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Mannich Reaction of Dihydropyridine Derivatives. II.[1] Reaction with Primary Amines[2]

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Dialkyl 4-aryl-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylates (I) were subjected to the Mannich reaction with excess paraformaldehyde and primary amine in ethanolic solution. Novel ring-system compounds, dialkyl *t*-6-aryl-1*H*,6*H*-2,3,6a,7,8,9-hexahydro-2,3a,8-triazaphenalene-5,*r*-6a-dicarboxylate derivatives (III), and some intermediary products were obtained stereoselectively. The reaction pathway and the stereochemistry of these products are discussed.

Keywords——dihydropyridinedicarboxylic acid; Mannich reaction; 1*H*,6*H*-2,3,6a,7,-8,9-hexahydro-2,3a,8-triazaphenalene-5,6a-dicarboxylic acid; 1,4,4a,5,6,7-hexahydro-1,6-naphthyridine-3,4a-dicarboxylic acid; 1-oxo-1,2,3,4,5,7,8,9,9a,10-decahydropyrido[4,3-*b*]-[1,6]naphthyridine-9a-carboxylic acid

In the preceding paper, we reported the Mannich reaction of dialkyl 4-aryl-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylates (I) with secondary amines and found that the reaction proceeds on the 2- and 6-methyl carbons.[1] The investigation was extended to primary amines, and novel ring-system compounds, dialkyl *t*-6-aryl-1*H*,6*H*-2,3,6a,7,8,9-hexahydro-2,3a,8-triazaphenalene-5,*r*-6a-dicarboxylate derivatives (III), and their intermediary products were obtained stereoselectively. In this paper, we describe the results of these experiments and discuss the reaction pathway and the stereochemistry of the products.

Reaction Products

Diethyl 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (Ib) was treated with a 5-fold molar excess of methylamine hydrochloride and a 10-fold molar excess of paraformaldehyde in boiling ethanol for 6 hr. From the basic fraction of the reaction mixture, light yellow crystals (IIIb-1), mp 148—150°, were obtained. Elemental analysis and mass (MS) spectroscopy of the compound gave the composition $C_{25}H_{33}N_3O_4$. When the quantities of the reagents were reduced to a 2.2- and a 3.5-fold molar excess, respectively, yellow crystals, $C_{24}H_{33}N_3O_4$ (IIb), mp 148—149°, were obtained with a small amount of IIIb-1. Treatment of the N-methyl derivative, dimethyl 1,2,6-trimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (Ig), with the quantities of the reagents used in the second case gave two kinds of yellow crystals, $C_{21}H_{26}N_2O_4$ (IVg), mp 171—173°, and $C_{22}H_{27}N_3O_3$ (V), mp 225—226° (dec.).

The infrared (IR) spectra (KBr) of the products, IIb, IIIb-1 and IVg, show two C=O stretching vibrations at about 1720 and 1680 cm^{-1}, indicating the presence of an unconjugated ester group as well as a conjugated one. That of V shows two absorption bands at 1710

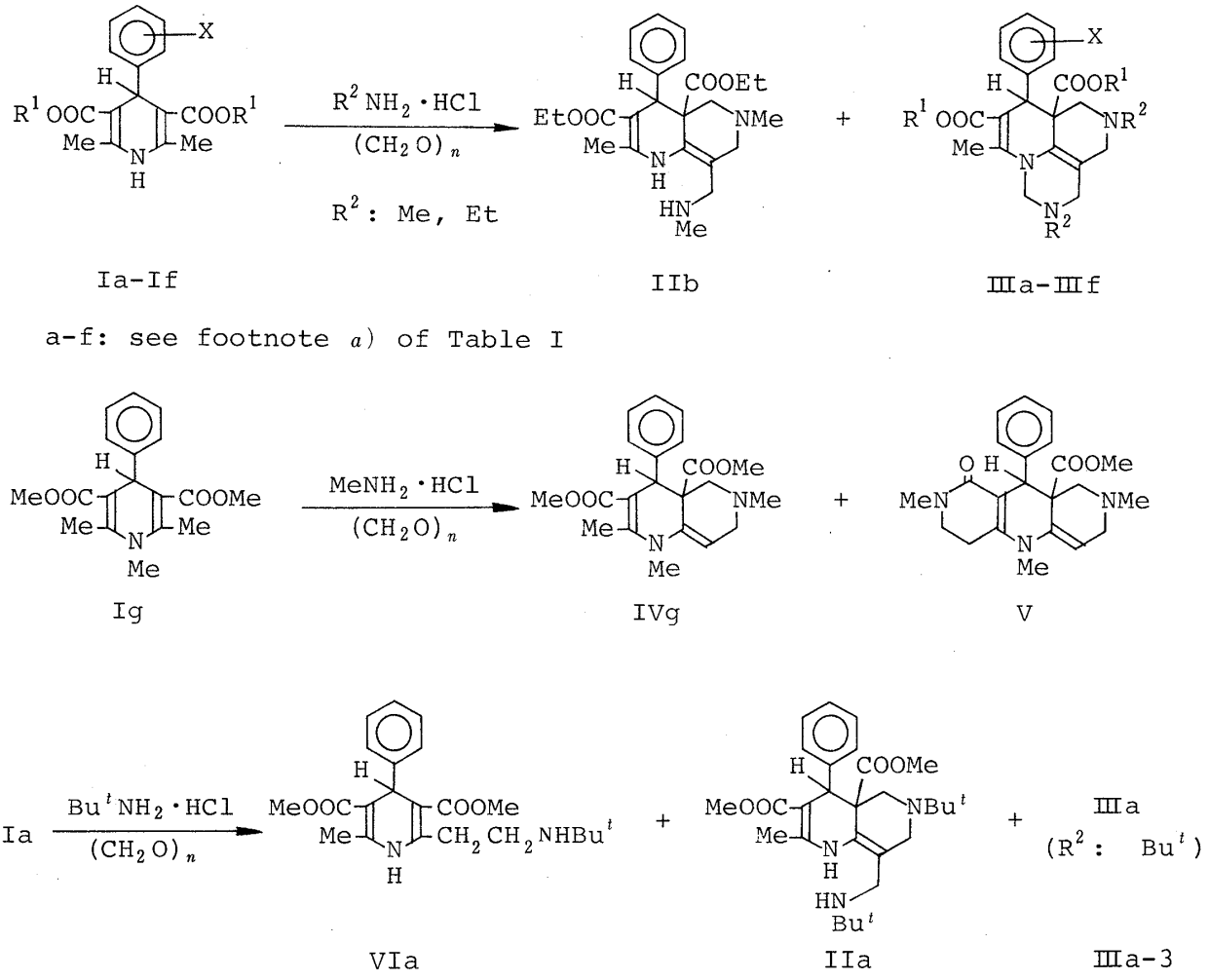

Chart 1

and 1605 cm^{-1} in this region, indicating the presence of only an unconjugated ester group. The ultraviolet (UV) spectra of these four products show an absorption maximum at about 320 nm and are quite different from those of the starting materials (about 240 and 350 nm).[1] These spectral data suggest that the products no longer have a 1,4-dihydropyridine skeleton and have an unconjugated ester group in their molecules.

The structures of these compounds were elucidated by nuclear magnetic resonance (NMR) spectroscopy (Fig. 1, Tables III and IV). The NMR spectra of IIb, IIIb-1 and IVg show that one of the two C-methyl groups of the starting materials is absent in the products and that the alkyl moieties of the two ester groups are not equivalent. The spectrum of V indicates that the two C-methyl groups and the alkyl residue of one of the two ester groups are lost. The protons of two new methyl groups are observed for IIb, IIIb-1 and V, and those of one methyl group are observed for IVg,; they were considered to be the protons of N-methyl groups on the basis of their chemical shifts and also the type of reaction.

Moreover, characteristically and suggestively, protons of four kinds of methylenes (A, B, C and D in increasing order of δ) are observed for IIIb-1 on its NMR spectrum. Protons of three kinds of methylenes (A, B and C) for IIb, protons of two kinds of methylenes (A and B) for IVg and V are also observed. The different kinds of signals are widely separated, and the geminal protons are all split into AB or AX pattern. The corresponding protons of A and B methylenes show almost the same δ values and coupling constants throughout the four compounds. The protons of C methylenes are also common to IIb and IIIb-1. These observations indicate that the four compounds have a common partial structure.

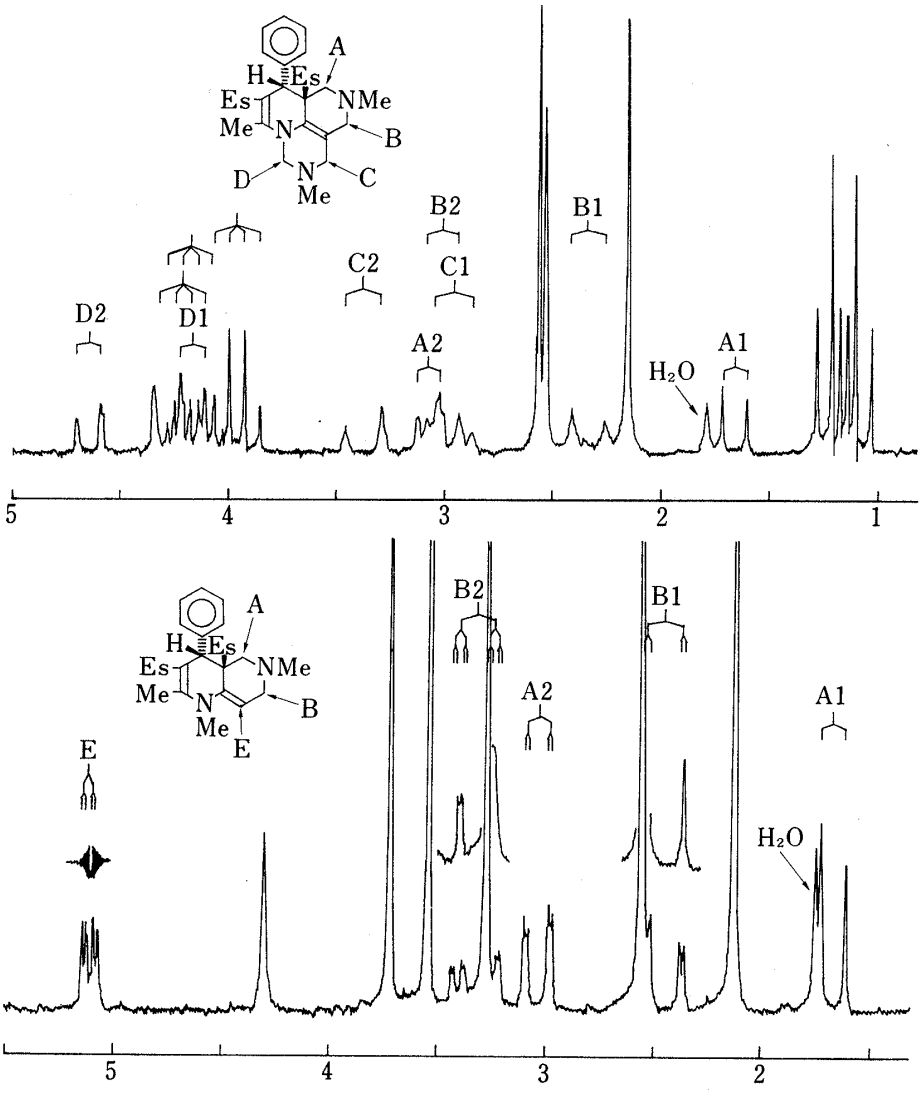

Fig. 1. NMR Spectra of IIIb-1 (above) and IVg (below)

Es: COOEt (IIIb-1), COOMe (IVg). In the case of IIIb-1, the geminal couplings in methylenes A–D were confirmed by proton decoupling or by the internuclear double resonance method.

The spectrum of IIb shows two NH protons at δ 9.18 and about 2.6 (ppm), while that of IIIb-1 shows no NH proton. From the differences in the number of methylenes and the molecular formulas of these two products, the structure having a methylene bridge between the two NH groups of IIb was inferred for IIIb-1. The difference of molecular formula between IIb and Ib is greater than that between IVg and Ig by one methylaminomethyl group. Though the spectrum of IIb does not show any olefinic proton, that of IVg shows one at δ 5.10. Thus, the structure constructed by replacement of the olefinic proton with a methylaminomethyl group was proposed for IIb.

In the Mannich reaction with secondary amines, the substitution occurs at the 2- (and 6-)methyl carbons.[1] The hydrogen atom on the 2-methyl carbon of Ig is presumably replaced by a methylaminomethyl group in a similar way. In this case, however, formaldehyde reacts further and a methylene bridge is formed between NH and the nucleophilic center of the enaminoester to give compound IVg. From the spectral data, the molecular formulas and the reaction pathway described below, the structures of IVg and other products were concluded to be as shown in Chart 1.

The Mannich reactions of seven 1,4-dihydropyridine derivatives (Ia—Ig) with methyl-

Table I. Reaction Conditions and Products

Sarting material[a,b]	$R^2NH_2 \cdot HCl$ R^2	(mol ratio)	Paraform-aldehyde (mol ratio)	Reflux time (hr)	Reaction product[c] and yield (%)[d]
Ia	Me	5	10	5	IIIa-1 49
Ia	Et	5	10	6	IIIa-2·2HCl·3/2H_2O 41
Ia	Bu^t	5	10	24	IIa 18[e] IIIa-3 1 VIa 4
Ib	Me	2.2	3.5	24	IIb 17[f] IIIb-1 5
Ib	Me	5	10	6	IIIb-1 50
Ib	Me	5	10+5[g]	4+1.5[g]	IIIb-1 43
Ib	Me	10	10	6	IIIb-1 46
Ib	Et	5	10	8	IIIb-2 31
Ic	Me	5	10	3	IIIc 54
Ic	Me	10	10	2	IIIc 41
Id	Me	5	10	24	IIId 58
Ie	Me	5	10	3.5	IIIe 52
If	Me	5	10	4	IIIf·2HCl·5/2H_2O 56
Ig[h]	Me	1.5	3	26	IVg 26[i] V 2

a) The R^1 and X substituents in I—VI (Chart 1) are as follows. a: Me, H; b: Et, H; c: Me, 4-MeO; d: Me, 4-NO_2; e: Me, 2-Me; f: Me, 2-NO_2.
b) In these experiments, 3.0 g of the starting materials was used with 30 ml of EtOH.
c) See Table II.
d) Isolated yield.
e) The starting material was recovered in a yield of 36%.
f) The starting material was recovered in a yield of 6%.
g) After reflux for 4 hr with a 10-fold molar excess of paraformaldehyde, an additio nal 5-fold molar excess of it was added and the reaction mixture was refluxed again for 1.5 hr.
h) A mixture of EtOH and $CHCl_3$ (1: 1) was used instead of EtOH.
i) The starting material was recovered in a yield of 12%.

Table II. Physical Data for II, III, IV and V

Compd. No.	R^{2a}	mp (°C) Recrystn. solvent	IR ν_{max}^{KBr} (cm^{-1})[b]	UV λ_{max}^{EtOH} (nm) (log ε)	Formula	Analysis (%) Calcd (Found) C	H	N	MS (*m/z*) M^+
IIa	—	158—160 Et_2O–Hex.	3250—3000 1720, 1680, 1580	320(4.35)	$C_{28}H_{41}N_3O_4$	69.53 (69.38	8.55 8.60	8.69 8.51)	483
IIb	—	148—149 EtOH–Hex.	3220, 1720, 1680 (sh.) 1665, 1565	318(4.37)	$C_{24}H_{33}N_3O_4$	67.42 (67.27	7.78 7.97	9.83 9.76)	427
IIIa-1	Me	193—196.5 EtOH	1720, 1685 (sh.) 1680, 1560	323(4.39)	$C_{23}H_{29}N_3O_4$	67.13 (67.10	7.10 7.20	10.21 10.17)	
IIIa-2	Et	126—129[c] EtOH–H_2O	1730, 1680, 1560	323(4.35)	$C_{25}H_{33}N_3O_4$	68.31 (68.47	7.57 7.61	9.56 9.71)	
IIIa-3	Bu^t	191—194 EtOH–H_2O	1720, 1670, 1550	326(4.40)	$C_{29}H_{41}N_3O_4$	70.27 (70.38	8.34 8.60	8.48 8.65)	495
IIIb-1	Me	148—150 EtOH	1735 (sh.) 1720, 1675, 1560	322(4.38)	$C_{25}H_{33}N_3O_4$	68.31 (68.49	7.57 7.55	9.56 9.51)	439
IIIb-2	Et	114—115 Hex.	1735, 1670, 1560	323(4.38)	$C_{27}H_{37}N_3O_4$	69.35 (69.14	7.98 7.91	8.99 8.82)	467
IIIc	Me	150—152 EtOH–Hex.	1720, 1660, 1600, 1550	226(4.12) 322(4.38)	$C_{24}H_{31}N_3O_5$	65.28 (65.14	7.08 7.29	9.52 9.35)	

Compd. No.	R[2a)]	mp (°C) Recrystn. solvent	IR ν_{max}^{KBr} (cm^{-1})[b)]	UV λ_{max}^{EtOH} (nm) (log ε)	Formula	Analysis (%) Calcd (Found) C	H	N	MS (*m/z*) M^+
IIId	Me	217—220 (dec.) EtOH	1720, 1685 (sh.) 1680, 1560		$C_{23}H_{28}N_4O_6$	60.51 (60.51	6.18 6.18	12.27 11.88)	
IIIe	Me	187.5—190.5 EtOH	1725, 1680 (sh.) 1675, 1560	321 (4.28)	$C_{24}H_{31}N_3O_4$	67.74 (67.78	7.34 7.07	9.88 9.66)	
IIIf	Me	165—166[d)] $CHCl_3$–Et_2O	1725, 1680, 1565, 1520		$C_{23}H_{28}N_4O_6$	60.51 (60.25	6.18 6.30	12.27 12.13)	
IVa[e)]	—	194—197 EtOH–Hex.	3310, 1720, 1685, 1580	317 (4.41)	$C_{23}H_{30}N_2O_4$	69.32 (69.09	7.59 7.77	7.03 7.10)	398
IVb[e)]	—	160—162 EtOH–H_2O	3310, 1710, 1680, 1580	316 (4.38)	$C_{22}H_{28}N_2O_4$	68.72 (68.89	7.34 7.51	7.29 7.06)	384
IVg	—	171—173 EtOH	1730, 1680, 1640, 1560	322 (4.40)	$C_{21}H_{26}N_2O_4$	68.09 (67.97	7.07 6.92	7.56 7.30)	370
V	—	225—226 (dec.) AcOEt	1710, 1630 (sh.) 1605	244 (3.78) 323 (4.30)	$C_{22}H_{27}N_3O_3$	69.27 (69.13	7.13 7.35	11.02 10.90)	381

a) See Chart 1.
b) Absorption bands in the ranges of 4000—3000 cm^{-1} and 1750—1500 cm^{-1} are shown.
c) HCl salt: mp 142° (dec.) (EtOH–Et_2O). *Anal.* Calcd for $C_{25}H_{33}N_3O_4 \cdot 2HCl \cdot 3/2H_2O$: C, 55.66; H, 7.10; N, 7.79; Cl, 13.14. Found: C, 55.55; H, 7.28; N, 7.66; Cl, 12.74. MS *m/z*: 439 (M^+).
d) HCl salt: mp 180—181° (dec.) (MeOH–Et_2O). *Anal.* Calcd for $C_{23}H_{28}N_4O_6 \cdot 2HCl \cdot 5/2\ H_2O$: C, 48.09; H, 6.14; N, 9.75; Cl, 12.34. Found: C, 47.75; H, 5.90; N, 9.54; Cl, 12.56. MS *m/z*: 456 (M^+).
e) Synthesized by an alternative method.

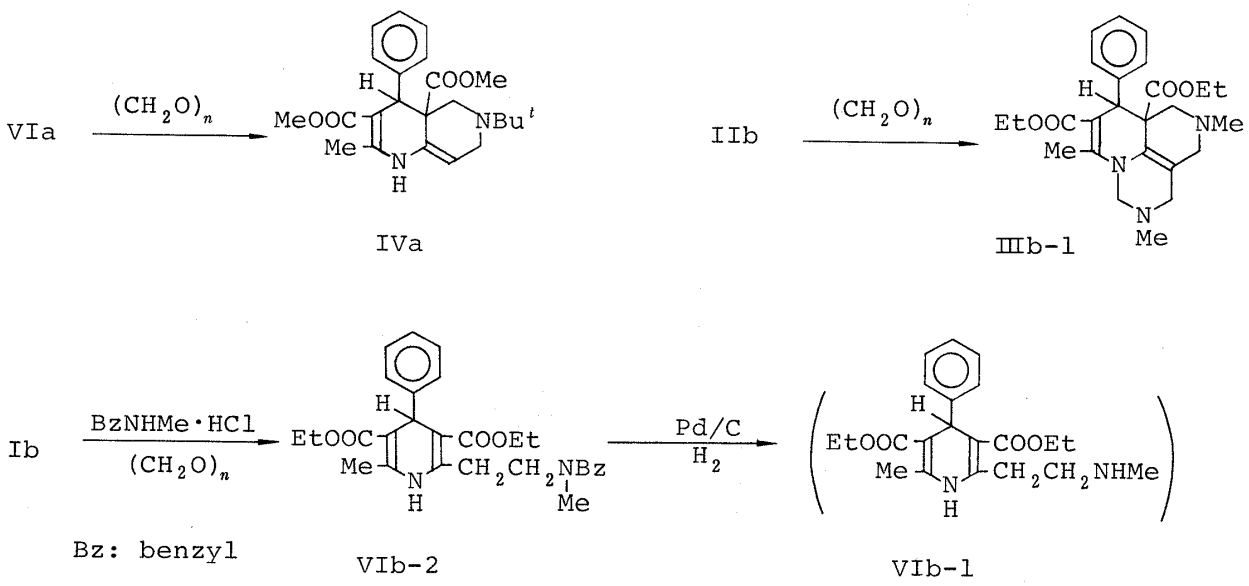

Chart 2

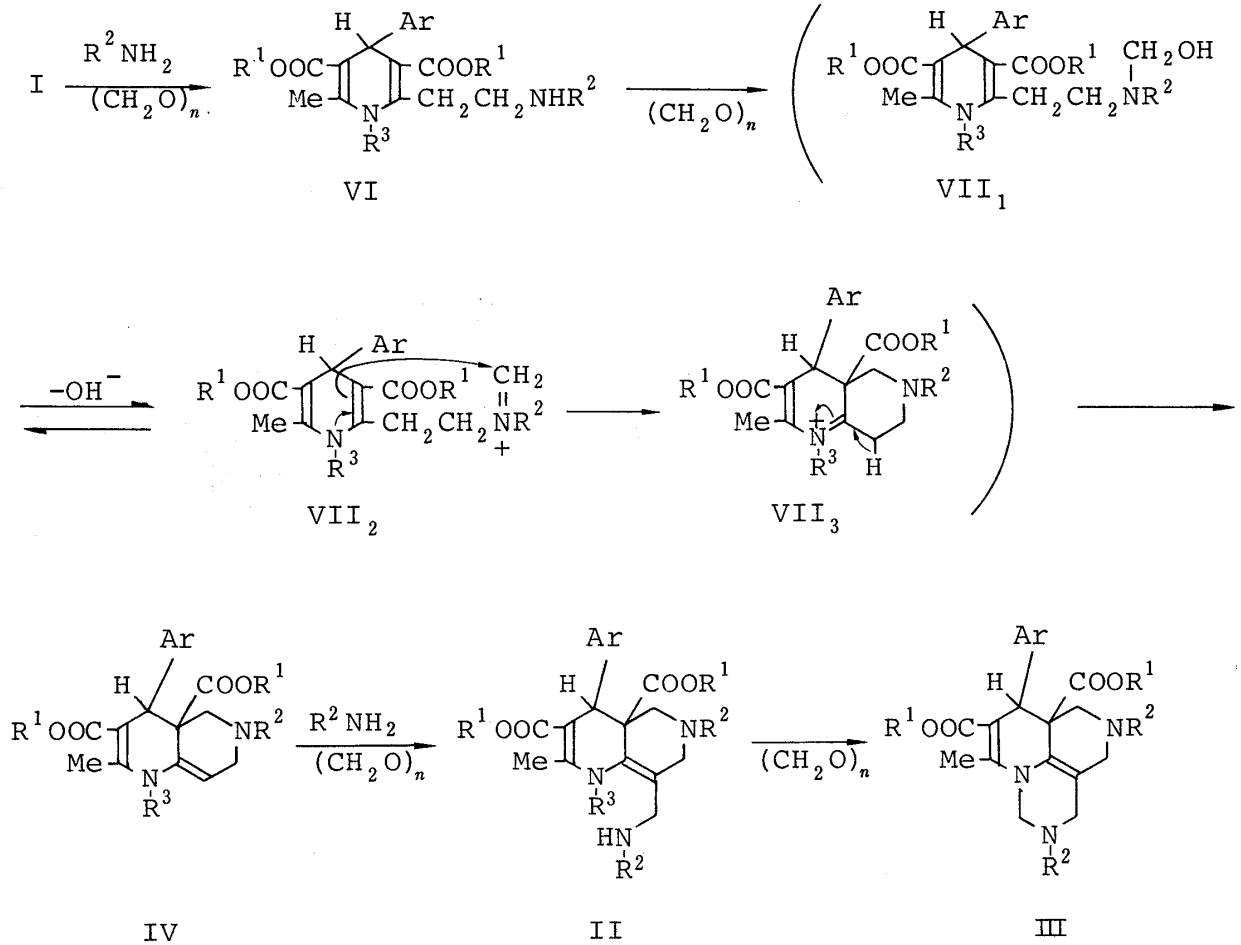

Chart 3

amine and ethylamine were examined similarly. In addition to non-crystallizable viscous substances, yellow crystals of III, IV and V were obtained (Tables I and II).

Reaction Pathway

The Mannich reaction of Ia with *tert*-butylamine hydrochloride gave IIa (18%), IIIa-3 (1%) and VIa (4%) with a recovery of Ia (36%) after 24 hours' boiling (Chart 1). Compound VIa was considered to be the intermediary product in the formation of IIa and IIIa-3, as described above. As expected, VIa was converted to the fused ring compound IVa by treatment with paraformaldehyde (Chart 2).

Compound VIb-1, synthesized by another route (Chart 2), was converted to IVb by treatment with paraformaldehyde. Compound IVb reacted further with the Mannich reagent to afford IIIb-1 and IIb. Moreover, IIb gave the tricyclic compound IIIb-1 on reaction with paraformaldehyde.

The reaction pathway and reaction mechanism may be as shown in Chart 3.

Stereochemistry of the Products

The following information was obtained from the NMR spectrum of IVg. The olefinic proton (E) is coupled with the two B methylene protons; the coupling constants are 2.0 Hz with the proton which resonates at higher magnetic field (B1) and 5.0 Hz with the one at lower field (B2) (Table III). This means that the dihedral angle between E and B2 is smaller than that between E and Bl.[3] A long-range coupling (J=1.5 Hz) is observed between the lowfield proton of A methylene (A2) and B2. This indicates that the A2–C–N–C–B2 bonds are almost coplanar (W rule).[3c] The chemical shift of the methylene proton which resonates at the highest

TABLE III. NMR Spectral Data[a] for IV and V

Compd. No.	Al[b]	A2	B1	B2	E	R¹(o)[c]	R¹(b)[c]	R²(B)[d]	R³	H(A)[e]	Me(A)[f]
IVa	1.47 d 11.5	3.23 d 11.5	2.78 dd 16.0 2.0	3.27 dd 16.0 4.5	5.14 dd 4.5 2.0	3.54 3H s	3.72 3H s	0.88 9H s	6.24 s	4.29 s	2.37 3H s
IVb	1.60 d 11.5	3.02 dd 11.5 1.0	2.47 dd 16.0 2.0	3.22 ddd 16.0 5.0 1.0	5.15 dd 5.0 2.0	1.14 3H t 7.0 3.98 2H q 7.0	1.22 3H t 7.0 4.22 2Hdq[g] 7.0 1.5	2.13 3H s	6.25 s	4.31 s	2.36 3H s
IVg	1.67 d 11.0	3.03 dd 11.0 1.5	2.44 dd 16.0 2.0	3.31 ddd 16.0 5.0 1.5	5.10 dd 5.0 2.0	3.53 3H s	3.71 3H s	2.13 3H s	3.26 3H s	4.30 s	2.56 3H s
V[h]	1.68 d 11.0	3.07 dd 11.0 1.5	2.48 dd 16.0 2.0	3.32 ddd 16.0 5.0 1.5	5.14 dd 5.0 2.0	—	3.72 3H s	2.16 3H s	3.21 3H s	4.38 s	—

a) 100 MHz, $CDCl_3$ solution with TMS as an internal standard. δ (ppm), (number of proton), appearance of signal J(Hz) are shown. All signals correspond to one proton, unless otherwise noted. The signals of aromatic protons are reasonable for all the compounds and are omitted from the table.
b) For the symbols, refer to Chart 3, Fig. 1 and Fig. 2.
c) R¹ (o) and R¹ (b) represent the protons of the alkyl groups of the ester, bonded to the olefinic and the bridgehead carbons, respectively.
d) Protons of the alkyl group bonded to the nitrogen atom in the B-ring.
e) Proton in the A-ring.
f) Protons of the methyl group attached to the A-ring.
g) Two quartets are observed (dq=double quartets.).
h) Methyl protons of N-methyl amide and methylene protons in the cyclic amide appear at δ 2.83 (3H, s) and 2.6—2.8 (2H, m), 3.2—3.4 (2H, m), respectively.

TABLE IV. NMR Spectral Data[a] for II and III

Compd. No.	A1[b]	A2	B1	B2	C1	C2	(R³) D1	(R³) D2	R¹(o)	R¹(b)	R²(B)	R²[c]	H(A)	Me(A)
IIa[d]	1.42 d 11.5	3.17[e] d 11.5	2.71 d 16.0	3.13 d 16.0	3.04 d 13.5	3.42 d 13.5	(9.68) (s)		3.52 3H s	3.67 3H s	0.89 9H s	1.18 9H s	4.25 s	2.37 3H s
IIb[f]	1.58 d 11.0	3.00 d 11.0	2.42 d 16.0	3.14 d 16.0	3.06 d 13.0	3.61 d 13.0	(9.18) (s)		1.18 3H t 7.0 3.98 2H q 7.0	1.21 3H t 7.0 4.19 2H q 7.0	2.16 3H s	2.50 3H s	4.28 s	2.39 3H s
IIIa-1	1.65 d 11.5	3.06 d 11.5	2.32 d 15.5	3.01 d 15.5	2.94 d 17.0	3.37 d 17.0	4.17 d 11.0	4.65 d 11.0	3.51 3H s	3.71 3H s	2.15 3H s	2.55[g] 3H s	4.33 s	2.53[g] 3H s
IIIa-2	1.52 d 11.0	3.19 d 11.0	2.38 d 16.5	3.05 d 16.5	2.99 d 16.5	3.44 d 16.5	4.25 d 11.0	4.77 d 11.0	3.50 3H s	3.70 3H s	0.96 3H t 7.0 1.99— 2.40[h] 2Hm	1.19 3H t 7.0 2.73 2H q 7.0	4.32 s	2.53 3H s

Compd. No.	A1[b]	A2	B1	B2	C1	C2	(R³) D1	(R³) D2	R¹(o)	R¹(b)	R²(B)	R²[c]	H(A)	Me(A)
IIIa–3	1.48 d 11.5	3.24 d 11.5	2.65 d 14.0	3.17 d 14.0	3.21 2H s		3.84 d 10.5	4.98 d 10.5	3.50 3H s	3.67 3H s	0.90 9H s	1.19 9H s	4.27 s	2.54 3H s
IIIb–1	1.66 d 11.0	3.07 d 11.0	2.33 d 15.5	3.01 d 15.5	2.95 d 17.0	3.37 d 17.0	4.17 d 11.0	4.65 d 11.0	1.10 3H t 7.0 3.96 2H q 7.0	1.21 3H t 7.0 4.19[h] 2H dq 7.0 3.5	2.15 3H s	2.56[g] 3H s	4.34 s	2.53[g] 3H s
IIIb–2	1.53 d 11.5	3.20 d 11.5	2.39 d 14.5	3.03 d 14.5	3.00 d 17.0	3.45 d 17.0	4.25 d 11.5	4.77 d 11.5	1.09 3H t 7.0 3.97 2H q 7.0	1.20 3H t 7.2 3.95— 4.35[h] 2H m	0.97 3H t 7.2 2.10— 2.40[h] 2H m	1.21 3H t 7.2 2.73 2H q 7.2	4.34 s	2.52 3H s
IIId	1.54 d 11.0	3.06 d 11.0	2.34 d 15.5	3.04 d 15.5	2.98 d 17.0	3.32 d 17.0	4.10 d 11.0	4.66 d 11.0	3.53 3H s	3.74 3H s	2.16 3H s	2.54 3H s	4.43 s	2.54 3H s
IIIe	1.60 d 11.0	3.15 d 11.0	2.30 d 15.0	2.98 d 15.0	2.94 d 17.0	3.39 d 17.0	4.16 d 11.0	4.67 d 11.0	3.50 3H s	3.72 3H s	2.13 3H s	2.57[g] 3H s	4.69 s	2.53[g] 3H s

a) 100 MHz, $CDCl_3$ solution with TMS as an internal standard. δ (ppm), (number of proton), appearance of the signal, J(Hz) are shown. All signals correspond to one proton, unless otherwise noted. The signals of aromatic protons are reasonable for all the compounds and are omitted from the table.
b) For the symbols, see footnotes *b*)—*f*) of Table III.
c) Protons of an alkyl group bonded to the nitrogen atom which is linked to methylene C (and D).
d) The NH proton bonded to methylene C appears at δ 1.30 (broad).
e) The signals of methylene A–D protons, except those of Al and Dl, are slightly broadened, indicating some complicated long-range interactions among them.
f) The NH proton bonded to methylene C appears at δ 2.63 (broad).
g) Assigned tentatively.
h) The protons are observed as two sets of quartets or a multiplet. In the former case, they are referred to as double quartets.

magnetic field (A1, 1.67 ppm) is abnormally high for an N-methylene proton and the differences of the δ values between the geminal protons of A and B methylenes are abnormally large (A, 1.36 ppm; B, 0.87 ppm).

As the stereochemical structure which agrees with the above observations, the structure shown in Fig. 2 was proposed on the basis of Dreiding stereomodels. The phenyl and the bridgehead ester groups are *trans* and diaxial. The conformations of ring A and B are, 1,3-diplanar[4] and half-chair forms, respectively. The plane of the benzene ring is vertical to ring A and is preferentially oriented through the N^1, C^4 atoms of ring A, owing to the steric interactions with the axial protons of ring B. On the basis of this stereostructure, the upfield shifts of axial protons of A and B methylenes can be explained clearly by an anisotropic effect of the benzene ring. The *cis* isomer or equatorial phenyl conformations of this compound could not account for the upfield shifts of A1 and B1 protons.

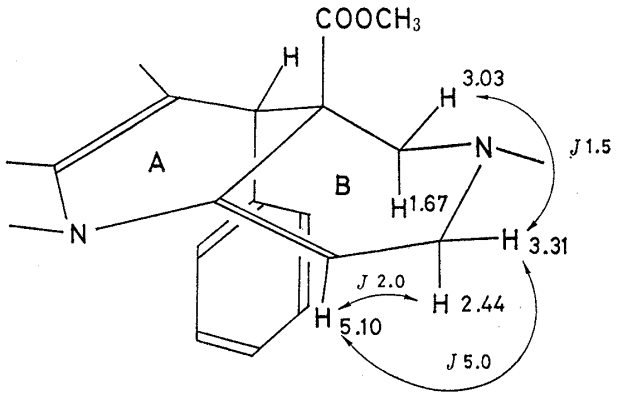

Fig. 2. Stereostructure of IVg
NMR data are also shown. δ (ppm), J (Hz).

Although a long-range coupling between the protons of A2 and B2 is not

necessarily observed clearly for the other products (II, III, IV and V), the same configuration and almost the same conformation are postulated for these products. The upfield shifts of A1 (δ 1.42—1.70) and the downfield shifts of D methylene protons (δ 3.84—4.98) are readily understandable on this basis.

The methylene protons of one of the two ethyl groups in IIIb-1, IIIb-2, IVb (COOEt) and in IIIa-2, IIIb-2 (NEt) appear as two sets of quartets or a multiplet, while those of the other methylene protons appear normally as a quartet (Fig. 1). These abnormalities may be due to the presence of conformational isomers and/or the chirality of the molecule.[5]

The chemical shifts of the A1 proton and those of the A2, B1 protons in II and III are shifted in opposite directions in a regular manner according to the bulkiness of the N-substituent. Conformers other than that shown in Fig. 2 may exist in $CDCl_3$ solution, and the population of them may be affected by the bulkiness of the N-substituent.

The reason for the stereoselectivity in this reaction is unclear.

Experimental

Melting points are uncorrected. IR spectra were recorded with a Hitachi 215 or 260-10 spectrophotometer and UV absorptions were measured with a Shimadzu MPS-5000 spectrometer. NMR spectra were recorded with a Varian HA-100D spectrometer and MS with a Hitachi RM-61 spectrometer. Column chromatography was done using Silica gel 60 (Merck).

Some representative examples of the Mannich reaction are shown below.

Diethyl 2,6-Dimethyl-8-methylaminomethyl-*t*-4-phenyl-1,4,4a,5,6,7-hexahydro-1,6-naphthyridine-3,*r*-4a-dicarboxylate (IIb)——A mixture of 3.0 g (9.1 mmol) of Ib, 1.35 g (20 mmol) of methylamine hydrochloride, 0.96 g (32 mmol) of paraformaldehyde and 30 ml of EtOH was refluxed for 24 hr. After removal of the solvent *in vacuo*, the residue was dissolved in $CHCl_3$. The $CHCl_3$ layer was extracted with dil. HCl, washed with 10% Na_2CO_3 and satd. NaCl, and the solvent was distilled off to give 2.50 g of an oil. The oil was chromatographed on silica gel ($CHCl_3$ as an eluent), and the resulting crystals were rinsed with EtOH to recover 0.18 g (6%) of the starting material, mp 153—156°. The acidic extract was made alkaline with Na_2CO_3 and a viscous oil which separated out was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with satd. NaCl, dried (Na_2SO_4), and concentrated *in vacuo* to give 1.9 g of an oil. The oil crystallized on addition of small amounts of Et_2O and hexane to give 1.16 g of a mixture. Column chromatography (2% MeOH in $CHCl_3$) of the mixture afforded 0.19 g (5%) of IIIb-1 (mp 146—149°) and 0.93 g of crude IIb. Recrystallization of crude IIb from EtOH–hexane gave 0.65 g (17%) of IIb, mp 148—149°. Compound IIIb-1 was identical with the standard sample described below.

Diethyl 2,4,8-Trimethyl-*t*-6-phenyl-1*H*,6*H*-2,3,6a,7,8,9-hexahydro-2,3a,8-triazaphenalene-5,*r*-6a-dicarboxylate (IIIb-1)——A mixture of 3.0 g (9.1 mmol) of Ib, 3.1 g (46 mmol) of methylamine hydrochloride, 2.7 g (90 mmol) of paraformaldehyde and 30 ml of EtOH was refluxed for 6 hr. After treatment as described above, 0.30 g of neutral fraction and 4.25 g of basic fraction were obtained, each as an oil. Column chromatography ($CHCl_3$) of the basic fraction followed by recrystallization from EtOH gave 1.98 g (50%) of IIIb-1, mp 148—150°.

Dimethyl 1,2,6-Trimethyl-*t*-4-phenyl-1,4,4a,5,6,7-hexahydro-1,6-naphthyridine-3,*r*-4a-dicarboxylate (IVg) and Methyl 2,5,8-Trimethyl-1-oxo-*t*-10-phenyl-1,2,3,4,5,7,8,9,9a,10-decahydro-pyrido[4,3-*b*][1,6]naphthyridine-*r*-9a-carboxylate (V)——A mixture of 3.0 g (9.5 mmol) of Ig,[1] 0.96 g (14 mmol) of methylamine hydrochloride, 0.86 g (29 mmol) of paraformaldehyde and 15 ml each of $CHCl_3$ and EtOH was refluxed for 26 hr. After treatment as described above, 3.5 g and 2.3 g of oily substances were obtained from the neutral and the basic fractions, respectively. Column chromatography ($CHCl_3$ and then $CHCl_3$–MeOH, 1 : 1) followed by recrystallizations of the basic substances, gave 0.41 g of IVg, mp 171—173°, and 0.07 g of V, mp 225—226° (dec.). From the neutral substances, 0.27 g of the starting material (Ig) was crystallized. Column chromatography ($CHCl_3$) of the mother liquor followed by recrystallizations gave another crop of Ig (0.09 g) and 0.50 g of IVg.

Dimethyl 2-(2-*tert*-Butylaminoethyl)-6-methyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (VIa), Dimethyl 6-*tert*-Butyl-8-*tert*-butylaminomethyl-2-methyl-*t*-4-phenyl-1,4,4a,5,6,7-hexahydro-1,6-naphthyridine-3,*r*-4a-dicarboxylate (IIa) and Dimethyl 2,8-Di-*tert*-butyl-4-methyl-*t*-6-phenyl-1*H*,6*H*-2,3,6a,7,8,9-hexahydro-2,3a,8-triazaphenalene-5,*r*-6a-dicarboxylate (IIIa-3)——A mixture of 3.0 g (10 mmol) of dimethyl 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (Ia), 5.5 g (50 mmol) of *tert*-butylamine hydrochloride, 3.0 g (100 mmol) of paraformaldehyde and 30 ml of EtOH was refluxed for 24 hr. Treatment as described above gave 3.3 g of a neutral fraction and 1.5 g of a basic fraction. The neutral fraction crystallized on addition of a small amount of MeOH and gave 0.55 g of the starting material, mp 196—198°. The mother liquor was chromatographed ($CHCl_3$, followed by 2% MeOH in $CHCl_3$ and MeOH–$CHCl_3$ 1 : 1) to give another crop of the starting material (0.54 g, mp 194—196°), 0.65 g of IIa and 0.15 g of VIa. Compound IIa was

recrystallized from EtOH–H_2O to give 0.54 g of pure IIa, mp 158—160°. Compound VIa was identical with the standard sample. From the basic fraction, 0.34 g of IIa was crystallized on addition of a small amount of Et_2O. From the mother liquor, after purification by column chromatography ($CHCl_3$) followed by recrystallization, 0.07 g of IIIa-3, mp 191—194° was obtained. The standard sample of VIa was obtained by another reaction under reaction conditions similar to those described above. After recrystallization from hexane, VIa melted at 128—130°. *Anal.* Calcd for $C_{22}H_{30}N_2O_4$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.08; H, 7.54; N, 7.55. IR ν_{max}^{KBr} cm^{-1}: 3290 (NH), 1680 (C=O), 1620 (C=C). NMR δ (ppm), 1.14 (9H, s, CMe_3), 2.32 (3H, s, 6-Me), 2.70—3.40 (4H, m, $C\underline{H}_2C\underline{H}_2N$), 3.62, 3.64 (6H, two singlets, COOMe), 5.01 (1H, s, 4-H), 7.0—7.4 (5H, m, Ph), 10.12 (1H, broad s, NH). UV λ_{max}^{EtOH} nm (log ε): 240 (4.27), 356 (3.86).

Diethyl 2-(2-Benzylmethylaminoethyl)-6-methyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (VIb-2)——A mixture of 4.0 g (12 mmol) of Ib, 2.87 g (18 mmol) of benzylmethylamine hydrochloride, 0.73 g (24 mmol) of paraformaldehyde and 40 ml of EtOH was refluxed for 24 hr. By treatment similar to that described above, 6.5 g of neutral substances were obtained. After purification by column chromatography and recrystallization from hexane, 2.92 g (52%) of VIb-2, mp 92—94°, was obtained. An analytical sample had mp 93—94.5° (hexane). *Anal.* Calcd for $C_{28}H_{34}N_2O_4$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.86; H, 7.30; N, 6.34. IR ν_{max}^{KBr} cm^{-1}: 1680 (C=O), 1640 (C=C).

Diethyl 2,6-Dimethyl-*t*-4-phenyl-1,4,4a,5,6,7-hexahydro-1,6-naphthyridine-3,*r*-4a-dicarboxylate (IVb)——Compound VIb-2 (2.0 g, 4.3 mmol) was dissolved in 20 ml of EtOH and hydrogenated with 1.0 g of 5% Pd-C under warming. After about 3 hr, the absorption of hydrogen ceased. After removal of the catalyst, the solution was refluxed with 0.65 g (23 mmol) of paraformaldehyde for 1 hr. After removal of the solvent *in vacuo*, the residue was rinsed with hexane and filtered to give 1.15 g of crude IVb. Recrystallization from EtOH–H_2O gave 0.99 g (60%) of IVb, mp 160—162°.

Compound IIIb-1 from the Mannich Reaction of IVb——Compound IVb (0.50 g, 1.3 mmol) was refluxed with 0.11 g (1.6 mmol) of methylamine hydrochloride and 0.09 g (3 mmol) of paraformaldehyde in 5 ml of EtOH for 4 hr. After removal of the solvent *in vacuo*, H_2O was added to the residue. The resulting mixture was made alkaline with Na_2CO_3, and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with satd. NaCl, then the solvent was evaporated off *in vacuo*. Column chromatography of the residue, followed by recrystallization (EtOH–hexane) gave 0.19 g (33%) of IIIb-1, mp 148—150°. Although IIb was detected by TLC, it could not be isolated.

Compound IIIb-1 from the Reaction of IIb with Paraformaldehyde——A mixture of 0.50 g (1.2 mmol) of IIb, 0.35 g (12 mmol) of paraformaldehyde and 7.5 ml of EtOH was refluxed for 30 min. After removal of insoluble materials by filtration, the solvent was evaporated off *in vacuo*. The crystalline residue was rinsed with hexane and filtered. The crystals weighed 0.43 g (84%) (mp 147—149°) and were identical with the standard sample of IIIb-1.

Dimethyl 6-*tert*-Butyl-2-methyl-*t*-4-phenyl-1,4,4a,5,6,7-hexahydro-1,6-naphthyridine-3,*r*-4a-dicarboxylate (IVa) from VIa——A mixture of 0.41 g (1.1 mmol) of VIa, 0.20 g (0.67 mmol) of paraformaldehyde and 10 ml of EtOH was refluxed for 1.5 hr. The solvent was removed *in vacuo*, and the crystalline residue was recrystallized from EtOH–hexane to give 0.08 g (19%) of IVa, mp 194—197°.

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