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Mannich Reaction of Dihydropyridine Derivatives. I. Reactions with Secondary Amines[1]

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Dialkyl 4-aryl-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylates (III) were subjected to the Mannich reaction with excess paraformaldehyde and secondary amine hydrochloride in boiling ethanolic solution. When the compounds III were treated with a 5- to 7-fold molar excess of the aldehyde and amine salt, 2,6-bis(2-disubstituted aminoethyl)-dihydropyridine derivatives (V) were obtained in good yields. On treatment with a 2- to 3-fold molar excess of the reactants, compounds III were converted to 2-(2-disubstituted aminoethyl)-6-methyldihydropyridine derivatives (IV) and V. When dioxane was used as a solvent with a 6-fold molar excess of the reactants, the tetrakis(dimethylaminomethyl)derivative (VII) was obtained.

Keywords——dihydropyridinedicarboxylic acid; Mannich reaction; aminomethylation; enaminoester; γ-substitution; bis(disubstituted aminoethyl)dihydropyridinedicarboxylic acid

The Mannich reaction of cyclic enaminoketones[3] (I) and heterocyclic compounds[4] containing an enaminoketone moiety (II) has been reported by several authors. In these reactions, whether intermolecular[3a,4a,b] or intramolecular,[3b,c,4c] the reactive site is limited to the α-carbon atom only. However, reactions of enaminoketone derivatives with electrophilic reagents, such as alkyl halides, aldehydes, *etc.*, proceed not only on the nitrogen, oxygen and α-carbon atoms but also on the γ-carbon atom.[5] Therefore it is conceivable that enaminoketone or enaminoester compounds may undergo the Mannich reaction at their γ-carbon atom in special cases.

As part of a search for new pharmacologically active compounds, dialkyl 4-aryl-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylates (III) (enaminoester compounds) were allowed to react with excess paraformaldehyde and secondary amine hydrochloride in ethanolic solution. This paper describes the results of these reactions, which are the first examples of the Mannich reaction at the γ-carbon atom in a cyclic enaminoester series.

Compounds III were treated with a 5- to 7-fold molar excess of paraformaldehyde and secondary amine hydrochloride, and a small amount of hydrochloric acid in boiling ethanol for 18 hr (reaction condition A). Compounds III, except for the nitrophenyl derivatives (IIIe, j), were converted to dialkyl 4-aryl-2,6-bis(2-disubstituted aminoethyl)-1,4-dihydropyridine-3,5-dicarboxylates (V) in 59 to 78% yields. In the case of IIIe, j, the reaction proceeded

1) A part of this work was presented at the 29th meeting of Kinki Branch, Pharmaceutical Society of Japan, Kyoto, November, 1979.
2) Location: *33-94, Enoki-cho, Suita, Osaka 564, Japan.*
3) *a*) H.J. Roth and H.E. Hagen, *Arch. Pharm. Ber. Dtsch. Pharm. Ges.*, **304**, 331 (1971); *b*) S. Miyano and N. Abe, *Chem. Pharm. Bull.*, **20**, 1588 (1972); *c*) S. Miyano, N. Abe, K. Sumoto, and K. Teramoto, *J. Chem. Soc., Perkin Trans. I*, **1976**, 1146.
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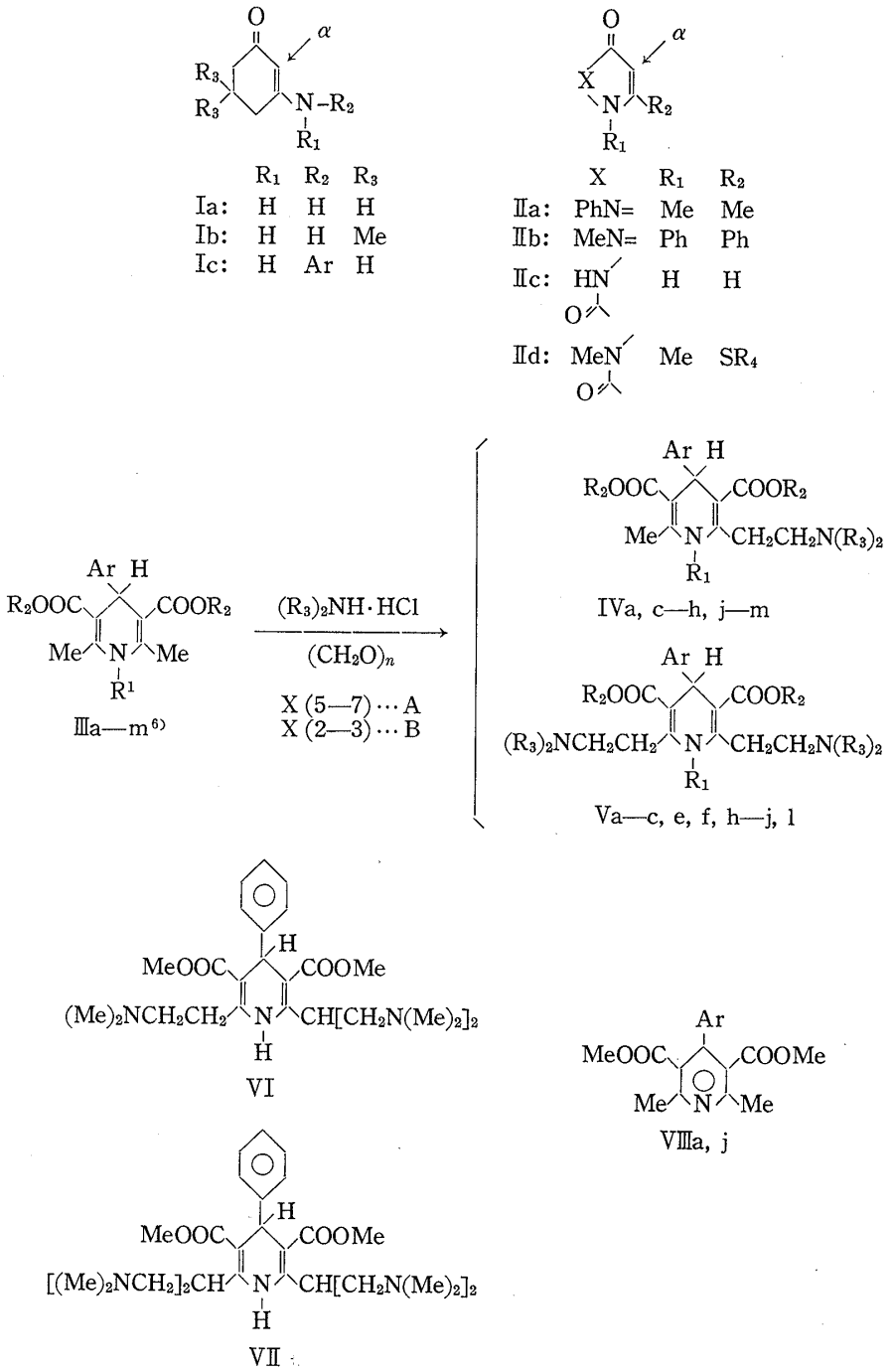

Chart 1

slowly and dialkyl 4-aryl-2-(2-disubstituted aminoethyl)-1,4-dihydro-6-methylpyridine-3,5-dicarboxylates (IV) and V were obtained in 21 to 35% yield for IV and 25 to 55% yield for V (Table I).

When a 2- to 3-fold molar excess of the reactants was used (reaction condition B), the reaction did not proceed fully, and a mixture of IV, V and a small amount of III was obtained. After separation of these compounds by column chromatography followed by recrystallizations, IV and V were obtained as pure compounds (Tables II and III).

When IIIa was treated in boiling dioxane with a 6-fold molar excess of paraformaldehyde

6) See the experimental section.

TABLE I. Yields and Physical Constants of V obtained under Reaction Condition A

Compd. No.	Ar	R_1	R_2	$N<^{R_3}_{R_3}$	Yield[a] (%)	mp (°C) Recrystn.[f] solvent	Formula	Analysis (%) Calcd (Found) C	H	N	Cl	MS (m/e) M^+
Va-1	Ph	H	Me	$N<^{Me}_{Me}$	78[b]	213—213.5 (dec.) EtOH–Et_2O	$C_{23}H_{33}N_3O_4$ ·2HCl	56.56 (56.17	7.22 7.34	8.60 8.53	14.52 14.38)	415
Va-2	Ph	H	Me	N⟨ ⟩O	66	103—106 Tol.–Hex.	$C_{27}H_{37}N_3O_6$	64.91 (65.00	7.47 7.61	8.41 8.53)		499
Vb-1	Ph	H	Et	$N<^{Me}_{Me}$	61	73—74[g] Hex.	$C_{25}H_{37}N_3O_4$	67.69 (67.81	8.41 8.20	9.47 9.33)		
Vc-1	2-MePh	H	Me	$N<^{Me}_{Me}$	53	87—89 Hex.	*i*)					
Vc-2	2-MePh	H	Me	N⟨ ⟩O	59	135—136 Et_2O–Hex.	*i*)					
Ve-1	2-NO_2Ph	H	Me	$N<^{Me}_{Me}$	30[c]	Oil	*i*)					
Ve-2	2-NO_2Ph	H	Me	N⟨ ⟩O	55[d]	Oil	*i*)					
Vi-1	4-MeOPh	H	Me	$N<^{Me}_{Me}$	67[b]	210—211 (dec.) EtOH–Et_2O	$C_{24}H_{35}N_3O_5$ ·2HCl	54.65 (54.34	7.26 7.18	7.97 7.94	13.44[j] 13.57)	445
Vi-2	4-MeOPh	H	Me	N⟨ ⟩O	60	152—153 Tol.–Hex.	$C_{28}H_{39}N_3O_7$	63.49 (63.57	7.42 7.21	7.93 7.78)		529
Vj-1	4-NO_2Ph	H	Me	$N<^{Me}_{Me}$	25[b,e]	227 (dec.) EtOH–Et_2O	$C_{23}H_{32}N_4O_6$ ·2HCl	51.69 (51.89	6.60 6.59	10.48 10.24	13.27 13.37)	460
Vl-1	Ph	Me	Me	$N<^{Me}_{Me}$	64[b]	240 (dec.) MeOH–Et_2O	$C_{24}H_{35}N_3O_4$ ·2HCl	57.36 (57.41	7.42 7.42	8.36 8.04	14.11 14.20)	429
Vl-2	Ph	Me	Me	N⟨ ⟩O	73[b]	220 (dec.)[h] EtOH–H_2O	$C_{28}H_{39}N_3O_6$ ·2HCl	56.46 (56.64	7.10 7.15	7.06 6.77	11.91[j] 11.74)	513

a) Yield of pure compound.
b) Obtained as the 2HCl salt.
c) IVe-1 was also obtained, 31%.
d) IVe-2, 21%.
e) IVj-1, 35%. mp 124—125° (toluene–hexane), *Anal.* Calcd for $C_{20}H_{25}N_3O_6$: C, 59.54; H, 6.25; N, 10.42. Found: C, 59.96; H, 6.15; N, 9.95.
f) Tol.: toluene. Hex.: hexane.
g) 2HCl salt, mp 195—197° (EtOH–Et_2O), *Anal.* Calcd for $C_{25}H_{37}N_3O_4$. 2HCl: C, 58.14; H, 7.61; N, 8.14; Cl, 13.73. Found: C, 57.83; H, 7.42; N, 7.97; Cl, 13.79.
h) Base, mp 135—136° (toluene–hexane), *Anal.* Calcd for $C_{28}H_{39}N_3O_6$: C, 65.47; H, 7.65; N, 8.18. Found; C, 65.74; H, 7.80; N, 7.93.
i) See Table II.
j) Contains 1/2 H_2O.

and dimethylamine hydrochloride for 6 hr, small amounts of the tetrakis (dimethylaminomethyl) derivative (VII) and Va-1 were obtained. A large part of the remaining product was an oily substance, considered to be a tris (dimethylaminomethyl) derivative (VI) from its nuclear magnetic resonance (NMR), ultraviolet (UV) and mass spectra (MS).

In no case, however, was the N^1-(disubstituted aminomethyl) derivative or the amide compound obtained.

It was clear from the NMR that IV, V and VII are formed by replacement of one or more hydrogens at the 2- (and 6-) methyl groups by aminomethyl groups (Tables IV and V). All the starting materials, III, show their two methyl groups as a singlet signal in the 2.3 to 2.5 ppm (δ) region in the NMR spectra. The spectra of compounds IV show the signal of one methyl group at almost the same position as in the corresponding starting material, and morever, show the signals of two kinds of methylene protons at about 2.5 ($-CH_2\underline{CH_2}N=$) and 3.1 ppm ($-\underline{CH_2}CH_2N=$). The spectra of V show no 2- or 6-methyl signal, and instead, the

Table II. Yields and Physical Constants of IV and V obtained under Reaction Condition B[a]

Compd. No.	Ar	R_1	R_2	$N<^{R_3}_{R_3}$	Yield[b] (%)	mp (°C) Recrystn.[c] solvent	Formula	Analysis (%) Calcd (Found) C	H	N	Cl
IVc-1	2-MePh	H	Me	$N<^{Me}_{Me}$	35	131—134 Et_2O–Hex.	$C_{21}H_{28}N_2O_4$	67.72 (67.58	7.58 7.81	7.52 7.28)	
Vc-1	2-MePh	H	Me	$N<^{Me}_{Me}$	7	87—89 Hex.	$C_{24}H_{35}N_3O_4$	67.10 (67.32	8.21 8.15	9.78 9.76)	
IVc-2	2-MePh	H	Me		38	207—209 EtOH	$C_{23}H_{30}N_2O_5$	66.64 (66.36	7.30 7.21	6.76 6.55)	
Vc-2	2-MePh	H	Me		8	135—136 Et_2O–Hex.	$C_{28}H_{39}N_3O_6$	65.47 (65.72	7.65 7.88	8.18 8.02)	
IVe-1	2-NO_2Ph	H	Me	$N<^{Me}_{Me}$	26	148—150 EtOH–H_2O	$C_{20}H_{25}N_3O_6$	59.54 (59.75	6.25 6.41	10.42 10.38)	
Ve-1	2-NO_2Ph	H	Me	$N<^{Me}_{Me}$	8	109—110 Et_2O–Hex.	$C_{23}H_{32}N_4O_6$	59.98 (60.38	7.00 7.15	12.17 11.91)	
IVe-2	2-NO_2Ph	H	Me		28	180—182 EtOH	$C_{22}H_{27}N_3O_7$	59.31 (59.25	6.11 6.18	9.43 9.38)	
Ve-2	2-NO_2Ph	H	Me		3	Oil	$C_{27}H_{36}N_4O_8$	58.58 (58.54	6.74 6.59	10.12[d] 10.16)	
IVf-1	2-ClPh	H	Me	$N<^{Me}_{Me}$	29	145—149 EtOH–H_2O	$C_{20}H_{25}ClN_2O_4$	61.14 (61.38	6.41 6.40	7.13 7.08	9.02 8.93)
Vf-1	2-ClPh	H	Me	$N<^{Me}_{Me}$	27	Oil	$C_{23}H_{32}ClN_3O_4$	60.19 (60.31	7.25 7.37	9.15 9.10	7.72[d] 7.87)
IVh-5	3-NO_2Ph	H	Et		19	196—198 EtOH	$C_{37}H_{42}N_4O_6$	69.57 (69.26	6.63 6.56	8.77 8.81)	
Vh-5	3-NO_2Ph	H	Et		9	157—158 $CHCl_3$–EtOH	$C_{55}H_{62}N_6O_6$	73.15 (73.29	6.92 6.95	9.31 9.10)	

a) Each pair of IV and V was obtained in a single experiment.
b) Yield for pure compound.
c) Hex.: hexane.
d) Contains 1/2 H_2O.

signals of two kinds of methylene protons are observed in the same region as those of IV. The methine and methylene protons of VII appear at 4.45 and 2.40—2.70 ppm, respectively, as multiplet signals.

The signals of the two kinds of methylene protons of IV and V are split in a complicated manner and there was no example of a pair of mirror image signals (A_2B_2 or A_2X_2 system). Those of the methylene and methine protons of VII are also complicated. The signal of methine protons of VII appears to be a quintet, but in fact consists of 8 signals. Apparently, they are the X part of an ABX system and all of them are further split into a triplet by a C_2X system ($J_{AX}=J_{CX}=6.5$ Hz, $J_{BX}=8.0$ Hz). These splitting features indicate that the geminal protons at the methylene carbons are not necessarily equivalent. This non-equivalency is probably due to restricted rotation of aminoethyl or diaminopropyl groups owing to steric hindrance and/or hydrogen bonding with N^1-hydrogen.

It is known that an α-methyl group of picoline derivatives undergoes the Mannich reaction easily.[7] It was confirmed by NMR, UV and infrared (IR) spectroscopy that IV, V and VII are dihydropyridine derivatives and not dehydrogenated pyridine derivatives (Table VI).

The NMR spectra of III show signals corresponding to the protons of the 4- and 1-positions at about 5 and 6 ppm, respectively. In the spectra of IV, V and VII, the signals of the same

7) F.F. Blicke, "Organic Reactions," Vol. 1, ed. by R. Adams, John Wiley and Sons, Inc., New York, 1942, p. 312.

TABLE III. Yields and Physical Constants of IV obtained under Reaction Condition B[a]

Compd. No.	Ar	R_1	R_2	$N<^{R_3}_{R_3}$ [b]	Yield[c] (%)	mp (°C) Recrystn.[f] solvent	Formula	Analysis (%) Calcd (Found) C	H	N	Cl
IVa-1	Ph	H	Me	$N<^{Me}_{Me}$	17[d]	141—143 AcOEt	$C_{20}H_{26}N_2O_4$	67.02 (67.22	7.31 7.36	7.82 7.79)	
IVa-2	Ph	H	Me	N⟨O⟩	26[d]	198—201 EtOH	$C_{22}H_{28}N_2O_5$	65.98 (65.85	7.05 6.99	7.00 6.87)	
IVd-3	2-MePh	H	Et	N⟨NMe⟩	14	203—205 $CHCl_3$–EtOH	$C_{26}H_{37}N_3O_4$	68.54 (68.41	8.19 8.56	9.22 9.08)	
IVd-4	2-MePh	H	Et	N⟨NPh⟩	11	212—215 $CHCl_3$–AcOEt	$C_{29}H_{35}N_3O_4$	71.14 (71.28	7.21 7.47	8.58 8.47)	
IVe-3	2-NO_2Ph	H	Me	N⟨NMe⟩	17	213—216 EtOH–H_2O	$C_{23}H_{30}N_4O_6$	60.25 (59.97	6.60 6.59	12.22 12.13)	
IVe-4	2-NO_2Ph	H	Me	N⟨NPh⟩	16	215—218 $CHCl_3$–EtOH	$C_{28}H_{32}N_4O_6$	64.60 (64.41	6.20 6.16	10.76 10.77)	
IVe-5	2-NO_2Ph	H	Me	N⟨NCHPh$_2$⟩	17	228—230 (dec.) $CHCl_3$–EtOH	$C_{35}H_{38}N_4O_6$	68.83 (68.89	6.27 6.60	9.18 9.00)	
IVe-6	2-NO_2Ph	H	Me	N⟨N–TMB⟩	19	180—183 $CHCl_3$–EtOH	$C_{32}H_{40}N_4O_9$	61.52 (61.59	6.45 6.60	8.97 8.96)	
IVf-2	2-ClPh	H	Me	N⟨O⟩	18	211—215 EtOH	$C_{22}H_{27}ClN_2O_5$	60.76 (60.45	6.26 6.48	6.44 6.42	8.15 7.88)
IVg-3	2-ClPh	H	Et	N⟨NMe⟩	19	211—213 $CHCl_3$–EtOH	$C_{25}H_{34}ClN_3O_4$	63.08 (63.34	7.20 7.26	8.83 8.72	7.45 7.67)
IVg-4	2-ClPh	H	Et	N⟨NPh⟩	16	214—215 $CHCl_3$–EtOH	$C_{30}H_{36}ClN_3O_4$	66.96 (66.72	6.74 6.75	7.81 7.64	6.59 6.86)
IVh-3	3-NO_2Ph	H	Et	N⟨NMe⟩	30	184—185 EtOH	$C_{25}H_{34}N_4O_6$	61.71 (61.57	7.04 7.18	11.52 11.46)	
IVh-4	3-NO_2Ph	H	Et	N⟨NPh⟩	20	187—189 $CHCl_3$–EtOH	$C_{30}H_{36}N_4O_6$	65.57 (65.18	6.61 6.57	10.21 9.99)	
IVh-6	3-NO_2Ph	H	Et	N⟨N–TMB⟩	31[e]	173—174 (dec.) $CHCl_3$–Et_2O	$C_{34}H_{44}N_4O_9$ ·2HCl	56.28 (56.34	6.39 6.20	7.72 7.47	9.77 9.49)
IVj-3	4-NO_2Ph	H	Me	N⟨NMe⟩	30	181—182 EtOH–H_2O	$C_{23}H_{30}N_4O_6$	60.25 (60.20	6.60 6.79	12.22 12.43)	
IVj-4	4-NO_2Ph	H	Me	N⟨NPh⟩	25	177—179 $CHCl_3$–EtOH	$C_{28}H_{32}N_4O_6$	64.60 (64.32	6.20 6.31	10.76 10.51)	
IVj-5	4-NO_2Ph	H	Me	N⟨NCHPh$_2$⟩	22	170—172 $CHCl_3$–EtOH	$C_{35}H_{38}N_4O_6$	68.83 (68.75	6.27 6.03	9.18 8.94)	
IVj-6	4-NO_2Ph	H	Me	N⟨N–TMB⟩	34[e]	219—222 (dec.) $CHCl_3$–EtOH	$C_{32}H_{40}N_4O_9$ ·2HCl	55.10 (54.98	6.07 6.07	8.03 8.35	10.16 10.29)
IVk-1	2,4-Cl_2Ph	H	Me	$N<^{Me}_{Me}$	26	164.5—166.5 EtOH–H_2O	$C_{20}H_{24}Cl_2N_2O_4$	56.22 (56.23	5.66 5.38	6.56 6.45	16.59 16.82)
IVl-1	Ph	Me	Me	$N<^{Me}_{Me}$	29[d]	123—125 EtOH–H_2O	$C_{21}H_{28}N_2O_4$	67.72 (67.89	7.58 7.75	7.52 7.33)	
IVl-2	Ph	Me	Me	N⟨O⟩	12[d]	132—134 EtOH–H_2O	$C_{23}H_{30}N_2O_5$	66.64 (66.45	7.30 7.30	6.76 6.73)	
IVm-1	2-Furyl	H	Me	$N<^{Me}_{Me}$	6	139—143 EtOH–H_2O	$C_{18}H_{24}N_2O_5$	62.05 (61.98	6.94 6.79	8.04 7.80)	
IVm-2	2-Furyl	H	Me	N⟨O⟩	19	138—139 Et_2O–Hex.	$C_{20}H_{26}N_2O_6$	61.52 (61.40	6.71 6.86	7.18 6.92)	

a) Fractions containing V were discarded.
b) TMB: 2,3,4-trimethoxybenzyl.
c) Yield of pure compound.
d) Formaline was used instead of paraformaldehyde.
e) 2HCl salt.
f) Hex.: hexane.

Table IV. NMR Data[a] for III

Compd. No.	Ar	R_1	R_2	R_1	2,6-Me	4-H	R_2	Arom.	Other
IIIa	Ph	H	Me	6.03 s 1H	2.32 s 6H	5.03 s 1H	3.67 s 6H	7.27 s 5H	—
IIIb	Ph	H	Et	6.17 s 1H	2.30 s 6H	5.03 s 1H	1.22 t 6H 4.12 q 4H	7.00—7.50 m 5H	—
IIIi	4-MeOPh	H	Me	6.03 s 1H	2.33 s 6H	5.00 s 1H	3.68 s 6H	6.78 d[b] 7.23 d 4H	3.78 s[c] 3H
IIIj	4-NO_2Ph	H	Me	6.13 s 1H	2.38 s 6H	5.15 s 1H	3.68 s 6H	7.50 d[b] 8.17 d 4H	—
IIIl	Ph	Me	Me	3.17 s 3H	2.48 s 6H	6.18 s 1H	3.72 s 6H	7.20 s 5H	—

a) δ in ppm. 60 MHz, $CDCl_3$ solution, with TMS as an internal standard.
b) An AA'BB' system appears as two doublets and the δ values of the centers of the AA' and BB' parts are shown.
c) MeO.

Table V. NMR Data[a] for IV and V

Compd. No.	R_1	$-CH_2CH_2N=$	6-Me	4-H	R_2	Arom.	Others
IVa-1	9.97 s 1H	2.50—2.70m 2.70—3.45m 4H	2.30 s 3H	5.03 s 1H	3.63 s 3.65 s 6H	7.08—7.40m 5H	2.32 s[e] 6H
IVj-1	10.25 s 1H	2.50—2.70m 2.70—3.45m 4H	2.31 s 3H	5.12 s 1H	3.62 s 3.64 s 6H	7.42 d[d] 8.05 d 4H	2.34 s[e] 6H
IVl-1	3.20 s 3H	2.38—2.54m[c] 3.04—3.18m 4H	2.45 s[c] 3H	5.14 s 1H	3.70 s 6H	7.14 s 5H	2.28 s[e] 6H
Va-1	10.18 s 1H	2.45—2.75m 2.75—3.20m 8H	—	5.01 s 1H	3.63 s 6H	7.00—7.40m 5H	2.31 s[e] 12H
Va-2[b]	9.72 s 1H	2.40—3.27m[c]	—	5.05 s 1H	3.67 s 6H	7.27 s 5H	2.40—2.83m[c,f] 3.63—3.97m[c,f]
Vb-1	10.09 s 1H	2.40—2.70m 2.85—3.20m 8H	—	5.00 s 1H	1.22 t 6H 4.08 q 4H	7.02—7.40m 5H	2.31 s[e] 12H
Vc-1[b]	10.30 s 1H	2.33—2.80m[c] 2.83—3.20m 8H	—	5.02 s 1H	3.62 s 6H	7.00—7.57m 4H	2.33 s[e] 12H 2.53 s[g] 3H
Vc-2[b]	9.85 s 1H	2.43—3.52m[c]	—	5.02 s 1H	3.63 s 6H	7.00—7.57m 4H	2.43—2.83m[c,f] 3.50—4.00m[f] 2.50—2.83[c,g]
Vf-1	10.17 s 1H	2.45—2.70m 2.96 t 8H (J=6.5 Hz)	—	5.40 s 1H	3.58 s 6H	6.95—7.48m 4H	2.30 s[e] 12H
Vi-1[b]	10.13 s 1H	2.46—2.70m 2.88—3.12m 8H	—	4.94 s 1H	3.64 s 6H	6.75 d[d] 7.19 d 4H	2.32 s 12H 3.76 s[h] 3H
Vi-2[b]	9.70 s 1H	2.40—3.27m[c]	—	5.00 s 1H	3.67 s[c] 6H	6.80 d[d] 7.27 d 4H	2.40—2.83m[c,f] 3.58—3.90m[c,f] 3.80 s[h] 3H

Compd. No.	R_1	$-CH_2CH_2N=$	6-Me	4-H	R_2	Arom.	Others
Vj-1	10.44 s 1H	2.40—2.70m 2.90—3.10m 8H	—	5.12 s 1H	3.64 s 6H	7.45 d[d] 8.09 d 4H	2.32 s[e] 12H
Vl-1	3.26 s 1H	2.47 t (J=7.5 Hz) 2.80—3.50m[c] 8H	—	5.14 s 1H	3.73 s 6H	7.17 s 5H	2.30 s[e] 12H
Vl-2	3.31 s 3H	2.42—2.70m[c] 2.90—3.31m 8H	—	5.16 s 1H	3.74 s 6H	7.17 s 5H	2.42—2.70m[c,f] 3.64—3.84m[c,f]

a) δ in ppm. 100 MHz except *b*), $CDCl_3$ solution of the free base, with TMS as an internal standard.
b) 60 MHz.
c) Overlapped with other signals. The number of protons is consistent with the structure as a whole.
d) An AA'BB' system appears as two doublets and the δ values of the centers of the AA' and BB' parts are shown.
e) NMe_2. *f*) N O. *g*) 2'-Me. *h*) MeO.

TABLE VI. UV Absorption Data for III, IV, V, VII and VIII

Compd. No.	λ_{max}^{EtOH} nm (log ε)
IIIa	238(4.27), 354(3.86)
IIIi	223(4.33), 276(3.64), 285(3.60), 358(4.02)
IIIj	234(4.32), 282(4.13)
IIIl	242(4.18), 347(3.82)
IVa-1	241(4.28), 356(3.86)
IVj-1	237(4.31), 282(4.14)
Va-1	242(4.28), 356(3.84)
Va-2	242(4.26), 356(3.81)
Vc-1	245(4.28), 359(3.88)
Vc-2	245(4.28), 359(3.88)
Vi-1	242[a](4.22), 278[a](3.72), 359(3.84)
Vl-1	248(4.23), 342(3.84)
Vl-2	247(4.27), 343(3.88)
VII	243(4.27), 358(3.83)
VIIIa	272[a](3.68)
VIIIj	273[a](4.18)

a) Shoulder.

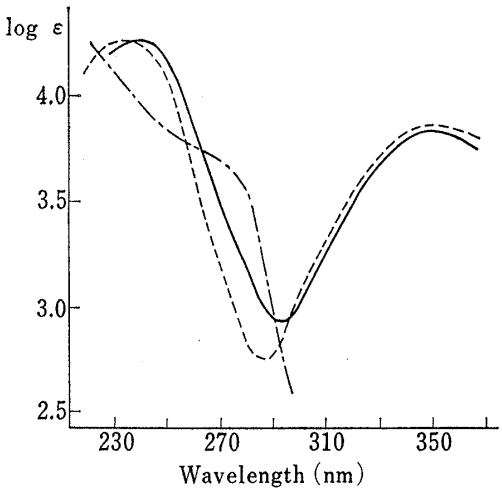

Fig. 1. UV Spectra of IIIa, Va-1 and VIIIa in EtOH

--------IIIa. ————Va-1. - - - - - -VIIIa.
The spectra of IVa-1 and VII are almost superimposable on that of Va-1.

protons appear at about 5 and 10 ppm, respectively. In the case of the 1-methyl derivatives, the spectra of the starting materials, III, and the products, IV and V, both show the signal of 1-methyl protons at about 3 ppm.

The UV spectra of IVa-1, Va-1 and VII, for example, show two absorption maxima at around 242 and 356 nm and are almost superimposable. The spectrum of IIIa also shows maxima at 238 and 354 nm and is very similar to those of IVa-1, Va-1 and VII. In contrast, those of the pyridine derivatives, VIII, have no absorption maximum and are quite different from those of III, IV, V and VII (Fig. 1).

Most of the C=O stretching vibrations of III, IV, V and VII are observed near 1680 cm^{-1}, and those of VIII at 1720 cm^{-1} (KBr disk). The lower IR frequencies of ester groups in 1,4-dihydropyridine-3,5-dicarboxylates compared to those of pyridine-3,5-dicarboxylates are well known.[8]

8) U. Eisner and J. Kuthan, *Chem. Rev.*, **72**, 1 (1972).

These spectral data support the structures of IV, V and VII shown in Chart 1. Some of these compounds appeared to have interesting pharmacological activities.

Experimental

Melting points are uncorrected. NMR spectra at 100 MHz were recorded with a Varian HA-100D spectrometer, and at 60 MHz with a Varian EM-360A spectrometer in $CDCl_3$ solution using tetramethylsilane as an internal standard. UV spectra were measured with a Shimadzu MPS-5000 spectrometer. IR spectra were recorded with a Hitachi 215 spectrophotometer. MS were recorded with a Hitachi RM-61 spectrometer.

Dialkyl 4-Aryl-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylates (IIIa—m)——Compounds IIIa—m were prepared by means of the "Hantzch synthesis."[9] The melting points of the known compounds were coincident with those in the literature. Ar, R_1 and R_2 of the reported compounds among compounds III are shown below. Ph, H, Me(IIIa);[10] Ph, H, Et(IIIb);[11] 2-MePh, H, Et(IIId);[12] 2-NO_2Ph, H, Me(IIIe);[13] 2-ClPh, H, Et(IIIg);[12] 3-NO_2Ph, H, Et(IIIh);[14] 4-NO_2Ph, H, Me(IIIj);[13] 2-furyl, H, Me(IIIm).[12] New compounds are as follows. Dimethyl 1,4-dihydro-2,6-dimethyl-4-(2-methylphenyl)pyridine-3,5-dicarboxylate (IIIc), mp 184—185° (MeOH). *Anal.* Calcd for $C_{18}H_{21}NO_4$: C, 68.55; H, 6.71; N, 4.44. Found: C, 68.44; H, 6.84; N, 4.24. Dimethyl 4-(2-chlorophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (IIIf), mp 190—192° (MeOH). *Anal.* Calcd for $C_{17}H_{18}ClNO_4$: C, 60.81; H, 5.40; Cl, 10.56; N, 4.17. Found: C, 60.81; H, 5.34; Cl, 10.80; N, 4.06. Dimethyl 1,4-dihydro-4-(4-methoxyphenyl)-2,6-dimethylpyridine-3,5-dicarboxylate (IIIi), mp 190—192° (MeOH). *Anal.* Calcd for $C_{18}H_{21}NO_5$: C, 65.24; H, 6.39; N, 4.23. Found: C, 65.15; H, 6.27; N, 4.12. Dimethyl 4-(2,4-dichlorophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (IIIk), mp 190—192.5° (MeOH). *Anal.* Calcd for $C_{17}H_{17}Cl_2NO_4$: C, 55.15; H, 4.63; Cl, 19.15; N, 3.78. Found: C, 55.03; H, 4.55; Cl, 19.46; N, 3.85. Dimethyl 1,4-dihydro-1,2,6-trimethyl-4-phenylpyridine-3,5-dicarboxylate (IIIl), mp 202.5—204.5° ($CHCl_3$–Et_2O). *Anal.* Calcd for $C_{18}H_{21}NO_4$: C, 68.55; H, 6.71; N, 4.44. Found: C, 68.63; H, 6.68; N, 4.61.

Mannich Reaction——Representative examples are shown below.

Reaction Condition A: A mixture of 3.0 g (0.01 mol) of IIIa, 1.49 g (0.05 eq) of paraformaldehyde, 4.06 g (0.05 mol) of dimethylamine hydrochloride, a few drops of conc. HCl and 30 ml of EtOH was heated under reflux for 18 hr. After removal of the solvent by evaporation *in vacuo*, H_2O was added, and the resulting solution was made alkaline with aq. Na_2CO_3 then extracted with $CHCl_3$. The $CHCl_3$ layer was washed with satd. NaCl solution, and dried over Na_2SO_4. After removal of the solvent *in vacuo*, 4.7 g of oily residue was obtained. The residue was converted to the HCl salt with EtOH–HCl and the crystalline salt was filtered off. This crude product (4.2 g) was recrystallized from EtOH–Et_2O to give 3.8 g (78%) of dimethyl 2,6-bis(2-dimethylaminoethyl)-1,4-dihydro-4-phenylpyridine-3,5-dicarboxylate (Va-1) dihydrochloride as a colorless powder. mp 213—213.5° (dec.). IR $\nu_{C=O}^{KBr}$ 1680 cm^{-1}.

Reaction Condition B: A mixture of 2.8 g (9.3 mmol) of IIIc, 0.59 g (19.7 meq) of paraformaldehyde, 1.59 g (19.5 mmol) of dimethylamine hydrochloride, a few drops of conc. HCl and 20 ml of EtOH was heated under reflux for 16 hr. After removal of the solvent *in vacuo*, H_2O was added and the resulting aq. solution was extracted with $CHCl_3$. The $CHCl_3$ layer was extracted again with 10% HCl, washed with 10% aq. Na_2CO_3 and satd. NaCl solution, then dried over Na_2SO_4. $CHCl_3$ was evaporated off *in vacuo*, and the resulting oily substance (2.5 g) was chromatographed on silica gel (silica gel 60, Merck) using $CHCl_3$ and then $CHCl_3$–MeOH (1: 1) as eluents. Starting material, IIIc, was obtained from the $CHCl_3$ eluate (0.1 g, 4%, mp 182—184°), and the crude crystals from the $CHCl_3$–MeOH eluate were recrystallized from Et_2O–hexane to give 1.17 g (35%) of dimethyl 2-(2-dimethylaminoethyl)-1,4-dihydro-6-methyl-4-(2-methylphenyl)-pyridine-3,5-dicarboxylate (IVc—l). mp 131—134°. IR $\nu_{C=O}^{KBr}$ 1680 cm^{-1}. The acidic layers mentioned above were combined and made alkaline with aq. Na_2CO_3, then the oily layer which separated out was extracted with $CHCl_3$. The crude crystals (0.9 g) obtained from the $CHCl_3$ extract were recrystallized from hexane to give 0.28 g (7%) of dimethyl 2,6-bis(2-dimethylaminoethyl)-1,4-dihydro-4-(2-methylphenyl)-pyridine-3,5-dicarboxylate (Vc—l). mp 87—89°. IR $\nu_{C=O}^{KBr}$ 1680 (shoulder), 1670 cm^{-1}.

Dimethyl 2,6-Bis[2-dimethylamino-1-(dimethylaminomethyl)ethyl]-1,4-dihydro-4-phenylpyridine-3,5-dicarboxylate (VII)——A mixture of 3.0 g (0.01 mol) of IIIa, 1.79 g (0.06 eq) of paraformaldehyde, 4.87 g

9) A. Hantzch, *Ann.*, **215**, 72 (1882); F. Brody and P.R. Ruby, "The Chemistry of Heterocyclic Compounds, Pyridine and Its Derivatives," Part I, ed. by E. Klinsberg, Interscience Publishers, Inc., New York, 1960, p. 500.
10) A.P. Phillips, *J. Am. Chem. Soc.*, **71**, 4003 (1949).
11) L.E. Hinkel and D.H. Hey, *Rec. Trav. Chim. Pays-Bas*, **48**, 1280 (1929).
12) B. Loev, M.M. Goodman, K.M. Snader, R. Tedesch, and E. Macko, *J. Med. Chem.*, **17**, 956 (1974).
13) F. Bossert and W. Vater, S. Africa Patent 6801482 (1968) [*C.A.*, **70**, 96641^d (1969)].
14) R. Leptit, *Chem. Ber.*, **20**, 1338 (1887).

(0.06 mol) of dimethylamine hydrochloride and 20 ml of dioxane was boiled for 6 hr. After removal of the solvent *in vacuo*, H_2O was added and the resulting solution was made alkaline with aq. Na_2CO_3. The oily substance which separated out was extracted with $CHCl_3$. The $CHCl_3$ layer was washed with satd. NaCl solution, dried over Na_2SO_4 and concentrated *in vacuo* to give an oily residue. After adding hexane to the residue, 0.62 g of crystals was filtered off. Recrystallization from hexane gave 0.39 g (7%) of VII as colorless needles. mp 121—123°. *Anal.* Calcd for $C_{29}H_{47}N_5O_4$: C, 65.75; H, 8.94; N, 13.22. Found: C, 66.00; H, 8.61, N, 13.06. NMR (δ): 2.26, 2.28 (24H in two singlet peaks, NMe_2); 2.30—2.76 (8H, m, $-CHC\underline{H}_2N=$); 3.64 (6H, s, $COO\underline{Me}$); 4.42 (2H, broad quintet, $=C\underline{H}CH_2N=$); 5.08 (1H, s, 4-H); 7.10—7.50 (5H, m, Ph); 10.28 (1H, s, NH). MS *m/e*: 529 (M^+); 471 ($M^+ - CH_2=\overset{+}{N}Me_2$); 452 ($M^+ - Ph$); 426 ($471 - Me_2NH$); 58 ($CH_2=\overset{+}{N}Me_2$). IR $\nu_{C=O}^{KBr}$ 1680 cm^{-1}. The hexane filtrate and the mother liquor of recrystallization were combined and the mixture was concentrated *in vacuo* to give 4.9 g of an oily residue. The oil was chromatographed over aluminium oxide (neutral alumina, Woelm) using AcOEt as an eluent. Another crop of VII (0.52 g, 10%), 2.43 g (52%) of an oily compound, and (after conversion to the HCl salt) 0.20 g (4%) of crystalline Va—l dihydrochloride were obtained. The oily compound gave the following spectral data. NMR (δ): 2.24, 2.27, 2.35 (18H in three singlet peaks, NMe_2); 2.30—2.70 (m, $-CH_2C\underline{H}_2N=$); 3.00—3.18 (2H, m, $-C\underline{H}_2CH_2N=$); 3.62, 3.65 (6H in two singlet peaks, COOMe); 4.61 (1H, quintet, $J=7.3$ Hz, $=C\underline{H}CH_2N=$); 5.04 (1H, s, 4-H); 7.05—7.50 (5H, m, Ph); 10.15 (1H, s, NH). MS *m/e*: 472 (M^+); 414 ($M^+ - CH_2=NMe_2$); 395 ($M^+ - Ph$); 369 ($414 - Me_2NH$); 58 ($CH_2=N^+Me_2$). IR $\nu_{C=O}^{neat}$ 1680 cm^{-1}.

Dimethyl 2,6-Dimethyl-4-(4-nitrophenyl)pyridine-3,5-dicarboxylate (VIIIj)——A suspension of IIIj (8.0 g) in 60 ml of H_2O was treated with 8 ml of conc. HNO_3 followed by $NaNO_2$ solution (5 g in 20 ml H_2O) from a dropping funnel under ice cooling, and the reaction mixture was heated at 80—90° for 1 hr. After cooling, the reaction mixture was made alkaline with Na_2CO_3. The precipitated crystals were collected by filtration and washed with H_2O. Recrystallization from MeOH gave 5.8 g of VIIIj. mp 149—150°. *Anal.* Calcd for $C_{17}H_{16}N_2O_6$: C, 59.30; H, 4.68; N, 8.14. Found: C, 59.28; H, 4.69; N, 8.25. IR $\nu_{C=O}^{KBr}$ 1720 cm^{-1}. Compound VIIIa was obtained by the same procedures as VIIIj. mp 135.5—137.5° (MeOH). (literature;[15] mp 139—140°).

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15) L. Kirchner, *Chem. Ber.*, **25**, 2788 (1892).