16. Simultaneous Formation of 8*H*-Isoquino[2,1-*b*][2,7]naphthyridin-8-ones and 13*H*-Pyrido[4′,3′:3,4]pyrrolo[2,1-*b*][3]benzazepin-13-ones, a Novel Potential Alkaloidal System

by **Kuppuswamy Nagarajan**[1])* and **Patrick J. Rodrigues**

R&D Centre, *Searle (India) Ltd.*, Thane 400 601, India

and **Munirathinam Nethaji***

Department of Inorganic & Physical Chemistry, Indian Institute of Science, Bangalore, India

and **Markus Vöhler** and **Wolfgang von Philipsborn***

Organisch-chemisches Institut der Universität Zürich, Winterthurerstrasse 190, CH-8057 Zürich

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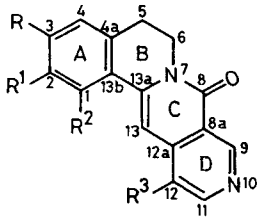
Condensation of 3,4-dihydro-6,7-dimethoxyisoquinoline (**4**) with 4-methylnicotinoyl chloride (**12**) in refluxing pyridine gives 5,6,13,13a-tetrahydro-2,3-dimethoxy-8*H*-isoquino[2,1-*b*][2,7]naphthyridin-8-one (**11**), along with some of its 13,13a-didehydro derivative **7**. A similar reaction of **4** with 4-(chloromethyl)nicotinoyl chloride (**14**) affords, in addition to **7**, the isomeric product 10,11-dihydro-7,8-dimethoxy-13*H*-pyrido[4′,3′:3,4]pyrrolo[2,1-*b*][3]benzazepin-13-one (**3**). Analogous pairs of products are obtained from 3,4-dihydro-6,7-(methylenedioxy)- and 3,4-dihydro-6,7,8-trimethoxy-isoquinolines (**15** and **18**, resp.). The structure of **3** was established by extensive NMR data and confirmed by single-crystal X-ray studies. Structure **7** has the ring system of the *Alangium* alkaloids like alangimarine (**1**), while the isomeric ring system **3** is predicted to be present in nature on biogenetic reasoning.

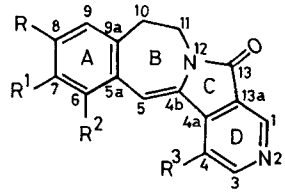
Introduction. – The alkaloids of *Alangium lamarckji* THW. represented by alangimarine (**1**) [1] have the interesting 8*H*-isoquino[2,1-*b*][2,7]naphthyridin-8-one ring system isosteric with 8-oxoprotoberberines [2]. Alkaloids of the latter group like prechilenine, in the correct oxidation state, were found to rearrange in nature to the isomeric isoindolobenzazepines, *e.g.* chilenine [3]. Aporhoedane (**2**) having this ring system was known earlier [4] and was synthesized [5]. Similar biogenetic transformations of *Alangium* alkaloids can give rise to natural products with the pyrido-[4′,3′:3,4]pyrrolo[2,1-*b*][3]benzazepine ring system, typified by **3** which are hitherto unkown in nature or by synthesis.

The first approach to the synthesis of isoquinonaphthyridines of type **1** predated the isolation of the alkaloids and involved the irradiation of the enamide of 3,4-dihydro-1-methylisoquinoline with nicotinoyl chloride [6]. Subsequently, this reaction was shown to occur also thermally but found to suffer from nonregiospecificity [7]. Notwithstanding this handicap, the thermal cyclization approach was successfully applied to the synthesis of alamarine, isoalamarine, and alamaridine [8]. Alternative approaches which do not suffer from the problem of nonregiospecificity start from the 3,4-dihydro-6,7-dimethoxy-

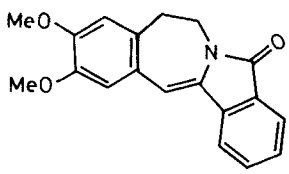
[1]) Present address: R&D Centre, *Bangalore Pharmaceuticals & Research Laboratory (P) Ltd.*, Bangalore-560 069, India.



1 R = MeO, R^1 = OH, R^2 = H, R^3 = CH_2=CH
7 R = R^1 = MeO, R^2 = R^3 = H
17 R,R^1 = OCH_2O, R^2 = R^3 = H
20 R = R^1 = R^2 = MeO, R^3 = H



3 R = R^1 = MeO, R^2 = R^3 = H
16 R,R^1 = OCH_2O, R^2 = R^3 = H
19 R = R^1 = R^2 = MeO, R^3 = H
25 R = R^1 = MeO, R^2 = H, R^3 = MeCH(OH) or CH_2=CH



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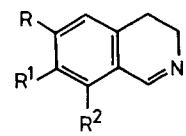
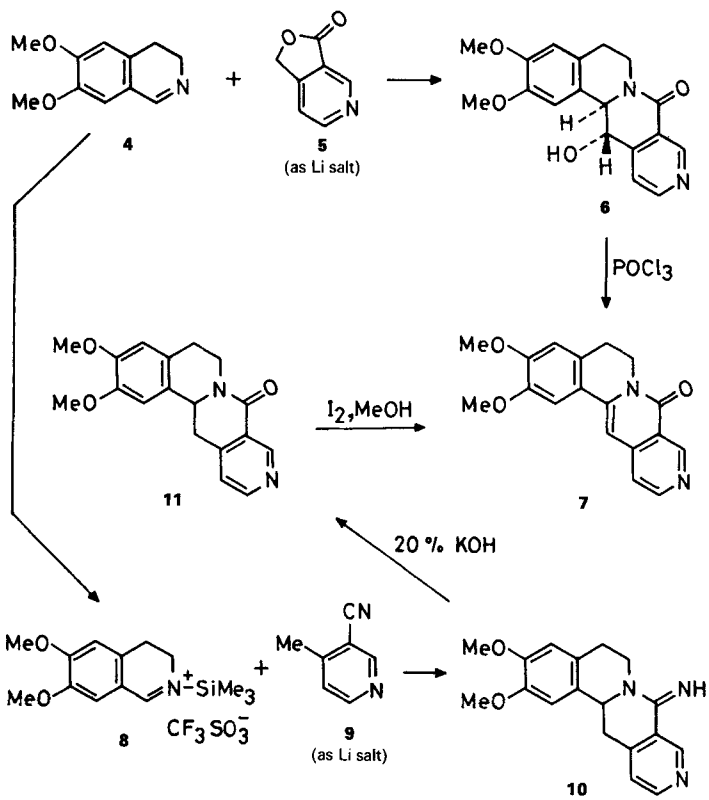


4 R = R^1 = MeO, R^2 = H
15 R,R^1 = OCH_2O, R^2 = H
18 R = R^1 = R^2 = MeO

Scheme 1

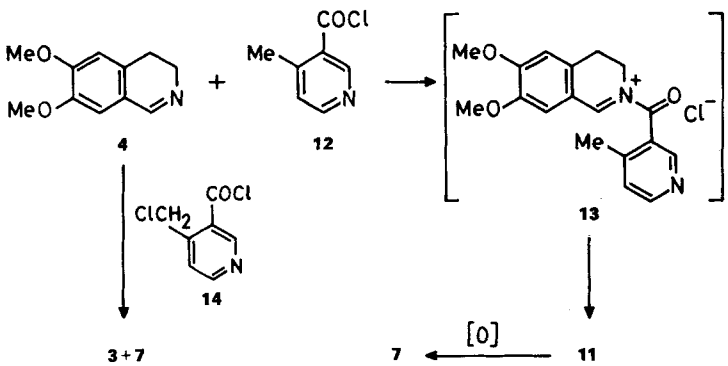


isoquinoline (**4**) and use the lithium salt of the azaphthalide **5** [9] (→ **6** → **7**) or the lithium salt of 4-methylnicotinonitrile (**9**) with activation of **4** by trimethylsilyl triflate (→ **8** → **10** → **11** → **7**; *Scheme 1*) [10]. While both approaches require strong deprotonating agents, the second one utilises, additionally, a powerful activator of the imine for nucleophilic addition.

In our continuing efforts [11] to develop newer routes to the *Alangium* alkaloids, we have been successful in designing an easy approach to the isoquinonaphthyridine **7** which resulted in the simultaneous formation of the isomeric pyridopyrrolobenzazepine **3**.

Results and Discussions. – We postulated that reaction of **4** with 4-methylnicotinoyl chloride (**12**; from the acid and oxalyl chloride [12]) in the presence of an aprotic base would result in quaternisation to **13**, followed by deprotonation and then intramolecular nucleophilic addition to form **11**. The reaction, in fact, occurred in refluxing pyridine to provide the known **11** [10] as the main product (10%) and impure **7** arising from autooxidation of **11** [6] (*Scheme 2*).

Scheme 2



In contrast to the behaviour of 4-methylnicotinic acid towards oxalyl chloride, its reaction with thionyl chloride led also to side-chain chlorination [13]. Spectroscopic (NMR, MS) examination of the crude product indicated it to consist of at least 50% of 4-(chloromethyl)nicotinoyl chloride (**14**). Reaction of **4** with an excess of this crude **14** in refluxing pyridine gave a gum consisting of two products which were separated by column chromatography and identified as the novel 10,11-dihydro-7,8-dimethoxy-13*H*-pyrido[4′,3′:3,4]pyrrolo[2,1-*b*][3]benzazepin-13-one (**3**) and the known isoquinonaphthyridinone **7** [6]. The structure of **3** was established unequivocally and differentiated from **7** by spectroscopic data.

The EI mass spectra of both **3** and **7** had the molecular-ion peaks as the base peak (*m/z* 308). However, in the IR spectrum, **3** showed the C=O band at 1704 cm^{-1} (γ-lactam), while **7** had it at 1655 cm^{-1} (δ-lactam).

The ^1H- and ^{13}C-NMR spectra of **3** and **7** were assigned using 2D-H,H-ROESY and C,H-correlation experiments. The results are listed in the *Exper. Part.* ^1H-NMR NOE studies of **3** revealed enhancements of the signals of MeO–C(7) (10.7%) and H–C(5) (13.5%) upon irradiation of the signal of H–C(6), and of H–C(6) (12.9%) and H–C(4) (10.3%) upon irradiation of H–C(5). The study led to unambiguous assignments of the chemical shifts as follows: MeO–C(8) at 3.933, MeO–C(7) at 3.934, H–C(5) at 6.66, H–C(9) at 6.73, and H–C(6)

at 6.90 ppm. NOE studies on **7** gave the following enhancement: MeO–C(2) (6.6%) and H–C(13) (12.5%) upon irradiation of H–C(1), and H–C(1) (15.8%) and H–C(12) (5%) upon irradiation of H–C(13). The study helped in assigning chemical shifts as follows: MeO–C(3) at 3.96, MeO–C(2) at 4.00, H–C(4) at 6.77, H–C(13) at 6.79, and H–C(1) at 7.27 ppm. The NOE studies incidentally corrected erroneous literature assignments [9], *viz.* H–C(1) or H–C(4) at 6.77 and H–C(13) at 7.27 ppm. As reported in *Table 1*, there is a semiquantitative correlation between internuclear distances and % NOE, the shortest distance (1.8 Å) giving the highest NOE (15.8%).

Table 1. *NOE Studies on Compounds* **3** *and* **7**

	Protons involved	Internuclear distance [Å]	NOE [%]
3	H–C(5), H–C(6)	2.4	12.9
	H–C(5), H–C(4)	2.3	10.3
7	H–C(13), H–C(1)	1.8	15.8
	H–C(13), H–C(12)	2.5	5.0

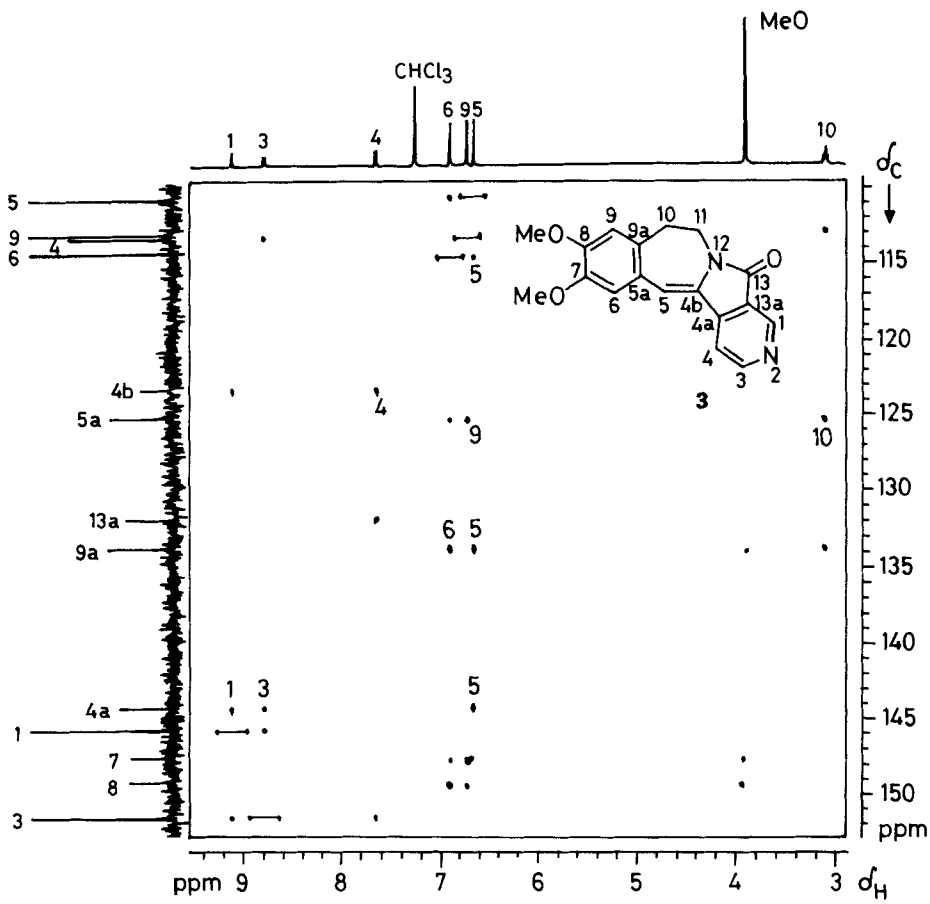


Fig. 1. *$^{13}C,^{1}H$ Inverse-correlated 2D NMR spectrum* (600 MHz) *of pyridopyrrolobenzazepine* **3**

The isomeric structures **3** and **7** were characterised by other differences. In the ^{1}H-NMR spectrum of **7**, CH_2(5) and CH_2(6) appeared as clean *t* at 2.97 and 4.36 pm, respectively, indicating full flexibility of the CH_2CH_2 unit in ring B. In the case of **3**, the signal of CH_2(10) was again a *t* (3.13 ppm), while that of CH_2(11) showed up as a broad hump at 4.2 ppm implying decreased flexibility. This is supported by an inspection of *Dreiding* models of **3** and **7**.

Further differentiation was observed in the long-range inverse-C,H-correlated 2D NMR spectra of **3** and **7**. Thus, in the case of **3** (*Fig. 1*), C(4a) showed strong (*i.e.* vicinal) ^3J(C,H) cross-peaks with *H*–C(1), *H*–C(3), and *H*–C(5), the first two being vicinal *trans*- and the last a vicinal *cis*-coupling. There was no correlation of C(4a) with *H*–C(4), in agreement with the corresponding very small geminal C,H coupling in pyridine (0.7 Hz). Likewise, C(6) was coupled to *H*–C(5) ($^3J_{cis}$) and C(4b) to *H*–C(4) ($^3J_{cis}$). C(5a) showed strong cross-peaks with *H*–C(9) and *H*–C(10), but none with the geminal *H*–C(5). These couplings could be seen in the fully coupled ^{13}C-NMR spectrum. C(13b) in **7**, on the other hand, showed cross-peaks with *H*–C(13) ($^3J_{cis}$), in addition to coupling with *H*–C(4) and CH_2(5).

Final confirmation of the novel structure of **3** came from single-crystal X-ray studies. The ORTEP diagram [14] is shown in *Fig. 2*.

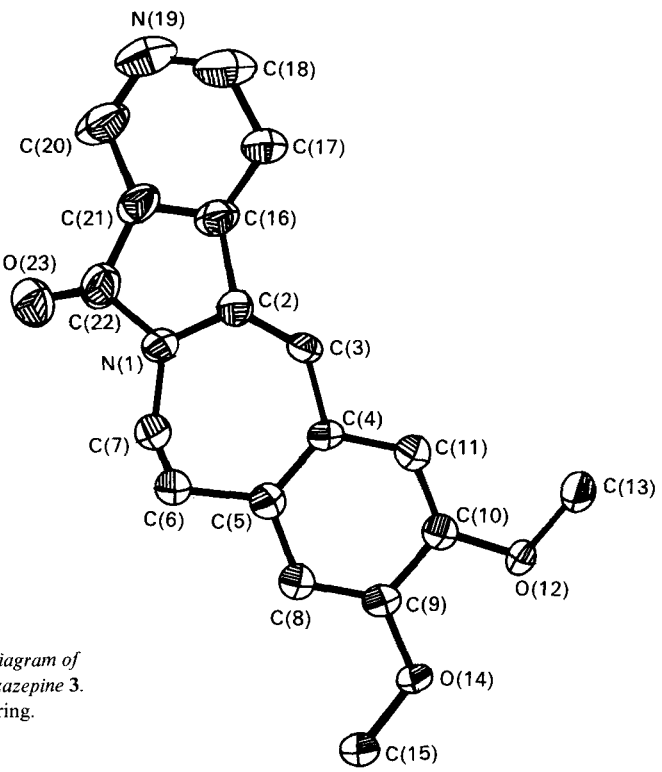
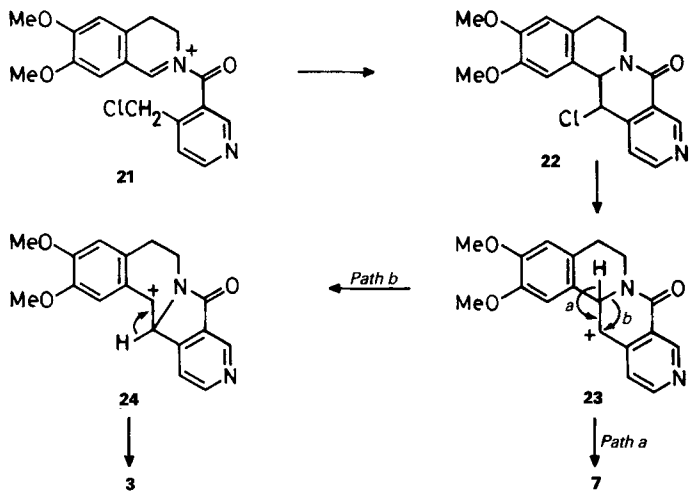


Fig. 2. *ORTEP Diagram of pyridopyrrolobenzazepine* **3**. Arbitrary numbering.

The formation of **3** and **7** from **4** is a general reaction. Thus, condensation of **14** with 3,4-dihydro-6,7-(methylenedioxy)isoquinoline (**15**) gave isomer pair **16** and **17**. Similarly, the dihydrotrimethoxyisoquinoline **18** yielded the isomer pair **19** and **20**. All new compounds were fully characterised by analytical and spectroscopic data. The pyrrolobenzazepine structures **16** and **19** had the characteristic humps as ^{1}H-NMR signals for CH_2(11), while clean *t*'s were observed for the corresponding CH_2(6) of the 6,6-structures **17** and **20**.

A speculative mechanism for the formation of the isomeric products from dihydroisoquinolines and 4-(chloromethyl)nicotinoyl chloride (**14**) is presented in *Scheme 3*. The initially formed quaternary acyl iminium chloride **21** can undergo intramolecular nucleophilic addition to species **22** and the latter be solvolyzed to carbenium ion **23**. Elimination of a proton (*Path a*) would give **7** and migration of the N–C bond (*Path b*) another carbenium ion, **24**. The latter can now lose a proton and thus produce **3**. *A priori* in the literature synthesis [9] of **7**, the intermediate **6** could be expected to yield **22** or **23** with $POCl_3$ which in turn should have afforded **3** in addition to **7** which was actually isolated.

Scheme 3



We plan to repeat the reaction and are synthesizing **5** for this purpose as well as to convert it to pure 4-(chloromethyl)nicotinoyl chloride (**14**). We expect that *pure* **14** and 3,4-dihydroisoquinolines will undergo a cleaner reaction to give the desired products in higher yields.

Conclusion. – Condensation of 4-methylnicotinoyl chloride (**12**) and 4-(chloromethyl)nicotinoyl chloride (**14**) with 3,4-dihydroisoquinolines **4**, **15**, and **18** in refluxing pyridine offers simple routes to the isoquino[2,1-*b*][2,7]naphthyridine ring system present in the *Alangium* alkaloids. In addition, the reaction involving **14** led to the formation of a new ring system, 13*H*-pyrido[4′,3′:3,4]pyrrolo[2,1-*b*][3]benzazepine. Although alkaloids incorporating this framework have not been encountered in nature so far, we expect, on biogenetic analogy with the prechilenine-chilenine conversion [3], that alkaloids of structure **25** are likely to be present in the *Alangium* species. Additionally, such alkaloids are isosteric with 5*H*-indolo[1,2-*b*][3]benzazepines having the ring system of **2** and marked cytotoxicity towards leukaemia P-388 cells [15]. We are hence attempting to elaborate such compounds and also to gain easy access to isoquinonaphthyridines with the correct side chains, as present in the *Alangium* alkaloids, by using 5-ethenyl- and 5-ethyl-4-methylnicotinic acids [16].

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Experimental Part

General. M.p.: uncorrected. UV/VIS Spectra: *Kontron-Uvikon-810* spectrophotometer; λ_{max} in nm (log ε). IR Spectra: in $CHCl_3$; *Shimadzu-4200* FT-IR spectrometer; in cm^{-1}. ^1H- and ^{13}C-NMR Spectra: in $CDCl_3$; *Bruker*-200-MHz and -600-MHz spectrometers, chemical shifts in ppm downfield from Me_4Si, *J* in Hz. Mass spectra: *Shimadzu-GC-MS-QP-1000* mass spectrometer using both EI and CI techniques; *m/z* (rel. intensity in %).

*5,6,13,13a-Tetrahydro-2,3-dimethoxy-8*H*-isoquino[2,1-*b*][2,7]naphthyridin-8-one* (**11**). A suspension of 4-methylnicotinic acid (= 4-methylpyridine-3-carboxylic acid; 0.548 g, 4 mmol) [16] in CH_2Cl_2 (40 ml) containing DMF (2 drops) was cooled to 0° and treated under stirring with oxalyl chloride (0.46 ml, 5.32 mmol). After being set aside for 15 min at 0° and for 2 h at 30°, CH_2Cl_2 and excess oxalyl chloride were distilled off. The residue (crude **12**) was washed with dry benzene (2 ml) and then treated with 3,4-dihydro-6,7-dimethoxyisoquinoline [17] (**4**; 0.382 g, 2 mmol) in dry pyridine (10 ml). The mixture was heated under reflux for 4 h and then evaporated: dark powder (0.5 g). Chromatography (silica gel (30 g), column in $CHCl_3$, then $CHCl_3$/MeOH 99.5:0.5) gave a clean yellow powder (0.196 g, 32%). TLC (silica gel, CH_2Cl_2/MeOH 9:1): 2 very close spots corresponding to **7** and **11**. Rechromatography (silica gel (20 g), column in benzene) with benzene/MeOH 98.5:1.5 first gave **7**/**11** 2:3 (51 mg) and then pure **11** (63 mg, 10.2%). **11**: Off-white crystals from MeOH. M.p. 172–173° ([10]: m.p. 173–175°). UV (MeOH): 280 (3.76), 355 (2.91). IR: 1650 (C=O). ^1H-NMR (200 MHz): 9.27 (*s*, H–C(9)); 8.66 (*d*, *J* = 5, H–C(11)); 7.20 (*d*, *J* = 5, H–C(12)); 6.80, 6.70 (2*s*, H–C(1), H–C(4)); 4.99 (*d*, *J* = 9.0, 2.0, H–C(13a)); 4.90 (*dd*, *J* = 13.0, 3.8 (H_{eq}–C(6)); 3.91, 3.90 (2*s*, MeO–C(3), MeO–C(2)); 3.23 (*dd*, *J* = 16.0, 3.9, H_{eq}–C(5)); 2.80–3.05 (*m*, H_{ax}–C(5), H_{ax}–C(6), CH_2(13)). MS: 310 (59, M^+), 309 (100), 295 (22), 279 (22). Anal. calc. for $C_{18}H_{18}N_2O_3$ (310.34): C 69.66, H 5.85, N 9.03; found: C 69.32, H 5.96, N 8.96.

Isomer Pairs **3**/**7**, **16**/**17**, *and* **19**/**20**: *General Procedure.* At 0°, 4-methylnicotinic acid [16] (1.1 g, 8 mmol) was stirred with thionyl chloride (25 ml, 342 mmol) for 6 h. After being left at 30° for 14 h, the mixture was filtered, the filtrate evaporated at 90° *in vacuo*, the residual gum washed with benzene (3 × 10 ml) and the solvent decanted. To the residue (crude **14**) were added the dihydroisoquinoline **4**, **15**, or **18** [17] (3.2 mmol) and dry pyridine (20 ml), and the mixture was heated under reflux for 4 h (TLC (silica gel, AcOEt/CH_2Cl_2 3:2): no dihydroisoquinoline left). Pyridine was evaporated and the residual solid soaked in H_2O (40 ml) overnight and extracted with CH_2Cl_2 (6 × 20 ml). Evaporation gave a brownish gum weighing *ca.* 1.2 times the amount of dihydroisoquinoline taken (TLC (silica gel, AcOEt/CH_2Cl_2 3:2): 3 compounds, *ca.* 1:3:3 in the order of increasing polarity). The crude product was chromatographed (silica gel (30 g), column in $CHCl_3$) with CH_2Cl_2/MeOH 98.5:0.5 gave elemental S (22 mg; m.p. 113–115°), followed by the pyridopyrrolobenzazepinone (yield *ca.* 10%; characteristic strong blue fluorescence in soln.; TLC (silica gel): intense yellow fluorescence under UV light) and isoquinonaphthyridinone (yield *ca.* 10%, pale blue fluorescence in soln.; TLC (silica gel): intense blue fluorescence under UV light). Quantitative separation of the two isomers was not possible.

*10,11-Dihydro-7,8-dimethoxy-13*H*-pyrido[4',3':3,4]pyrrolo[2,1-*b*][3]benzazepin-13-one* (**3**): Yellow crystals from CH_2Cl_2/MeOH. M.p. 210–212°. UV ($CHCl_3$): 265 (4.15), 383 (4.44). IR: 1704 (C=O). ^1H-NMR (600 MHz): 9.12 (sl. br. *s*, H–C(1)); 8.79 (*d*, *J* = 5.2, H–C(3)); 7.65 (*dd*, *J* = 5.2, 1, H–C(4)); 6.90 (*s*, H–C(6)); 6.73 (*s*, H–C(9)); 6.66 (*s*, H–C(5)); 4.2 (br. hump, CH_2(11)); 3.934, 3.933 (2*s*, 2 MeO); 3.13 (*t*, *J* = 4.8, CH_2(10)). ^{13}C-NMR (150.9 MHz): 164.3 (C(13)); 151.4 (C(3)); 149.1 (C(8)); 147.5 (C(7)); 145.6 (C(1)); 144.2 (C(4a)); 133.6 (C(9a)); 131.7 (C(13a)); 125.1 (C(5a)); 123.2 (C(4b)); 114.2 (C(6)); 113.2 (C(4)); 113.0 (C(9)); 110.6 (C(5)); 55.90, 55.86 (2 MeO); 41.7 (C(11)); 35.1 (C(10)). MS: 308 (100, M^+), 309 (98), 293 (46). Anal. calc. for $C_{18}H_{16}N_2O_3$ (308.34): C 70.11, H 5.23, N 9.09; found: C 69.84, H 5.33, N 9.17.

*5,6-Dihydro-2,3-dimethoxy-8*H*-isoquino[2,1-*b*][2,7]naphthyridin-8-one* (**7**): Yellow crystals from CH_2Cl_2/MeOH. M.p. 169–170°. UV (MeOH): 240 (4.15), 355 (4.32). IR 1655 (C=O). ^1H-NMR (600 MHz): 9.58 (*s*, H–C(9)); 8.67 (*d*, *J* = 5.2, H–C(11)); 7.37 (*d*, *J* = 5.2, H–C(12)); 7.27 (*s*, H–C(1)); 6.79 (*s*, H–C(13)); 6.77 (*s*, H–C(4)); 4.36 (*t*, *J* = 6.2, CH_2(6)); 4.00 (*s*, MeO–C(2)); 3.96 (*s*, MeO–C(3)); 2.97 (*t*, *J* = 6.2, CH_2(5)). ^{13}C-NMR (150.9 MHz): 161.7 (C(8)); 151.4 (C(9), C(3)); 150.3 (C(11), C(12a)?); 148.7 (C(2)); 142.55 (C(13a)); 141.95 (C(8a)); 129.6 (C(4a)); 121.4 (C(13b)); 118.7 (C(12)); 110.5 (C(4)); 108.3 (C(1)); 99.1 (C(13)); 56.3, 56.1 (2 MeO); 39.55 (C(6)); 27.9 (C(5)). MS: 308 (100, M^+), 307 (93), 306 (57), 293 (59). Anal. calc. for $C_{18}H_{16}N_2O_3$ (308.33): C 70.11, H 5.23, N 9.09; found: C 70.26, H 5.32, N 9.13.

10,11-Dihydro-7,8-(methylenedioxy)-13H-pyrido[4',3':3,4]pyrrolo[2,1-b][3]benzazepin-13-one (**16**): Yellow crystals from CH_2Cl_2/MeOH. M.p. 330–332°. UV ($CHCl_3$): 265 (4.17), 384 (4.43). IR: 1704 (C=O). ^{1}H-NMR (200 MHz): 9.11 (*s*, H–C(1)); 8.79 (*d*, *J* = 5.1, H–C(3)); 7.65 (*d*, *J* = 5.1, H–C(4)); 6.89 (*s*, H–C(6)); 6.72 (*s*, H–C(9)); 6.61 (*s*, H–C(5)); 6.01 (*s*, OCH_2O); 4.2 (br. hump, CH_2(11)); 3.09 (*t*, *J* = 4.6, CH_2(10)). MS: 292 (83, M^+), 291 (100), 277 (37). Anal. calc. for $C_{17}H_{12}N_2O_3$ (292.29): C 69.85, H 4.14, N 9.59; found: C 69.56, H 4.34, N 9.60.

5,6-Dihydro-2,3-(methylenedioxy)-8H-isoquino[2,1-b][2,7]naphthyridin-8-one (**17**): Yellow crystals from MeOH. M.p. 287–289°. UV (MeOH): 240 (4.29), 356 (4.42). IR: 1645 (C=O). ^{1}H-NMR (90 MHz): 9.48 (*s*, H–C(9)); 8.56 (*d*, *J* = 6, H–C(11)); 7.24 (*d*, *J* = 6, H–C(12)); 7.17 (*s*, H–C(1)); 6.65 (*s*, H–C(4), H–C(13)); 5.96 (*s*, OCH_2O); 4.24 (*t*, *J* = 6, CH_2(6)); 2.84 (*t*, *J* = 6, CH_2(5)). MS: 292 (87, M^+), 291 (100), 290 (78), 277 (96). Anal. calc. for $C_{17}H_{12}N_2O_3$ (292.29): 69.85, H 4.14, N 9.59; found: C 69.45, H 4.03, N 9.26.

10,11-Dihydro-6,7,8-trimethoxy-13H-pyrido[4',3':3,4]pyrrolo[2,1-b][3]benzazepin-13-one (**19**): Yellow crystals from CH_2Cl_2/MeOH. M.p. 156–158°. UV ($CHCl_3$): 267 (4.39), 381 (4.45). IR: 1700 (C=O). ^{1}H-NMR (200 MHz): 9.10 (*s*, H–C(1)); 8.78 (*d*, *J* = 5, H–C(3)); 7.72 (*d*, *J* = 5, H–C(4)); 7.10 (*s*, H–C(5)); 6.60 (*s*, H–C(9)); 4.3 (br. hump, CH_2(11)); 4.00, 3.90 (2*s*, 2 MeO); 3.88 (*s*, MeO); 3.10 (*t*, *J* = 4.6, CH_2(10)). MS: 338 (100, M^+), 337 (96), 336 (65), 323 (20). Anal. calc. for $C_{19}H_{18}N_2O_4$ (338.35): C 67.44, H 5.36, N 8.28; found: C 67.32, H 5.13, N 8.17.

5,6-Dihydro-1,2,3-trimethoxy-8H-isoquino[2,1-b][2,7]naphthyridin-8-one (**20**): Brownish yellow crystals from MeOH. M.p. 225–226°. UV (MeOH): 267 (4.99), 314 (4.25), 358 (4.29). IR: 1660 (C=O). ^{1}H-NMR (200 MHz): 9.58 (*s*, H–C(9)); 8.65 (*d*, *J* = 5, H–C(11)); 7.38 (*d*, *J* = 5, H–C(12)); 7.30 (*s*, H–C(13)); 6.45 (*s*, H–C(4)); 4.32 (*t*, *J* = 6, CH_2(6)); 4.0 (*s*, 2 MeO); 3.95 (*s*, MeO); 2.95 (*t*, *J* = 6, CH_2(5)). MS: 338 (22, M^+), 323 (100), 309 (80), 294 (24). Anal. calc. for $C_{19}H_{18}N_2O_4$ (338.35): C 67.44, H 5.36, N 8.28; found: C 67.32, H 5.13, N 8.17.

X-Ray Structure Analysis of **3**. Pale yellow crystals of **3** of the dimensions 0.4 × 0.35 × 0.3 mm were used for the three-dimensional intensity data collection. The intensity data were collected on an *Enraf-Nonius-CAD-4* automated diffractometer equipped with MoK_α radiation in the $\omega/2\theta$ scan mode. The unit cell dimensions were obtained using the least-squares method for 25 well centered, dispersed reflections in the range $12 \leqslant 2\theta \leqslant 23°$. Three standard reflections (0 6 2, 1 –3 6, –2 3 5) monitored every 3600 s of exposure time showed variations in intensity $< \pm 1\%$. The data collection scan angle was $(0.71 + 2.1 \tan\theta)°$ and the aperture width $(0.35+1.05 \tan\theta)$ mm. The maximum time spent on any measurement was 60 s and the background count half the scan time. The data were collected for the range $2 \leqslant 2\theta \leqslant 50°$, $0 \leqslant h \leqslant 9$, $0 \leqslant k \leqslant 15$, and $-17 \leqslant l \leqslant 17$. Out of 3011 reflections measured, 2557 were unique, and 1730 reflections with $|F_o| \geqslant 5.0\sigma(F_o)$ were considered observed and used for the structure solution and further refinement. The data were corrected for *Lorentz* and polarisation effects but not for absorption. The structure was obtained by direct methods using the program MULTAN-84 [18]. H-Atoms were located from the difference *Fourier* map. The structure was refined using the full-matrix least-squares method on $|F_o|$'s using the program SHELX 76 [19]. All non-H-atoms were subjected to anisotropic refinement, whereas the H-atoms were isotropically refined to a final $R = 0.047$ and $wR = 0.060$, with individual weighting scheme based on counting statistics where $w = (\sigma^2(F_o) + 0.01646|F_o|^2)^{-1}$; final $(\Delta/\sigma)_{max} = 0.02$; $(\Delta/\sigma)_{mean} = 0.01$; goodness of fit $(S) = 1.20$ for 273 parameters. Final difference *Fourier* map had no peaks $\geqslant 0.2$ eÅ^{-3}. Important crystal data are given in *Table 2*, supplementary material was deposited with the *Cambridge Crystallographic Data Centre*.

Table 2. *Crystal Data for* **3**

Formula	$C_{18}H_{16}N_2O_3$	Crystal system	monoclinic
Mol. wt.	308.34	Space group	$P2_1/n$
Density	1.406 g cm^{-3}	Cell dimensions	a = 7.634(1) Å
Cell volume V	1458.3(9) Å^3		b = 13.420(2) Å
Z	4		c = 14.308(3) Å
μ(MoK_α)	0.91 cm^{-1}		β = 95.57(3)°
Measurement temperature T	295 K		

REFERENCES

[1] S.C. Pakrashi, R. Mukhopadyay, R.R. Sinha, P.P. Ghosh Dastidar, B.Achari, E. Ali, *Indian J. Chem., Sect. B* **1985,** *24,* 19.

[2] M. Shamma, 'The Isoquinoline Alkaloids, Chemistry and Pharmacology', Academic Press, New York, 1972, p. 268.

[3] E. Valencia, A.J. Freyer, M. Shamma, V. Fajardo, *Tetrahedron Lett.* **1984,** *25,* 599.

[4] H.O. Bernhard, V. Snieckus, *Tetrahedron Lett.* **1971,** 4867.

[5] S. Ruchirawat, W. Lertwanawatana, S. Thianpatanagul, J.L. Cashaw, V.E. Davis, *Tetrahedron Lett.* **1984,** *25,* 3485.

[6] G.R. Lenz, *J. Heterocycl. Chem.* **1979,** *16,* 433.

[7] T. Naito, I. Ninomiya, *Heterocycles* **1980,** *14,* 959.

[8] T. Naito, O. Miyata, I. Ninomiya, S.C. Pakrashi, *Heterocycles* **1981,** *16,* 725; A. Bhattacharjya, R. Mukhopadhyay, S.C. Pakrashi, *Tetrahedron Lett.* **1986,** *27,* 1215; U.S. Chowdhury, *Tetrahedron* **1990,** *46,* 7893.

[9] Jahangir, D.B. Maclean, H.L. Holland, *Can. J. Chem.* **1986,** *64,* 1031.

[10] Jahangir, D.B. Maclean, M.A. Brook, H.L. Holland, *J. Chem. Soc., Chem. Commun.* **1986,** 1608.

[11] K. Nagarajan, P.J. Rodrigues, K. Go, R. Parthasarathy, *Tetrahedron Lett.* **1992,** *33,* 6011; K. Nagarajan, P.J. Rodrigues, M. Nethaji, *ibid.* **1992,** *33,* 7229.

[12] R. Adams, L.H. Ulrich, *J. Am. Chem. Soc.* **1920,** *42,* 599.

[13] N.A. Preobrazhenskii, A.A. Beer, *J. Gen. Chem. (U.S.S.R.)* **1945,** *15,* 667.

[14] C.K. Johnson, 'ORTEP. Report ORNL-3794', Oakridge National Laboratory, Tennessee, USA, 1965.

[15] B. Proska, J. Fuska, *Pharmazie* **1985,** *40,* 521.

[16] T.R. Govindachari, K. Nagarajan, S. Rajappa, *J. Chem. Soc.* **1957,** *551,* 2725.

[17] W.M. Whaley, T.R. Govindachari, in 'Organic Reactions', Ed.R. Adams, John Wiley, New York, 1951, Vol. VI, p. 74.

[18] P. Main, G. German, M.M. Woolfson, 'A Computer Programme for the Atomic Solution of Crystal Structures from X-Ray Diffraction Data', University of York, UK, 1984.

[19] G.M. Sheldrick, 'SHELX 76. Program for Crystal Structure Determination', University of Cambridge, England, 1976.