Studies on Naphthyridines. An Unexpected Product in Hantzsch Pyridine Synthesis

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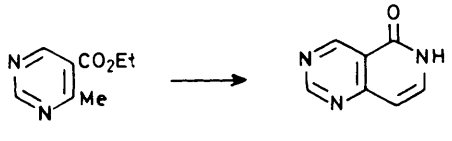
Besides the expected pyridinedicarboxylate (**4**), triethyl 2,7,8a-trimethyl-1,4,4a,5,8,8a-hexahydro-1,8-naphthyridine-3,4a,6-tricarboxylate (**6**) was also isolated in the Hantzsch pyridine synthesis starting from ethyl acetoacetate and hexamethylenetetramine in acetic acid. The 1,8-naphthyridine (**6**) was probably formed in the [4 + 2]cycloaddition of heterodiene (**5**) and the 1,4-dihydropyridinedicarboxylate (**3**). The observed regioselectivity was explained in terms of simple Hückel molecular orbital calculations. Diethyl 2,6-dimethylpyridine-3,5-dicarboxylate (**4**) gave ethyl 2-methyl-5-oxo-5,6-dihydro-1,6-naphthyridine-3-carboxylate (**9**) in high yield in a one-step reaction with 1,3,5-triazine in the presence of ethanolic sodium ethoxide, or in a two-step procedure with DMF diethyl acetal followed by ring closure with ammonia.

We recently reported[1] that the reaction of ethyl acetoacetate and 1,3,5-triazine yielded not only the expected ethyl 4-oxo-1,4-dihydropyridine-3-carboxylate, but also pyrido[4,3-*d*]pyrimidine-5(6*H*)-one (**2**). The latter product probably arose from the reaction of 1,3,5-triazine with ethyl 4-methylpyrimidine-5-carboxylate (**1**) present in the reaction mixture. We set out to extend the latter reaction to the synthesis of 1,6-naphthyridin-5(6*H*)-ones.



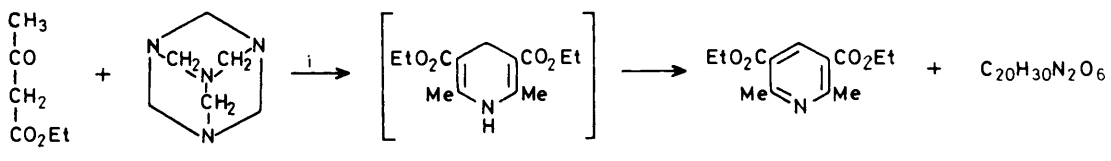
(**1**) (**2**)

1,6-Naphthyridin-5(6*H*)-ones are anti-inflammatory, anticonvulsant,[2,3] and insecticidal agents.[4] Several methods are known for their preparation from 2,3-disubstituted pyridines.[5–14] These syntheses, however, involve several steps and afford the 1,6-naphthyridin-5(6*H*)-ones in very low yields. For example, Ikekawa[5] started from ethyl 2-methylpyridine-3-carboxylate and obtained 1,6-naphthyridin-5(6*H*)-one in four steps in an overall yield of 3%. Baldwin *et al.* treated 2-methylpyridine-3-carbonitrile with *N*,*N*-dimethylformamide (DMF) dimethyl acetal and cyclized the product with hydrogen bromide in acetic acid to obtain a mixture of 1,6-naphthyridin-5(6*H*)-one and 5-bromo-1,6-naphthyridine.[7]

Synthesis of Diethyl 2,6-*Dimethylpyridine*-3,5-*dicarboxylate* (**4**).—To check the above conception for a new synthesis of the 1,6-naphthyridin-5(6*H*)-one skeleton, diethyl 2,6-dimethylpyridine-3,5-dicarboxylate (**4**), containing a similar moiety to ethyl 4-methylpyrimidine-5-carboxylate (**1**), was selected as starting material. When the pyridinedicarboxylate (**4**) was prepared by the well known Hantzsch synthesis[15,16] from ethyl acetoacetate and hexamethylenetetramine in acetic acid by the method of Checchi,[17] a new compound was isolated in 2.3% yield from the crude reaction mixture (Scheme 1).

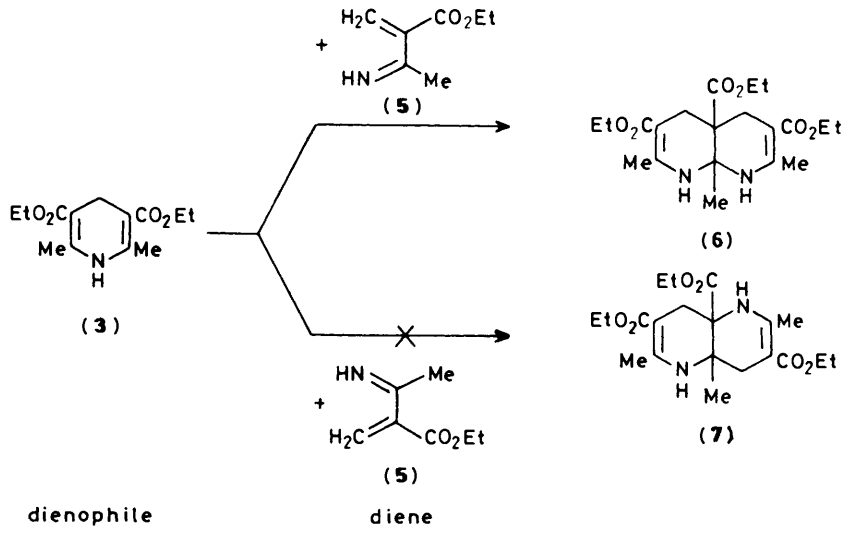
Microanalytical data and mass spectrometric studies on the minor product gave an empirical formula of $C_{20}H_{30}N_2O_6$. Its ^{1}H n.m.r. spectrum in $CDCl_3$ contains two triplets at δ_H 1.22 and 1.30, and two singlets at δ_H 1.50 and 2.22, with a 1:2 intensity ratio. The four-proton intensity broad singlet at δ_H 2.60 pertains to the protons of two ring methylene groups. The intense absorption bands at 1 730 and 1 675 cm^{-1} in the i.r. spectrum suggested the presence of two types of ester carbonyl group, while the bands at 3 360 and 3 330 cm^{-1} could be assigned to NH groups. On the basis of the spectroscopic examinations, the minor product was assumed to be a symmetrical bicyclic ring system, originating from a [4 + 2]-cycloaddition of heterodiene (**5**) (probably formed *in situ* from ethyl 2-methyleneacetoacetate[18] and ammonia) and the dienophile 1,4-dihydropyridine (**3**), an intermediate in the preparation of diester (**4**), present in the reaction mixture. Only a few [4 + 2]cycloadditions are known in which heterodienes are involved.[19,20]

Theoretically, heterodiene (**5**) could react in two ways with the 1,4-dihydropyridine (**3**), to yield either a 1,8-naphthyridine (**6**) or a 1,5-naphthyridine (**7**) (Scheme 2). The observed regioselectivity can be explained in terms of simple Hückel[21] and MINDO/2[22] molecular orbital calculations (Figure 1). The sum of coefficient products between interacting atomic orbitals is larger for (**6**) than for (**7**) both for the HOMO (dienophile)–LUMO (diene) and LUMO (dienophile)–HOMO (diene) interactions, indicating[23] that the formation of compound (**6**) is preferred. For the HOMO–LUMO interaction the Hückel and



(**3**) (**4**)

Scheme 1. *Reagents:* i, AcOH, 100 °C



Scheme 2.

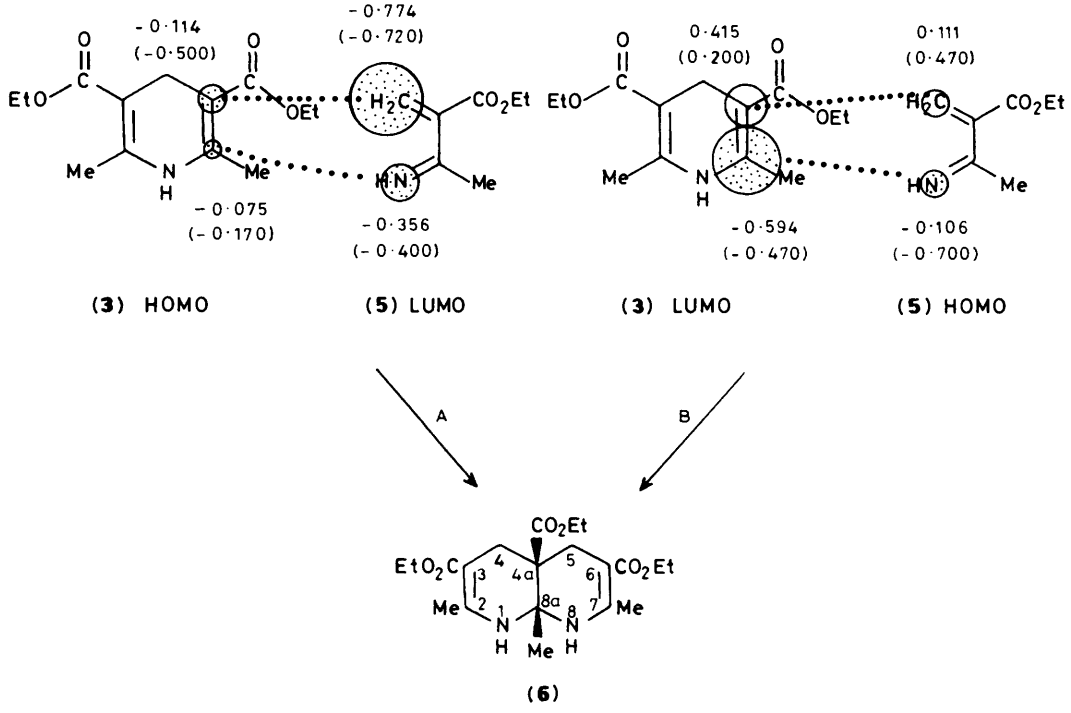


Figure 1. Coefficients of frontier orbital pairs as calculated by the MINDO/2 and (in parentheses) simple Hückel methods. Compounds (3) and (5) were modelled by replacing methyl and ethyl groups by hydrogen atoms. Molecular geometry of compound (3) was taken from S. Fortier, M. E. Fraser, N. J. Moore, Y. S. Park, R. A. Whitney, and G. S. Marks, *Acta Crystallogr., Sect. C*, 1985, **41**, 411, while that of (5) was constructed using standard bond lengths and angles

MINDO/2 methods give 0.428 and 0.115 for (6) and 0.322 and 0.099 for (7), respectively, while although the LUMO–HOMO interaction is allowed for the formation of 1,8-naphthyridine (6), the same interaction is symmetrically forbidden for that of 1,5-naphthyridine (7).

X-Ray crystallographic analysis gave further evidence of the presumed structure (see Figure 2). The same sign for the torsional angles N(1)–C(8a)–C(4a)–C(4) and N(8)–C(8a)–C(4a)–C(5) indicates a *cis*-fused ring connection. Both rings have an envelope conformation, resulting from the delocalization of the double bonds. The yield was low due to the instability of the 1,8-naphthyridine (6) in acidic media. When compound (6) was heated in acetic acid at 100 °C for 0.5 h, the pyridinedicarboxylate (4) was isolated in 98% yield. In neutral and basic solvents (ethanol, Pr^{i}OH, DMF), the bicyclic ring system (6) proved to be stable at elevated temperature for a long period. Compounds similar to (6) have not previously been observed as products in the Hantzsch pyridine synthesis.[15,16]

Synthesis of Ethyl 2-Methyl-5-oxo-5,6-dihydro-1,6-naphthyridine-3-carboxylate (9).—The 1,6-naphthyridin-5(6*H*)-one skeleton could readily be formed from the pyridine diester (4) in

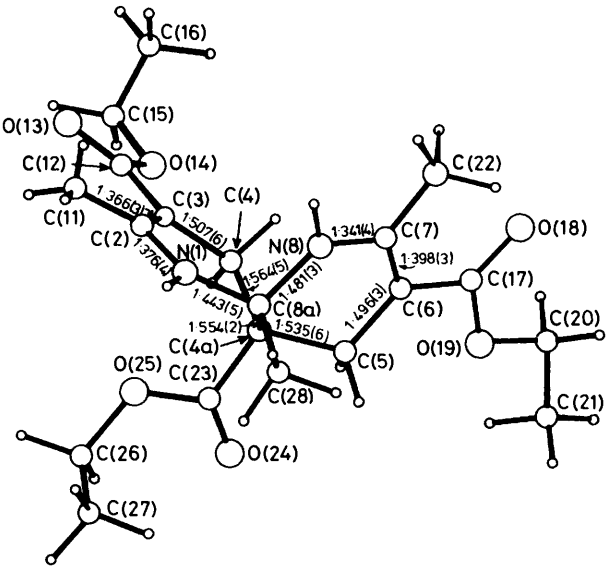
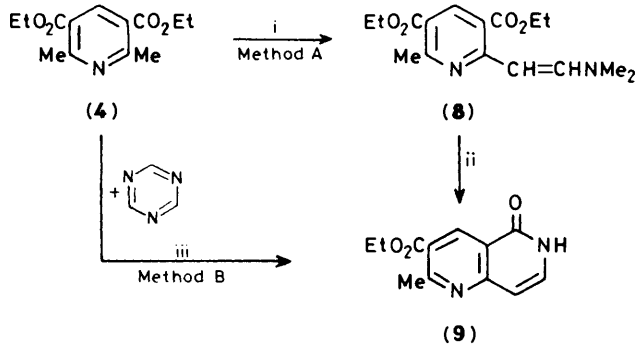


Figure 2. *X*-Ray molecular diagram of compound (**6**) with crystallographic atomic numbering. Selected bond lengths and bond angles are given (e.s.d.s in parentheses)

C(2)–N(1)–C(8a)	123.3(4)	C(4)–C(4a)–C(5)	109.7(4)
N(1)–C(2)–C(3)	119.8(4)	C(4a)–C(5)–C(6)	112.3(4)
C(2)–C(3)–C(4)	122.0(4)	C(5)–C(6)–C(7)	119.4(4)
C(3)–C(4)–C(4a)	114.4(4)	C(6)–C(7)–N(8)	119.8(4)
C(4)–C(4a)–C(8a)	108.3(4)	C(7)–N(8)–C(8a)	126.5(4)
N(1)–C(8a)–C(4a)	111.8(4)	N(8)–C(8a)–C(4a)	107.1(4)



Scheme 3. *Reagents:* i, $Me_2NCH(OEt)_2$/DMF/N_2, heat; ii, c. NH_4OH–EtOH; iii, NaOEt–EtOH, heat

a two-step (Method A) or a one-step (Method B) procedure (Scheme 3).

In Method A, the active methylene group of the pyridinedicarboxylate (**4**) was caused to react with DMF diethyl acetal in DMF, under nitrogen, at reflux temperature to yield diethyl 2-[2-(dimethylamino)vinyl]-6-methylpyridine-3,5-dicarboxylate (**8**). Compound (**8**) was cyclized to the 1,6-naphthyridin-5(6*H*)-one (**9**) by treatment with ammonium hydroxide in ethanol at ambient temperature. The total yield was 32.6%.

A higher yield could be achieved in the one-step procedure (Method B).

When the pyridine diester (**4**) was treated with 1,3,5-triazine[24,25] in the presence of ethanolic sodium ethoxide at reflux temperature, 1,6-naphthyridin-5(6*H*)-one (**9**) was prepared in 80.4% yield.

The structure of 1,6-naphthyridin-5(6*H*)-one (**9**) was characterized by u.v., i.r., m.s., and ^1H n.m.r. spectroscopy, and

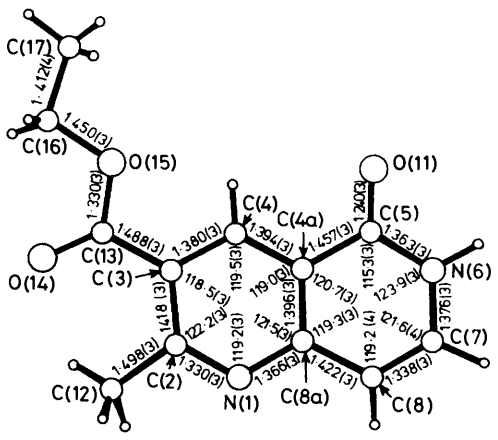


Figure 3. *X*-Ray molecular diagram of compound (**9**) with crystallographic atomic numbering. Selected bond lengths and bond angles are given (e.s.d.s in parentheses)

X-ray analysis (Figure 3). The dihedral angle between the plane of the 1,6-naphthyridinone skeleton of compound (**9**) and that of the ester group is 12°.

Experimental

All m.p.s are uncorrected. U.v. spectra were obtained in ethanol on a UNICAM SP 800 spectrophotometer. I.r. spectra were determined with KBr disks on a ZEISS UR 20 spectrophotometer. The ^1H and ^{13}C n.m.r. spectra were recorded in $CDCl_3$ with a Brucker WP-80 DS spectrometer. Chemical shifts were determined on the δ scale, with tetramethylsilane (δ 0) as internal standard. Mass spectra were measured with an MS-902 spectrometer operating at 70 eV.

Diethyl 2,6-*Dimethylpyridine*-3,5-*dicarboxylate* (**4**) *and Triethyl* 2,7,8a-*Trimethyl*-1,4,4a,5,8,8a-*hexahydro*-1,8-*naphthyridine*-3,4a,6-*tricarboxylate* (**6**).—A mixture of ethyl acetoacetate (56.0 g, 0.430 mol) and hexamethylenetetra-amine (56.0 g, 0.40 mol) in acetic acid (56 ml) was stirred for 30 min at 100 °C. Water (400 ml) was added to the mixture at 25 °C and the orange precipitate was filtered off, washed with water, and dried. The crude product (22.7 g) was treated with ethyl acetate (250 ml) and the insoluble part was filtered off. *Triethyl* 2,7,8a-*trimethyl*-1,4,4a,5,8,8a-*hexahydro*-1,8-*naphthyridine*-3,4a,6-*tricarboxylate* (**6**) (1.3 g, 2.3%) was obtained as white crystals, m.p. 200—201 °C (from ethyl acetate) (Found: C, 60.7; H, 7.7; N, 7.2. $C_{20}H_{30}N_2O_6$ requires C, 60.90; H, 7.67; N, 7.10%); $\lambda_{max.}$ 270 (log ε 4.48) and 285 (infl.) nm; $\nu_{max.}$ 3 360 and 3 330 (NH), 1 730 and 1 675 cm^{-1} (C=O); δ_H 1.22 (3 H, t, *J* 7.5 Hz, 4a-$CO_2CH_2CH_3$), 1.30 (6 H, t, *J* 7.5 Hz, 3- and 6-$CO_2CH_2CH_3$), 1.50 (3 H, s, 8a-Me), 2.22 (6 H, s, 2- and 7-Me), 2.60 (4 H, s, 4- and 5-H_2), 4.12 (6 H, q, *J* 7.5 Hz, 3-, 4a- and 6-$CO_2CH_2CH_3$), and 4.33 (2 H, s, 1- and 8-H); δ_C 14.06 (q, 8a-Me), 14.64 (q, 2- and 7-Me), 20.62 (q, 3- and 6-$CO_2CH_2CH_3$), 24.08 (q, 4a-$CO_2CH_2CH_3$), 29.72 (t, C-4 and -5), 42.41 (s, C-4a), 59.13 (t, 3- and 6-$CO_2CH_2CH_3$), 60.61 (t, 4a-$CO_2CH_2CH_3$), 65.95 (s, C-8a), 92.92 (s, C-3 and -6), 148.42 (s, C-2 and -7), 168.66 (3- and 6-$CO_2CH_2CH_3$), and 173.25 (s, 4a-$CO_2CH_2CH_3$); *m/z* 394 (M^+), 349 ($M^+ - 45$), 321 ($M^+ - 73$, 100%), 304 ($M^+ - 73 - 17$), 303 ($M^+ - 45 - 46$), 275 ($M^+ - 73 - 46$), and 252 ($M^+ - 142$).

The filtrate was evaporated to dryness and the residue was recrystallized from ethanol to give diethyl 2,6-dimethylpyridine-3,5-dicarboxylate (**4**) (19.7 g, 36.5%), m.p. 72—73 °C (lit.,[17] 70—72 °C).

Diethyl 2,6-Dimethylpyridine-3,5-dicarboxylate (**4**) *from Compound* (**6**).—Triethyl 2,7,8a-trimethyl-1,4,4a,5,8,8a-hexahydro-1,8-naphthyridine-3,4a,6-tricarboxylate (**6**) (7.88 g, 0.02 mol) was stirred in acetic acid (25 ml) at 100 °C for 30 min. Water (150 ml) was added to the yellow solution at 25 °C. The orange precipitate was filtered off, washed with water, and dried. Diethyl 2,6-dimethylpyridine-3,5-dicarboxylate (**4**) was obtained (4.92 g, 98%), m.p. and mixed m.p. with an authentic sample 72—73 °C (from ethanol).

Synthesis of Compound (**9**). *Method A.—Condensation I.* A mixture of diethyl 2,6-dimethylpyridine-3,5-dicarboxylate (**4**) (25.12 g, 0.1 mol) and DMF diethyl acetal (14.72 g, 0.1 mol) in DMF (100 ml) was stirred at reflux temperature under nitrogen for 16 h. After evaporation under reduced pressure the residue was poured into water (1 l) and extracted with benzene (6 × 200 ml), the extract was washed with water (2 × 200 ml), dried, and evaporated to dryness, and the residue was treated with light petroleum (20 ml) to give diethyl 2-[2-(*N*,*N*-dimethylamino)vinyl]-6-methylpyridine-3,5-dicarboxylate (**8**) as yellow crystals (14.6 g, 47.7%), m.p. 92—93 °C (from ethanol) (Found: C, 62.6; H, 7.3; N, 9.0. $C_{16}H_{22}N_2O_4$ requires C, 62.73; H, 7.24; N, 9.14%); $\lambda_{max.}$ 390 (log ε 4.44), 286 (infl.), and 270 nm (4.01); $\nu_{max.}$ 1 700 (C=O) and 1 640 cm^{-1} (C=C); δ_H 1.06—1.51 (6 H, m, 3- and 5-$CO_2CH_2CH_3$), 2.78 (3 H, s, 6-Me), 3.05 (6 H, s, NMe_2), 4.17 and 4.37 (4 H, q, *J* 7.5 Hz, 3- and 5-$CO_2CH_2CH_3$), 6.47 (1 H, d, *J* 14 Hz, 2-CH=CHNMe$_2$), 8.18 (1 H, d, *J* 14 Hz, 2-CH=CHNMe$_2$), and 8.72 (1 H, s, 4-H).

Condensation II. A mixture of diethyl 2,6-dimethylpyridine-3,5-dicarboxylate (**4**) (2.51 g, 0.01 mol) and DMF diethyl acetal (7.35 g, 0.05 mol) was stirred at 140 °C for 6 h, cooled, and diluted with light petroleum (b.p. 30—60 °C) (100 ml). After the mixture had been kept at 4 °C for 2 days the ethenamine derivative (**8**) was isolated by suction, and washed with light petroleum (yield 1.55 g, 50.7%), m.p. 94 °C (from ethanol).

Cyclization. A mixture of diethyl 2-[2-(dimethylamino)-vinyl]-6-methylpyridine-3,5-dicarboxylate (**8**) (3.06 g, 0.01 mol), 25% aqueous ammonium hydroxide (30 ml), and ethanol (30 ml) was stirred at room temperature for 36 h. Pale yellow *ethyl 2-methyl-5-oxo-5,6-dihydro-1,6-naphthyridine-3-carboxylate* (**9**) suction, and washed with water (yield 1.5 g, 64.3%), m.p. 260 °C (from methanol) (Found: C, 62.3; H, 5.3; N, 11.8. $C_{12}H_{12}N_2O_3$ requires C, 62.06; H, 5.21; N, 12.06%); $\lambda_{max.}$ 320 (log ε 4.12) and 250 nm (3.97); $\nu_{max.}$ 3 175 (NH), 1 730 (C=O ester), and 1 665 cm^{-1} (C=O ring); δ_H[$(CD_3)_2SO$] 1.47 (3 H, t, *J* 7 Hz, $CO_2CH_2CH_3$), 2.90 (3 H, s, 2-Me), 4.43 (2 H, q, *J* 7 Hz, $CO_2CH_2CH_3$), 6.62 (1 H, dd, $J_{7,8}$ 8, $J_{4,8}$ 1 Hz, 8-H), 7.60 (1 H, d, $J_{7,8}$ 8 Hz, 7-H), 8.87 (1 H, d, $J_{4,8}$ 1 Hz, 4-H), and 11.65 (1 H, s, 6-H).

Synthesis of Compound (**9**). *Method B.*—To ethanolic sodium ethoxide [prepared from sodium (2.3 g, 0.1 g-atom) and ethanol (200 ml)] were added the pyridinedicarboxylate (**4**) (25.12 g, 0.1 mol) and 1,3,5-triazine (8.11 g, 0.1 mol). The mixture was stirred and heated under reflux for 2 h. After evaporation of solvent at atomospheric pressure, water (150 ml) was added, and the pH was adjusted to 7 with 10% hydrochloric acid. The 1,6-naphthyridine (**9**) was isolated by suction, and washed with water (yield 18.7 g, 80.4%), m.p. 250—252 °C.

Column chromatography on silica gel with chloroform–methanol (10:1) as eluant yielded pale yellow crystals of the ester (**9**) (12.9 g, 55.5%), m.p. and mixed m.p. 260 °C.

Crystallography.—Crystal data for (**6**). $C_{20}H_{30}N_2O_6$, M = 394.47. Monoclinic, a = 14.068(2), b = 13.485(1), c = 20.902(2) Å, β = 148.65(9)°, V = 2 063.0 Å^3, D_c = 1.27 g cm^{-3}, Z = 4, μ(Cu-K_α = 1.5418 Å) 12.22 cm^{-1}, space group $P2_1/c$. Data were collected on an Enraf-Nonius CAD-4 diffractometer with monochromated Cu-K_α radiation up to θ = 80°. 3 429 out of 4 373 reflections were considered observed [$I > 4\sigma(I)$]. All calculations were carried out on a PDP 11/34 minicomputer by the use of the Enraf-Nonius SDP program package with local modification. The structure was solved by program MULTAN-78.[26] The set with the best combined figure of merit revealed 26 atoms (R = 0.1). The hydrogen-atom positions were determined from a difference Fourier map and they were refined isotropically. The two cycles of isotropic and two cycles of anisotropic refinement concluded with R = 0.07, R_w = 0.11 for 3 429 reflections. Atomic co-ordinates are given in Table 1; the anisotropic thermal parameters, hydrogen-atom co-ordinates, and bond lengths and angles are listed in Supplementary Publication No. SUP 56477 (7 pp.).*

Table 1. Fractional co-ordinates (× 10^4) for compound (**6**) (e.s.d.s in parentheses)

	x	*y*	*z*
N(1)	−3 153(3)	3 792(3)	2 979(2)
C(2)	−2 231(3)	4 554(3)	3 213(2)
C(3)	−965(3)	4 346(3)	3 479(2)
C(4)	−622(3)	3 304(3)	3 445(2)
C(5)	−1 347(3)	1 484(3)	3 188(2)
C(6)	163(3)	1 317(3)	4 527(2)
C(7)	215(3)	1 878(3)	5 118(2)
N(8)	−1 102(3)	2 545(3)	4 478(2)
C(4a)	−2 125(3)	2 539(3)	2 779(2)
C(8a)	−2 703(3)	2 760(3)	3 147(2)
C(11)	−2 757(3)	5 547(3)	3 154(2)
C(12)	128(3)	5 137(3)	3 827(2)
O(13)	87(2)	6 019(2)	3 920(2)
O(14)	1 265(2)	4 767(3)	4 026(2)
C(15)	2 415(4)	5 478(5)	4 326(3)
C(16)	4 120(6)	5 580(7)	5 572(4)
C(17)	1 605(0)	601(0)	5 217(0)
O(18)	3 039(3)	460(3)	6 321(2)
O(19)	1 097(2)	46(2)	4 409(2)
C(20)	2 450(4)	−675(4)	4 970(2)
C(21)	1 574(5)	−1 222(5)	3 926(3)
C(22)	1 651(4)	1 801(4)	6 451(2)
C(23)	−3 698(3)	2 584(4)	1 402(2)
O(24)	−4 047(4)	1 971(4)	831(2)
O(25)	−4 557(3)	3 454(3)	884(2)
C(26)	−6 089(5)	3 555(5)	−451(3)
C(27)	−7 698(5)	3 091(6)	−1 127(4)
C(28)	−4 336(3)	2 134(4)	2 430(3)

Table 2. Fractional co-ordinates (× 10^4) for compound (**9**) (e.s.d.s in parentheses)

	x	*y*	*z*
N(1)	6 852(2)	9 696(1)	3 659(1)
C(2)	7 464(3)	10 393(1)	4 403(1)
C(3)	7 607(3)	9 952(1)	5 349(1)
C(4)	7 067(3)	8 762(1)	5 499(1)
C(4a)	6 406(3)	8 032(1)	4 723(1)
C(5)	5 811(3)	6 779(1)	4 868(1)
N(6)	5 226(2)	6 140(1)	4 059(1)
C(7)	5 167(3)	6 618(2)	3 159(1)
C(8)	5 695(3)	7 769(2)	3 013(1)
C(8a)	6 336(3)	8 516(1)	3 809(1)
O(11)	5 813(2)	6 300(1)	5 661(9)
C(12)	8 014(3)	11 662(2)	4 150(1)
C(13)	8 354(3)	10 724(2)	6 174(1)
O(14)	8 599(3)	11 803(1)	6 158(1)
O(15)	8 700(2)	10 059(1)	6 963(1)
C(16)	9 497(5)	10 687(2)	7 818(1)
C(17)	9 956(5)	9 838(3)	8 563(2)

* For details of the Supplementary Publications Scheme see Instructions for Authors (1986), *J. Chem. Soc., Perkin Trans. 1*, 1986, issue 1. Structure factors are available from the editorial office on request.

Crystal data for (**9**). $C_{12}H_{12}N_2O_3$, M = 232.24. Monoclinic, a = 7.408(1), b = 10.892(1), c = 14.200(2) Å, β = 97.62(2)°, V = 1 135.7 Å^3, D_c = 1.36 g cm^{-3}, Z = 4, μ(Cu-K_α = 1.5418 Å) 8.36 cm^{-1}, space group $P2_1/c$. Data were collected on an Enraf-Nonius CAD-4 diffractometer with monochromated Cu-K_α radiation up to θ = 80°. 2 337 out of 1 513 reflections were considered observed [$I > 2\,\sigma(I)$]. Computational details were the same as described for compound (**6**). Full-matrix refinement resulted in R = 0.051, R_w = 0.048. Atomic co-ordinates are given in Table 2; the anisotropic thermal parameters, hydrogen-atom co-ordinates, and bond lengths and angles are listed in Supplementary Publication No. SUP 56477 (7 pp.).*

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