

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

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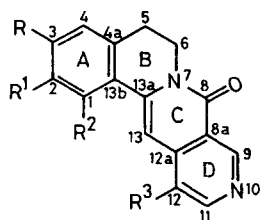
(26. VIII. 93)

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.

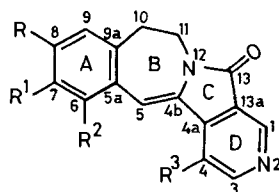
Introduction. – The alkaloids of *Alangium lamareckji* Thw. represented by alangimarine (**1**) [1] have the interesting 8*H*-isoquino[2,1-*b*][2,7]naphthyridin-8-one ring system isosteric with 8-oxoprotoberberines [2]. Alkaloids of the latter group like prechilenine, in the correct oxidation state, were found to rearrange in nature to the isomeric isoindolobenzazepines, e.g. chilene [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 unknown 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-

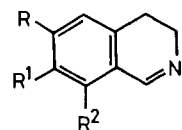
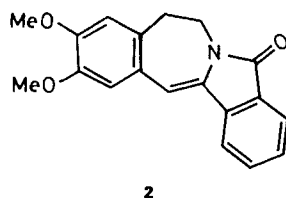
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- 1** $R = \text{MeO}$, $R^1 = \text{OH}$, $R^2 = \text{H}$,
 $R^3 = \text{CH}_2=\text{CH}$
7 $R = R^1 = \text{MeO}$, $R^2 = R^3 = \text{H}$
17 $R, R^1 = \text{OCH}_2\text{O}$, $R^2 = R^3 = \text{H}$
20 $R = R^1 = R^2 = \text{MeO}$, $R^3 = \text{H}$

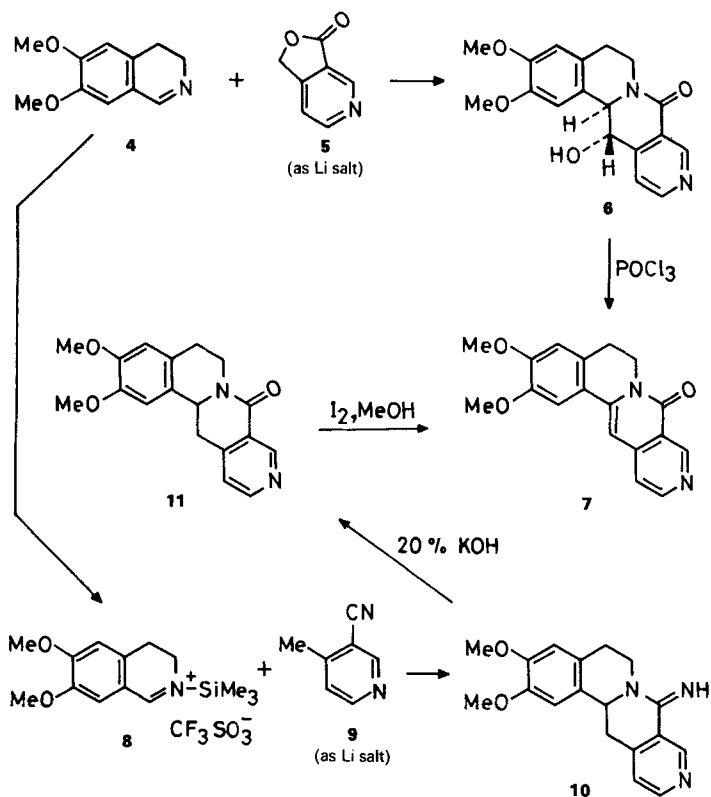


- 3** $R = R^1 = \text{MeO}$, $R^2 = R^3 = \text{H}$
16 $R, R^1 = \text{OCH}_2\text{O}$, $R^2 = R^3 = \text{H}$
19 $R = R^1 = R^2 = \text{MeO}$, $R^3 = \text{H}$
25 $R = R^1 = \text{MeO}$, $R^2 = \text{H}$,
 $R^3 = \text{MeCH(OH)}$ or $\text{CH}_2=\text{CH}$



- 4** $R = R^1 = \text{MeO}$, $R^2 = \text{H}$
15 $R, R^1 = \text{OCH}_2\text{O}$, $R^2 = \text{H}$
18 $R = R^1 = R^2 = \text{MeO}$

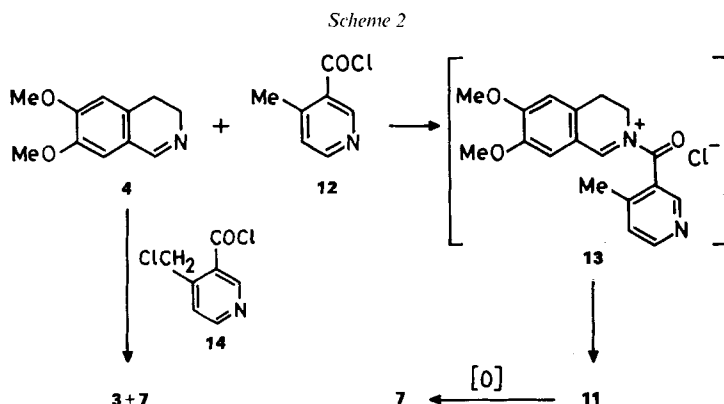
Scheme 1



isoquinoline (**4**) and use the lithium salt of the azaphthalide **5** [9] ($\rightarrow \mathbf{6} \rightarrow \mathbf{7}$) or the lithium salt of 4-methylnicotinonitrile (**9**) with activation of **4** by trimethylsilyl triflate ($\rightarrow \mathbf{8} \rightarrow \mathbf{10} \rightarrow \mathbf{11} \rightarrow \mathbf{7}$; *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*).



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-13H-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.

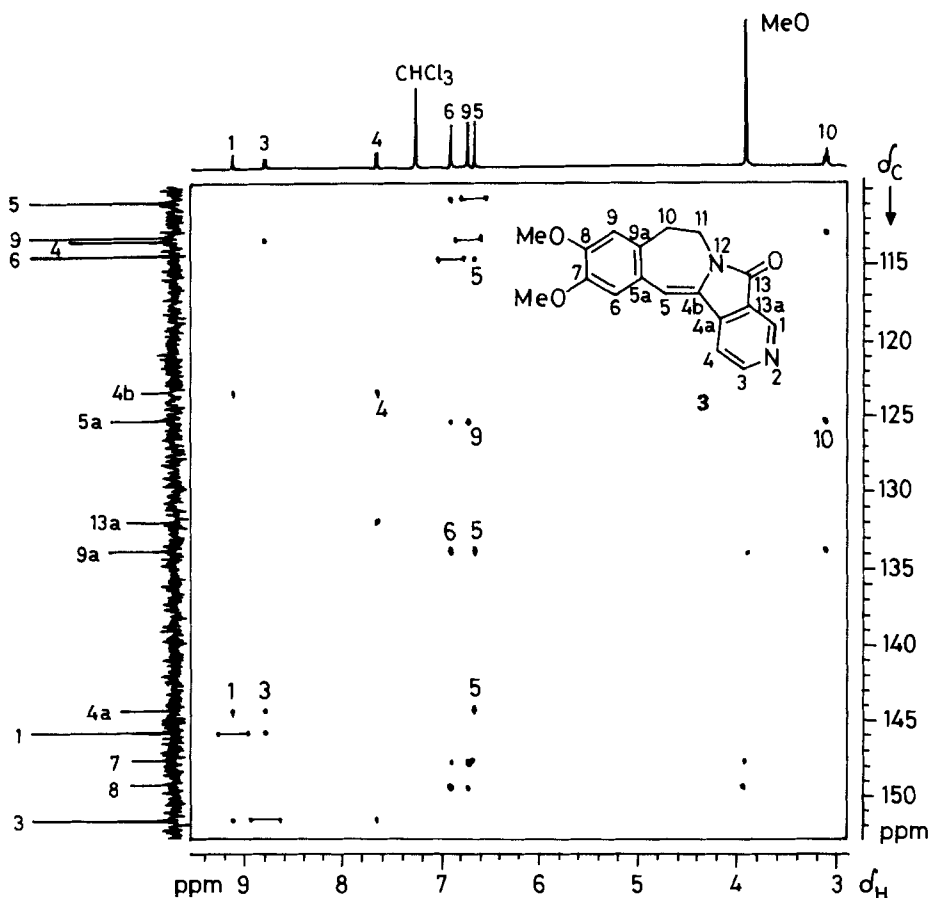
The EI mass spectra of both **3** and **7** had the molecular-ion peaks as the base peak (m/z 308). However, in the IR spectrum, **3** showed the C=O band at 1704 cm^{-1} (γ -lactam), while **7** had it at 1655 cm^{-1} (δ -lactam).

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

The isomeric structures **3** and **7** were characterised by other differences. In the ^1H -NMR spectrum of **7**, $\text{CH}_2(5)$ and $\text{CH}_2(6)$ appeared as clean t at 2.97 and 4.36 ppm, respectively, indicating full flexibility of the CH_2CH_2 unit in ring B. In the case of **3**, the signal of $\text{CH}_2(10)$ was again a t (3.13 ppm), while that of $\text{CH}_2(11)$ 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) $^3J(\text{C},\text{H})$ cross-peaks with $\text{H}-\text{C}(1)$, $\text{H}-\text{C}(3)$, and $\text{H}-\text{C}(5)$, the first two being vicinal *trans*- and the last a vicinal *cis*-coupling. There was no correlation of C(4a) with $\text{H}-\text{C}(4)$, in agreement with the corresponding very small geminal C,H coupling in pyridine (0.7 Hz). Likewise, C(6) was coupled to $\text{H}-\text{C}(5)$ ($^3J_{\text{cis}}$) and C(4b) to $\text{H}-\text{C}(4)$ ($^3J_{\text{cis}}$). C(5a) showed strong cross-peaks with $\text{H}-\text{C}(9)$ and $\text{H}-\text{C}(10)$, but none with the geminal $\text{H}-\text{C}(5)$. 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 $\text{H}-\text{C}(13)$ ($^3J_{\text{cis}}$), in addition to coupling with $\text{H}-\text{C}(4)$ and $\text{CH}_2(5)$.

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

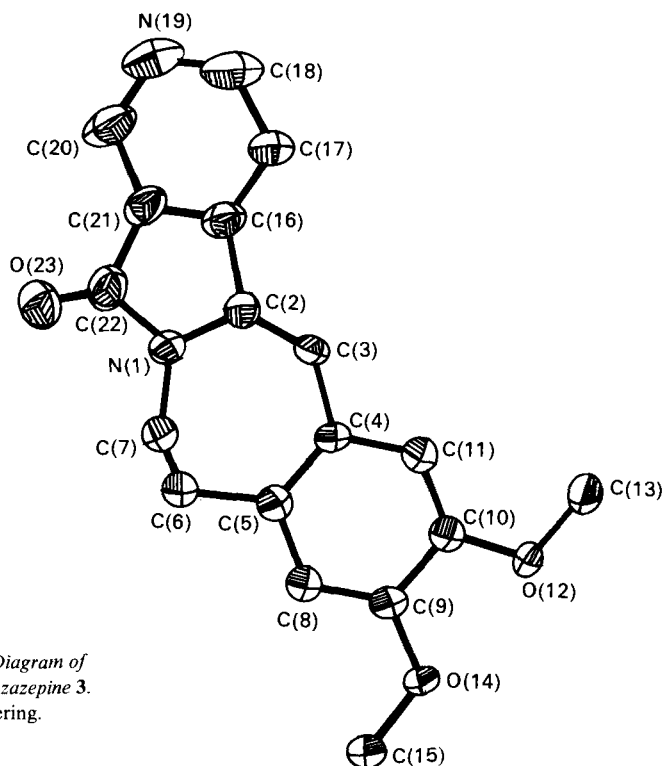
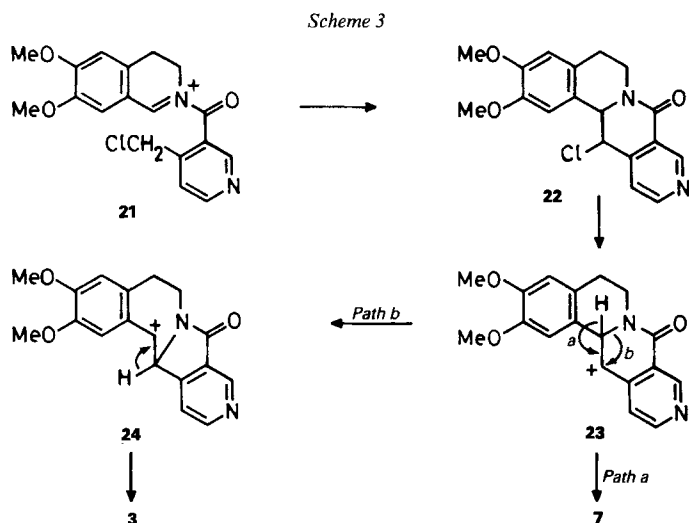


Fig. 2. ORTEP Diagram of pyridopyrrolobenzazepine **3**. Arbitrary numbering.

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 ^1H -NMR signals for $\text{CH}_2(11)$, while clean t 's were observed for the corresponding $\text{CH}_2(6)$ 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.



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].

We wish to thank Prof. K. Venkatesan, Indian Institute of Science, Bangalore, for useful discussions, Dr. A. Banerji, Bhabha Atomic Research Centre and Director Hoechst Research Centre, Bombay, for some NMR spectra, and Dr. V. Manohar and associates for analytical inputs.

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-8H-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 $\text{CHCl}_3/\text{MeOH}$ 99.5:0.5) gave a clean yellow powder (0.196 g, 32%). TLC (silica gel, $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 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. $172\text{--}173^\circ$ ([10]: m.p. $173\text{--}175^\circ$). UV (MeOH): 280 (3.76), 355 (2.91). IR: 1650 ($\text{C}=\text{O}$). ^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 (2s, 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 (2s, 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 $\text{C}_{18}\text{H}_{18}\text{N}_2\text{O}_3$ (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, $\text{AcOEt}/\text{CH}_2\text{Cl}_2$ 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, $\text{AcOEt}/\text{CH}_2\text{Cl}_2$ 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 $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 98.5:0.5 gave elemental S (22 mg; m.p. $113\text{--}115^\circ$), 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-13H-pyrido[4',3':3,4]pyrrolo[2,1-b][3]benzazepin-13-one (3): Yellow crystals from $\text{CH}_2\text{Cl}_2/\text{MeOH}$. M.p. $210\text{--}212^\circ$. UV (CHCl_3): 265 (4.15), 383 (4.44). IR: 1704 ($\text{C}=\text{O}$). ^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 (2s, 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 $\text{C}_{18}\text{H}_{16}\text{N}_2\text{O}_3$ (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-8H-isoquino[2,1-b][2,7]naphthyridin-8-one (7): Yellow crystals from $\text{CH}_2\text{Cl}_2/\text{MeOH}$. M.p. $169\text{--}170^\circ$. UV (MeOH): 240 (4.15), 355 (4.32). IR 1655 ($\text{C}=\text{O}$). ^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 $\text{C}_{18}\text{H}_{16}\text{N}_2\text{O}_3$ (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 $\text{CH}_2\text{Cl}_2/\text{MeOH}$. M.p. 330–332°. UV (CHCl_3): 265 (4.17), 384 (4.43). IR: 1704 ($\text{C}=\text{O}$). $^1\text{H-NMR}$ (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, $\text{CH}_2(11)$); 3.09 (t, $J = 4.6$, $\text{CH}_2(10)$). MS: 292 (83, M^+), 291 (100), 277 (37). Anal. calc. for $\text{C}_{17}\text{H}_{12}\text{N}_2\text{O}_3$ (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 ($\text{C}=\text{O}$). $^1\text{H-NMR}$ (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, $J = 6$, $\text{CH}_2(6)$); 2.84 (t, $J = 6$, $\text{CH}_2(5)$). MS: 292 (87, M^+), 291 (100), 290 (78), 277 (96). Anal. calc. for $\text{C}_{17}\text{H}_{12}\text{N}_2\text{O}_3$ (292.29): C 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 $\text{CH}_2\text{Cl}_2/\text{MeOH}$. M.p. 156–158°. UV (CHCl_3): 267 (4.39), 381 (4.45). IR: 1700 ($\text{C}=\text{O}$). $^1\text{H-NMR}$ (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, $\text{CH}_2(11)$); 4.00, 3.90 (2s, 2 MeO); 3.88 (s, MeO); 3.10 (t, $J = 4.6$, $\text{CH}_2(10)$). MS: 338 (100, M^+), 337 (96), 336 (65), 323 (20). Anal. calc. for $\text{C}_{19}\text{H}_{18}\text{N}_2\text{O}_4$ (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 ($\text{C}=\text{O}$). $^1\text{H-NMR}$ (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, $J = 6$, $\text{CH}_2(6)$); 4.0 (s, 2 MeO); 3.95 (s, MeO); 2.95 (t, $J = 6$, $\text{CH}_2(5)$). MS: 338 (22, M^+), 323 (100), 309 (80), 294 (24). Anal. calc. for $\text{C}_{19}\text{H}_{18}\text{N}_2\text{O}_4$ (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 $0.4 \times 0.35 \times 0.3$ 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 $12 \leq 2\theta \leq 23^\circ$. Three standard reflections (0 6 2, 1 $\bar{3}$ 6, $\bar{2}$ 3 5) monitored every 3600 s of exposure time showed variations in intensity $< \pm 1\%$. The data collection scan angle was $(0.71 + 2.1 \tan \theta)^\circ$ 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 $2 \leq 2\theta \leq 50^\circ$, $0 \leq h \leq 9$, $0 \leq k \leq 15$, and $-17 \leq l \leq 17$. Out of 3011 reflections measured, 2557 were unique, and 1730 reflections with $|F_o| \geq 5.0\sigma(F_o)$ 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 $(\Delta/\sigma)_{\max} = 0.02$; $(\Delta/\sigma)_{\text{mean}} = 0.01$; goodness of fit (S) = 1.20 for 273 parameters. Final difference *Fourier* map had no peaks $\geq 0.2 \text{ e}\text{\AA}^{-3}$. 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	$\text{C}_{18}\text{H}_{16}\text{N}_2\text{O}_3$	Crystal system	monoclinic
Mol. wt.	308.34	Space group	$P2_1/n$
Density	1.406 g cm^{-3}	Cell dimensions	$a = 7.634(1) \text{ \AA}$
Cell volume V	$1458.3(9) \text{ \AA}^3$		$b = 13.420(2) \text{ \AA}$
Z	4		$c = 14.308(3) \text{ \AA}$
$\mu(\text{MoK}_\alpha)$	0.91 cm^{-1}		$\beta = 95.57(3)^\circ$
Measurement temperature T	295 K		

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