b (3,95)	71,3	5,9	3,5	$C_{24}H_{23}NO_5$	71,1	5,7	3,5	82
IIId	124—125	7,88 (d, Pb), 8,33 (d, Ph)	7,83 (s)	1,06	3,94	4,75	7,23 (s)	1715 (89), 1698 (88), 1663 (81), 1618 (82), 1532 (79)	205 (4,50), 262 (4,37), 305[b] (4,09)	64,0	6,6	5,2	$C_{24}H_{22}N_2O_7$	64,0	6,2	4,9	73
IIIe	77—79	1,32 (t, CH_3), 4,33 (q, CH_2)	7,84 (s)	1,09	4,00	4,66	7,16 (s)	1738 (76), 1710 (83), 1678 (63), 1620 (71)	205 (4,35), 255 (4,38), 315 (3,75)	64,7	6,2	3,5	$C_{20}H_{23}NO_6$	64,3	6,2	3,6	88
IIIf	155—157	1,09 (t, CH_3), 3,94 (q, CH_2), 4,24 (s, CH_2)	7,28 (s)	1,18	4,16	4,24	7,16 (s)	1748 (69), 1702 (80), 1668 (81), 1580 (79)	207 (4,24), 227 (4,11), 246[b] (4,10), 368 (3,89)	65,5	6,5	3,2	$C_{21}H_{25}NO_6$	65,1	6,5	3,6	61
IIIg	154—156	3,14 (s, CH_3)	7,72 (s)	1,14	4,07	4,84	7,22 (s)	1702 (82), 1662 (42), 1610 (75)	207 (4,34), 237 (4,23), 317 (3,75)	59,6	3,5	5,6	$C_{18}H_{21}NO_6S$	60,0	5,6	3,7	40

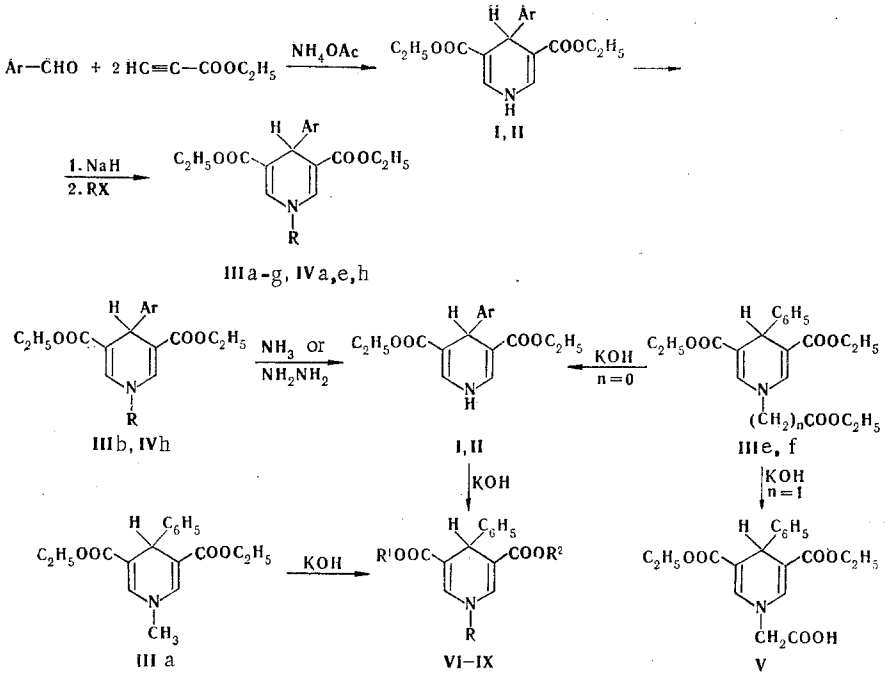
IVa	94	3,21 (s, CH_3)	7,22 (s)	1,05	3,94	4,58	7,06 (d, Ph), 7,22 (d, Ph), 3,61 (s OCH_3),	1705 (92), 1690[b] (84), 1608 (69), 1585 (84), 1512 (80)	204 (4,19), 222 (4,28), 253 (3,98), 283[b] (3,48), 376 (3,95)	66,4	7,1	4,4	$C_{19}H_{23}NO_5$	66,1	6,7	4,1	95
IVe	128—130	1,25 (t, CH_3), 4,28 (q, CH_2)	7,74 (s)	1,06	3,96	4,55	3,60 (s, CH_3), 3,68 (d, Ph), 7,04 (d, Ph)	1728 (90), 1702 (91), 1665 (79), 1608 (88), 1510 (82)	205 (4,32), 271 (4,34), 310[b] (3,79)	62,1	6,5	3,7	$C_{21}H_{25}NO_7$	62,5	6,3	3,5	78
IVh	144—145	3,20 (s, CH_3)	7,89 (s)	1,08	4,00	4,61	3,64 (s, CH_3), 6,82 (d, Ph), 7,10 (d, Ph)	1705 (90), 1668 (79), 1615 (88), 1510 (76)	205 (4,29), 255 (4,38), 306 (3,81)	64,8	6,1	3,4	$C_{20}H_{23}NO_6$	64,3	6,2	3,7	62
V	184—186	4,31 (s, CH_2)	7,24 (s)	1,05	3,91	4,60	7,17 (s)	1742 (59), 1698 (79), 1678 (78), 1638 (51), 1572 (78)	206 (4,19), 229 (4,07), 244[b] (4,03), 372 (3,87)[c]	63,1	6,1	4,2	$C_{19}H_{21}NO_6$	63,5	5,9	3,9	50
VI	222 d	3,35 (s, CH_3)	7,32 (s)	1,14	3,99	4,68	7,24 (s)	1700 (92), 1660[b] (66), 1580 (82)	206 (4,16), 229 (4,06), 243[b] (4,01), 374 (3,82)[c]	66,5	5,9	5,2	$C_{16}H_{17}NO_4$	66,9	6,0	4,9	90
VII	197—198	3,17 (s, CH_3)	7,22 (s)	—		4,62	7,14 (s)	1680 (70), 1648 (69), 1575 (62)	207 (4,19), 226 (4,11), 243[b] (4,04), 371 (3,85)[c]	64,5	5,0	5,7	$C_{14}H_{13}NO_4$	64,9	5,1	5,4	92
VIII	215[e]	9,00 (t, H)	7,30 (d)	1,04	3,92	4,67	7,13 (s)	1702 (59), 1660[b] (39), 1608 (45), 1530[b] (32)	207 (4,22), 223[b] (4,09), 235[b] (4,05), 275[b] (3,08), 363 (3,87)[c]	65,6	5,5	5,4	$C_{15}H_{15}NO_4$	65,9	5,5	5,1	84
IX	233—234	8,90 (t, H)	7,23 (d)	—		4,63	7,14 (s)	1682 (84), 1650 (81), 1598 (71)	208 (4,27), 221[b] (4,16), 235[b] (4,08), 269[b] (3,15), 360 (3,90)[c]	64,1	4,7	6,1	$C_{13}H_{11}NO_4$	63,7	4,5	5,7	88

[a]For monoesters VI, VIII, and 5-$COOC_2H_5$ the signals of the COOH protons are broad singlets at 10.68 (VI), 10.50 (VII), 11.50 (VIII), and 11.60 (IX). [b]Shoulder. [c]In a 0.1 M KOH solution in ethanol the compounds have the following absorption bands: V 378 (3.75), VI 368 (3.75), VII 357 (3.73), VIII 360 (3.81). [d]Partially decarboxylated above 205°C. [e]With decarboxylation.

The resulting dihydropyridines I and II in the presence of sodium hydride readily form the corresponding anions, which react with alkyl halides and acid chlorides, as well as halo acid esters, to give 1-substituted derivatives of 4-aryl-3,5-diethoxycarbonyl-1,4-dihydropyridine (III and IV) in good yields.

It should be noted that in this case one observes the smooth formation of 1-isopropyl derivative IIIb, which, because of steric hindrance, is impossible when methyl substituents are present in the 2 and 6 positions [4, 5]. Evidently for this reason we were unable to obtain 1-acetyl-4-phenyl-3,5-diethoxycarbonyl-2,5-dimethyl-1,4-dihydropyridine by acylation of the corresponding anion.

Compounds IIIc, d and IVh can be regarded as peculiar tertiary amides of the corresponding acid, which is manifested graphically in their properties. In the reaction of the above-mentioned dihydropyridines with ammonia and hydrazines the N—CO bond is cleaved to give the free amine, i.e., dihydropyridine I. Correspondingly, IIIe and IVe, as derivatives of carbamic acid, also readily form 4-aryl-3,5-diethoxycarbonyl-1,4-dihydropyridines via alkaline hydrolysis. In the case of 4-phenyl-3,5-diethoxycarbonyl-1,4-dihydropyridin-1-ylacetic acid (IIIf), in which the ethoxycarbonyl grouping is separated from the ring by a methylene group, the tendency to undergo decarboxylation during hydrolysis is completely lost, and acid V is formed as the reaction product. It must be pointed out that in the reaction of esters IIIf with an equimolar amount of alkali only the ester group of the aliphatic chain undergoes hydrolysis, while the ethoxycarbonyl groups in the 3 and 5 positions remain unchanged; this is in agreement with the data in [8]. The ester groups of 1,4-dihydropyridine-3,5-dicarboxylic acids (I, IIIa) are also capable of undergoing hydrolysis. We found conditions under which the alkaline hydrolysis of one or both groups of 1-unsubstituted dihydropyridine I and its 1-methyl derivative IIIa is realized; this distinguishes them from esters of 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylic acids, for the hydrolysis of which a substituent attached to the nitrogen atom is necessary [9].



I, III Ar=C_6H_5; II, IV Ar=$C_6H_4OCH_3$-4; X=halogen; a R=CH_3; b R=*iso*-C_3H_7; c R=COC_6H_5; d R=$COC_6H_4NO_2$-4; e R=$COOC_2H_5$; f R=$CH_2COOC_2H_5$; g R=SO_2CH_3; h R=$COCH_3$; VI R=CH_3, R^1=C_2H_5, R^2=H; VII R=CH_3, R^1=R^2=H; VIII R=R^2=H, R^1=C_2H_5; IX R=R^1=R^2=H

The IR spectra in the 1500-1800 cm^{-1} region of 1,4-dihydropyridines IIIc, d and IVh are unsuitable for identification, since the absorption band of the starting 1-unsubstituted esters I and II is found in the region of the absorption of the CO group of 1-acyl-1,4-dihydropyridines (1660-1670 cm^{-1}) [10, 11] (Table 1). A strong hypsochromic shift (of 50 nm) of the long-wave maximum of the dihydropyridine system is observed in the UV spectra of these compounds (IIIc-e, IVe, h). The opposite effect is observed in the spectra of compounds with an isolated CO group attached to the nitrogen atom (IIIf, V): the distinct ab-

sorption of an aliphatic acid CO group is observed in the IR spectra at 1750 cm^{-1}, whereas the UV spectra differ little from the spectrum of 1-unsubstituted dihydropyridine I. In the case of 1-alkyl derivatives the long-wave UV absorption band is shifted bathochromically (by ~10 nm) with respect to 1-unsubstituted dihydropyridine. This is also valid in the series of esters IIIa, b and IVa, as well as in the case of acids VI and VII, and is in agreement with the principles of the effect of 1-alkyl substituents in 2,6-unsubstituted derivatives of 1,4-dihydropyridines [12].

The UV spectra of acids VI-IX in alkaline media change surprisingly little. Only a small hypsochromic shift of the long-wave absorption maximum, viz., 6-7 nm for the monocarboxylic acids (VI, VIII) and 12-15 nm for the dicarboxylic acids (VI, IX), is observed in the spectra recorded in 0.1 N KOH in ethanol. This is unexpected in the case of the existence of the carboxy group in the ionized form.

EXPERIMENTAL

The IR spectra of suspensions of the compounds in Nujol were recorded with a UR-20 spectrometer. The UV spectra in ethanol were recorded with a Specord UV-vis spectrophotometer. The PMR spectra were obtained with R-12 (60 MHz), BS 487C (80 MHz), and WH-90 (90 MHz) spectrometers with hexamethyldisiloxane as the internal standard. The physicochemical characteristics of the compounds are presented in Table 1. The homogeneity of the synthesized substances was verified by thin-layer chromatography (TLC) on Silufol UV-254 plates in a chloroform–hexane–acetone system (9:7:1).

Ethyl 4-Aryl-1,4-dihydropyridine-3,5-dicarboxylates (I, II). A mixture of 0.05 mole of the aromatic aldehyde, 10.2 ml (0.1 mole) of ethyl propiolate, and 8.7 g (0.075 mole) of ammonium acetate in 10 ml of glacial acetic acid was heated until an exothermic reaction commenced, after which the reaction mixture was poured into 100 ml of cold water, and the precipitate was removed by filtration and recrystallized from ethanol.

1-Substituted 1,4-Dihydropyridines (III, IV). A 0.29-g (0.012 mole) sample of sodium hydride was added to a solution of 0.01 mole of dihydropyridine I or II in the minimum volume of hexametapol. After the formation of the anion was complete, the calculated amount of reagent, viz., 0.02 mole of alkyl iodide or ethyl bromoacetate, 0.015 mole of the chloride of the corresponding acid or ethyl chloroformate, was added. After 2 h, the reaction mixture was poured into 150 ml of cold water, and the mixture was allowed to stand overnight. The crude reaction product was separated and recrystallized from ethanol.

Reactions of IIId and IVh with Ammonia and Hydrazines. A 0.014-mole sample of 1-substituted dihydropyridine and 0.028 mole of ammonia (a 25% aqueous solution) or hydrazine (in the form of hydrazine hydrate) or 1,1-dimethylhydrazine was refluxed in 30 ml of ethanol for 3 h, after which the reaction mixture was evaporated to one-third of its original volume and cooled, and dihydropyridine I was separated. No melting-point depression was observed for a mixture with a genuine sample of I, and the PMR and UV spectra were identical.

Hydrolysis of 1,3,5-Triethoxycarbonyl-1,4-dihydropyridine (IIIe). A 3.37-g (0.01 mole) sample of IIIe and 0.56 g (0.01 mole) of KOH were refluxed in 30 ml of ethanol for 5 h, after which the mixture was evaporated, and the dry residue was treated with hot water. After cooling, ester I was separated. The yield after recrystallization was 71%.

Hydrolysis of Ethyl 1,4-Dihydropyridin-1-ylacetate (IIIf). Equimolar amounts of IIIf and potassium hydroxide were refluxed in ethanol for 5 h, after which the mixture was evaporated, and the dry residue was treated with hot water. After cooling, the unchanged IIIf was separated, and the filtrate was acidified with dilute (1:2) HCl. The precipitated V was removed by filtration and recrystallized from a small volume of acetonitrile.

Hydrolysis of Esters I and IIIa. A 0.0075-mole sample of ester I or IIIa was refluxed for 10 h in 50 ml of ethanol with either 0.42 g (0.0075 mole for the preparation of monocarboxylic acids VI and VIII) or 1.68 g (0.03 mole for the preparation of dicarboxylic acids VII and IX) of potassium hydroxide. The solvent was evaporated in vacuo, and the dry residue was treated with hot water, cooled, and removed by filtration. The filtrate was acidified with cold dilute (1:2) HCl to pH 1. The acid was removed by filtration, squeezed thoroughly, and recrystallized rapidly: VI and VIII from acetonitrile, and VII and IX from glacial acetic acid.

LITERATURE CITED

1. F. Michell and H. Dralle, Lieb. Ann., 670, 57 (1963).
2. R. E. Lyle and D. A. Nelson, J. Org. Chem., 28, 169 (1963).
3. R. A. Dommisse and F. C. Alderweireldt, Bull. Soc. Chim. Belg., 82, 441 (1973).
4. A. É. Sausin', V. K. Lusis, G. Ya. Bubur, and Yu. I. Beilis, Khim. Geterotsikl. Soedin., No. 11, 1508 (1978).
5. J. Kuthan and J. Palaček, Collect. Czech. Chem. Commun., 39, 3711 (1974).
6. A. M. Kats, V. V. Solov'eva, G. Ya. Dubur, and I. B. Mazheika, Izv. Akad. Nauk Latv. SSR, Ser. Khim., No. 6, 715 (1976).
7. T. Chennat and U. Eisner, J. Chem. Soc., Perkin Trans. I, No. 110, 926.
8. M. Iwamami, T. Shibannuma, M. Fujimoto, R. Kawai, K. Tamizava, T. Takenaka, K. Takahasi, and M. Murakami, Chem. Pharm. Bull. Jpn., 27, 1426 (1979).
9. A. É. Sausin', V. K. Lusis, B. S. Chekavichus, and G. Ya. Dubur, Khim. Geterotsikl. Soedin., No. 2, 272 (1978).
10. K. N. Kilminster and M. Sainsburg, J. Chem. Soc., Perkin Trans. I, No. 18, 2269 (1972).
11. W. Steglich and G. Hoefle, Chem. Ber., 102, 1129 (1969).
12. P. I. Brignell, U. Eisner, and P. G. Farrell, J. Chem. Soc., B, No. 11, 1083 (1966).

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

B. S. Chekavichus, A. É. Sausin', and G. Ya. Dubur

UDC 547.827'26:542.938:543.422

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

Institute of Organic Synthesis, Academy of Sciences of the Latvian SSR, Riga 226006.
Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 8, pp. 1072-1077, August, 1982. Original article submitted September 16, 1981.

 0009-3122/82/1808-0818$07.50