



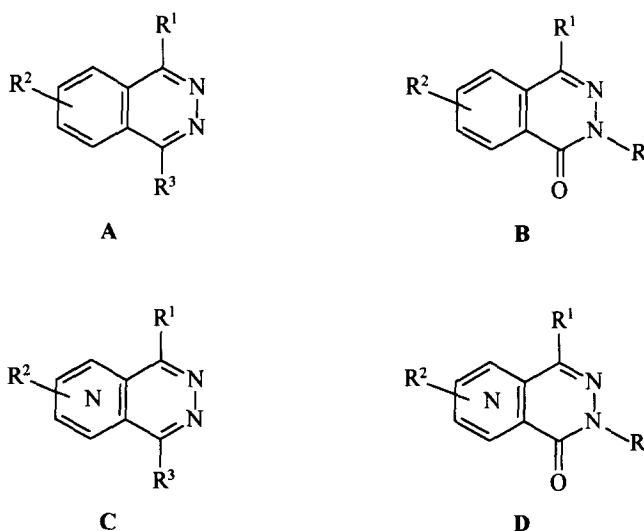
A Concise Regioselective Synthesis of Hydroxyazaisoindolinones and Their Conversion into Pyridopyridazinones

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Abstract: The synthesis of pyridopyridazinones **7** and **8** via the reaction of hydroxyazaisoindolinones **5** and **6** with hydrazine hydrate is described. Compounds **7** and **8** were then subjected to reactions with alkyl halides to furnish N-alkyl derivatives. Only in the reaction of pyridopyridazinone **8** with benzyl bromide was the O-benzylpyridopyridazine **14b** formed in addition to the N-benzylpyridopyridazinone **14a**.

During the past few decades increasing interest in the synthesis and properties of phthalazines **A**, phthalazinones **B**, pyridopyridazines **C**, and pyridopyridazinones **D** (Scheme 1) has been observed.



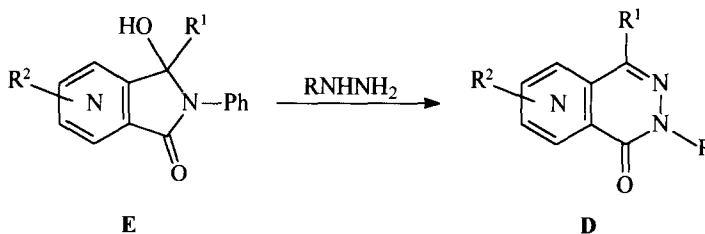
Scheme 1

Compounds of the type **A** and **B** show antihypertensive,¹ antiallergic, antiasthmatic and antihistaminic,² bronchodilatory,³ diuretic and saluretic,^{1b} tuberculostatic,⁴ and antimicrobial⁵ activity. They inhibit blood platelet aggregation,^{3, 6} are efficient in the treatment of diabetic complications⁷ and have been tested as cardiac⁸ agents. It was also found that phthalazine derivatives are useful as inhibitors of HIV proteases.⁹ Some compounds of the type **A** and **B** are used successfully as medicines or are undergoing clinical testing.^{1a, 2, 3, 7, 8c} There is a huge number of patents concerning the application of phthalazinones **B** as components of copying materials.¹⁰ Substances of the type **A** and **B** can also serve as pigments¹¹ and plant growth regulators.¹²

Pyridopyridazines **C** and pyridopyridazinones **D** show diuretic,¹³ antihypertensive,^{13e, 14} and anticonvulsant, antispasmodic and muscle relaxant^{14a, 14b} activity. They inhibit blood platelet aggregation¹⁵ and are active in the treatment of diabetic complications.^{7c, 16} Compounds of the type **C** and **D** were also tested as cardiac¹⁷ and tuberculostatic agents,^{14b} as fungicides,^{14b} and as herbicides.¹⁸ Their use as antiasthmatics, analgesics and inflammation inhibitors is also claimed.¹⁹

In contrast to the phthalazinones **B**, their aza analogs **D** are as yet relatively little studied, as concerns their synthesis, chemical properties and further applications. The primary reasons for this are the difficulties associated with the preparation of pyridine starting materials which can easily be transformed into pyridopyridazinones **D**. Most synthetic methods for azaphthalazinones **D**, as well as for phthalazinones **B**, are based on formation of the pyridazinone ring. The only general method for the synthesis of the system **D** involves the cyclization of *o*-acylpyridinecarboxylic acids^{14b} and their derivatives (esters^{14b} and disubstituted amides²⁰) or of methyl esters of *o*-cyanopyridinecarboxylic acids²¹ with hydrazine and monosubstituted hydrazines.

Continuing our interest in synthesis of pyridopyridazinones of the type **D**,²⁰ we present a new approach to their synthesis (Scheme 2) applying a method which was previously employed in only a few cases to the preparation of phthalazinones **B**.^{1b, 6b, 22} Probable mechanisms of this transformation have been proposed by Yellin and coworkers.^{1b}



Scheme 2

3-Hydroxyisoindolinones, as well as other hydroxylactams, behave in many reactions like ring - chain

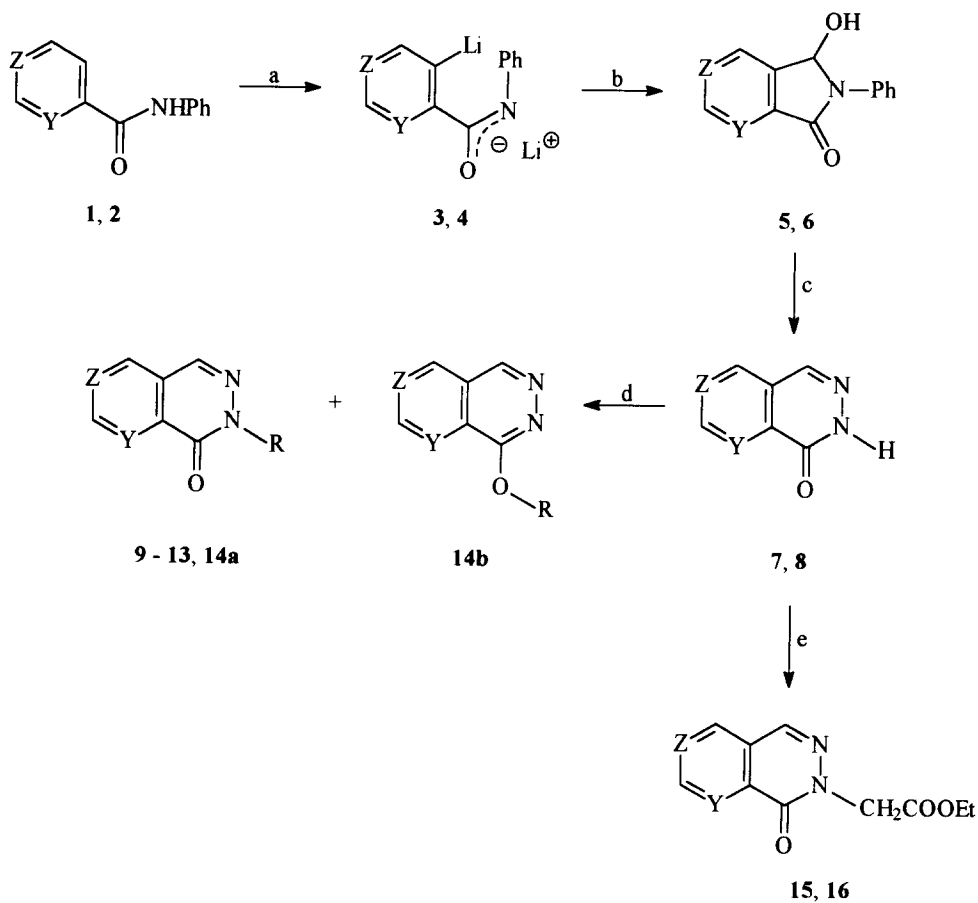
tautomers of the keto(aldehyde)amide - hydroxylactame type. In principle, this type of compounds can be considered as (i) a source of N-acyliminium cations well known to react with various types of nucleophiles²³ and (ii) masked *o*-acylbenzamides, which are used in reactions with anionic species (e.g., Wittig reaction²⁴ or base-catalysed condensation reactions^{24a}).

On the basis of this viewpoint, we investigated the reaction of hydroxyzaisoindolinones **E** with hydrazine, as depicted in the Scheme 2, and we report the results herein. Previous limitations of this methodology are related to the problems connected with the selectivity of the synthesis of corresponding 3-hydroxyisoindolinones, which usually require multistep processes. The presented preparative route avoids these problems since hydroxyzaisoindolinones **E**, as well as 3-hydroxyisoindolinones, are now regioselectively synthesized in one-pot procedure, as was recently reported.²⁵

As depicted in the Scheme 3, the anilides **1** and **2** (prepared from the corresponding, commercially available pyridinecarboxylic acids²⁶) were first allowed to react with two equivalents of *n*-butyllithium in tetrahydrofuran (THF) generating the regioselectively lithiated species **3** and **4**. The treatment of the lithioderivatives **3** and **4** with dimethylformamide (DMF) furnished the desired hydroxyzaisoindolinones **5** (68%) and **6** (76%), which are masked *o*-formylpyridinecarboxanilides. In the next step, the compounds **5** and **6** were converted, with elimination of aniline, into the corresponding pyridopyridazinones **7** (63%) and **8** (75%) by reaction with hydrazine hydrate.

Since the majority of phthalazinones of practical significance are N-substituted derivatives, we examined the N-alkylation reactions of the pyridopyridazinones **7** and **8**. Most of the substituents chosen were those which could be easily modified further. The potassium salts of azaphthalazinones **7** and **8** were reacted with alkyl halides (MeI, CH₂=CHCH₂Br and PhCH₂Br) according to the procedure given formerly.²⁰ In the case of methyl iodide and allyl bromide, the corresponding N-methyl- **9** (55%), **10** (61%) and N-allyl- **11** (28%), **12** (59%) azaphthalazinones were formed. In the reaction of pyridopyridazinones **7** and **8** with benzyl bromide, the former (**7**) gave the N-benzyl derivative **13** (30%) and the latter (**8**) gave a mixture of N-benzyl **14a** (38%) and O-benzyl **14b** (17%) derivatives. The isomers **14a** and **14b** were separated by chromatography and their structures were confirmed by the ¹H NMR, ¹³C NMR and IR spectra on the following evidence:

- (i) In the ¹H NMR spectra of the compounds **14a** and **14b**, no signals due to N-H protons are present. Instead, signals which correspond to the protons of benzyl groups can be found. The pattern of the aromatic region in the spectrum of the benzyl derivative **14a** is the same as in the spectra of pyridopyridazinones **8**, **10**, **12** and **16**, whereas in the spectrum of the compound **14b** the signal of the proton from the position 4 of pyridazine ring (4-H) is significantly (about 1 ppm) downshielded.
- (ii) In the ¹³C NMR spectra of the benzyl derivatives **14a** and **14b**, the signals of methylene carbons appear at 54.0 and 66.9 ppm, respectively. The chemical shifts of benzyl, methylene carbons were predicted using



1, 3, 5, 7, 15: Y = N, Z = CH

2, 4, 6, 8, 16: Y = CH, Z = N

9: Y = N, Z = CH, R = Me

10: Y = CH, Z = N, R = Me

11: Y = N, Z = CH, R = CH₂CH=CH₂

12: Y = CH, Z = N, R = CH₂CH=CH₂

13: Y = N, Z = CH, R = CH₂Ph

14: Y = CH, Z = N, R = CH₂Ph

a. *n*-BuLi in THF/hexane, -78°C→0°C

b. (i) DMF, -78°C→0°C; (ii) H₃O⁺

c. N₂H₄·H₂O, Δ

d. (i) KOH in MeOH, Δ; (ii) RX, Δ

e. RX in Me₂CO, K₂CO₃, Δ

Scheme 3

the computer program C-13 Module for ChemWindow²⁷ that gave value for the N-benzylpyridopyridazinone 53.7 ppm and for the O-benzylpyridopyridazine 77.8 ppm. The experimental value 54.0 ppm for the compound **14a** is in an excellent agreement with that anticipated for the N-substituted azaphthalazinone, whereas the chemical shift 66.9 ppm for the derivative **14b**, although 11 ppm lower than that predicted for the O-substituted azaphthalazine, is in accordance with the foreseen direction of the shielding effects.

- (iii) In the IR spectra of both compounds **14a** and **14b** there are no N-H bands. Similarly as in the spectra of the pyridopyridazinones **7-13**, **15**, **16** and those obtained previously,²⁰ the spectrum of the benzyl derivative **14a** displays the C=O band at 1665 cm⁻¹ which is absent in the spectrum of the benzyl compound **14b**.

When the azaphthalazinones **7** and **8** were reacted with ethyl bromoacetate in dry acetone in the presence of anhydrous potassium carbonate the corresponding N-carboethoxymethyl derivatives **15** (69%) and **16** (68%) were formed. The structures of the compounds **15** and **16** were fully confirmed by the ¹H NMR, ¹³C NMR and IR spectra. In view of the formation of derivatives **15** and **16** in the above reaction, the result reported by Soliman and coworkers²⁸ for the reaction of 4-biphenyl-1(2H)-pthalazinone with ethyl chloroacetate conducted under identical conditions is quite surprising. The authors claimed that the O-substituted derivative was formed and not the N-substituted derivative, assigning the band at 1670 cm⁻¹ to the azomethine bond not to the pyridazinone ring carbonyl group. They also gave a very uncharacteristic ¹H NMR spectrum that cannot be used for the distinguishing of the product structure. Our confirmation of the structures of the compounds **15** and **16** was based on the following evidence:

- (i) In the ¹H NMR spectra of the compounds **15** and **16**, no signals due to N-H protons are present. Instead, signals which correspond to the protons of carboethoxymethylene groups can be found. The pattern of the aromatic region in the spectra of the carboethoxymethyl derivatives **15** and **16** remains the same as in the spectra of pyridopyridazinones **7**, **9**, **11**, **13** and **8**, **10**, **12**, **14a**, respectively.
- (ii) In the ¹³C NMR spectra of the compounds **15** and **16**, signals corresponding to the carbons of carboethoxymethylene groups are present. The predicted²⁷ chemical shift of the N-methylene carbon (NCH₂CO) for the N-carboethoxymethylpyridopyridazinones **15** and **16** is 51.5 ppm, whereas for the isomeric O-carboethoxymethylpyridopyridazines it is 75.6 ppm. The experimental values 52.9 and 53.0 ppm for the compounds **15** and **16**, respectively, are in an excellent agreement with the value anticipated for the N-substituted derivative.
- (iii) In the IR spectra of the compounds **15** and **16**, no N-H bands can be found, whereas two C=O bands belonging to the ester carbonyl groups at 1745 and 1750 cm⁻¹ and to the pyridazinone carbonyl groups at 1680 and 1675 cm⁻¹, respectively, are present. The latter bands clearly belong to the pyridazinone carbonyl groups and not to the azomethine bonds, which is confirmed by the same absorption frequency of the C=O bands in the spectra of pyridopyridazinones **7-13**, **14a** and those obtained previously.²⁰ Another reason that these bands cannot be assigned to the azomethine bonds is that in the O-benzyl derivative **14b**,

the C=N bands appear together with the C=C bands in the region below 1605 cm^{-1} .

In conclusion, the described methodology represents an effective route for the preparation of pyridopyridazinones and their derivatives, starting from easily available pyridinecarboxanilides.

EXPERIMENTAL PART

General. Melting points were determined using a Boetius hot stage apparatus and they are uncorrected. The ^1H NMR spectra were recorded at 300 MHz on a Varian Gemini 300 or at 60 MHz on a Tesla BS-467 spectrometers and the ^{13}C NMR spectra were recorded at 75 MHz on a Varian Gemini 300 spectrometer. In all cases when the solvent used was DMSO- d_6 and the spectra were registered on a Tesla BS-467 spectrometer, Me_4Si was used as an external reference, while in the remaining cases Me_4Si was used as an internal reference. A Zeiss-Jena Specord 71-IR spectrometer was used for the IR spectra. Analytical thin layer chromatography tests (TLC) were carried out on Merck silica gel plates (Kieselgel 60 F_{254} , layer thickness 0.2 mm). Column chromatography separations were performed on Macherey Nagel & Co. silica gel (MN Kieselgel 60 0.075-0.15mm/100-200 mesh ATSM) using 30 g of silica gel per 1 g of the separated mixture. *n*-Butyllithium in hexane (Aldrich) was titrated each time before use. Tetrahydrofuran (THF) used was passed through a column of neutral alumina, heated under reflux over calcium hydride, then distilled from it and stored in dark over sodium chips.^{29a} Dimethylformamide (DMF) used was dried by azeotropic distillation with anhydrous benzene, shaken with activated, neutral alumina (Brockmann I), filtered, then distilled under argon at reduced pressure and stored over type 4A molecular sieves.^{29b} Anilides **1** and **2** were prepared from commercially available pyridinecarboxylic acids according to the method given previously.²⁶

Hydroxyazaisoindolinones 5 and 6. Hydroxyazaisoindolinones **5** and **6** were obtained according to the procedure reported previously.^{25f}

*5,6-Dihydro-5-hydroxy-6-phenyl-7H-pyrrolo[3,4-*b*]pyridin-7-one (5).* M.p. $239\text{--}241^\circ\text{C}$ (ethanol) (lit.^{25f} m.p. $237\text{--}239^\circ\text{C}$). Yield 68%.

*2,3-Dihydro-3-hydroxy-2-phenyl-1H-pyrrolo[3,4-*c*]pyridin-1-one (6).* M.p. $221\text{--}223^\circ\text{C}$ (ethanol) (lit.^{25f} m.p. $223\text{--}225^\circ\text{C}$). Yield 76%.

Pyridopyridazinones 7 and 8. The hydroxyazaisoindolinone **5** or **6** (5.66 g, 0.025 mol) and 98% solution of hydrazine monohydrate (25 cm^3) were heated under reflux for 2 h. The excess of the hydrazine monohydrate was then removed under reduced pressure, water (25 cm^3) was added to the residue and the whole lot was neutralized with the concentrated hydrochloric acid and cooled in a refrigerator for 2 h. The separated product was filtered and purified by recrystallization. Melting points, recrystallization solvents, yields, elemental analyses and spectral data of the products **7** and **8** are given in the Tables 1 and 2.

General Procedure for the Reaction of Pyridopyridazinones 7 and 8 with Methyl Iodide, Allyl Bromide and Benzyl Bromide. The pyridopyridazinone **7** or **8** (0.74 g, 0.005 mol), potassium hydroxide (0.31 g, 0.0055 mol) and methanol (20 cm³) were heated under reflux for 15–20 min. Then, the appropriate alkyl halide (0.0055 mol) was added dropwise and the heating under reflux was continued for another 1 h. After cooling to room temperature the whole lot was neutralized with 18% solution of hydrochloric acid, all volatile materials were removed under reduced pressure and the residue was continuously extracted in a Soxhlet apparatus. See below for individual differences in the isolation and purification of the products. Melting points, recrystallization solvents, yields, elemental analyses and spectral data of the products **9–14** are given in the Tables 1 and 2.

*7-Methylpyrido[2,3-*d*]pyridazin-8(7*H*)-one (9).* Prepared from pyridopyridazinone **7** (0.74 g, 0.005 mol) and methyl iodide (0.78 g, 0.0055 mol). The solid obtained after extraction with benzene was purified by column chromatography (acetone) and recrystallization.

*2-Methylpyrido[3,4-*d*]pyridazin-1(2*H*)-one (10).* Prepared from pyridopyridazinone **8** (0.74 g, 0.005 mol) and methyl iodide (0.78 g, 0.0055 mol). The solid obtained after extraction with benzene was purified by recrystallization.

*7-Allylpyrido[2,3-*d*]pyridazin-8(7*H*)-one (11).* Prepared from pyridopyridazinone **7** (0.74 g, 0.005 mol) and allyl bromide (0.67 g, 0.0055 mol). The oily solid obtained after extraction with chloroform was purified by column chromatography (chloroform – methanol 19 : 1) and recrystallisation.

*2-Allylpyrido[3,4-*d*]pyridazin-1(2*H*)-one (12).* Prepared from pyridopyridazinone **8** (0.74 g, 0.005 mol) and allyl bromide (0.67 g, 0.0055 mol). The solid obtained after extraction with benzene was purified by recrystallization.

*7-Benzylpyrido[2,3-*d*]pyridazin-8(7*H*)-one (13).* Prepared from pyridopyridazinone **7** (0.74 g, 0.005 mol) and benzyl bromide (0.94 g, 0.0055 mol). The oily solid obtained after extraction with benzene was purified by column chromatography (chloroform – methanol 19 : 1) and recrystallisation.

*2-Benzylpyrido[3,4-*d*]pyridazin-1(2*H*)-one (14a) and 1-benzylxyrido[3,4-*d*]pyridazine (14b).* Prepared from pyridopyridazinone **8** (0.74 g, 0.005 mol) and benzyl bromide (0.94 g, 0.0055 mol). The analysis (TLC, chloroform – methanol 19 : 1) of the solid obtained after extraction with chloroform indicated the presence of at least two main components (*R_f* 0.50 and 0.05) which were separated by column chromatography (chloroform – methanol 19 : 1) and then recrystallised. The first compound eluted was identified as pyridopyridazinone **14a** and the second one as pyridopyridazine **14b**.

N-Carboethoxymethylpyridopyridazinones 15 and 16. The pyridopyridazinone **7** or **8** (0.74 g, 0.005 mol), ethyl bromoacetate (0.92 g, 0.0055 mol), anhydrous potassium carbonate (2.07 g, 0.015 mol) and anhydrous acetone (12 cm³) were heated under reflux for 5 h. After cooling to room temperature the insoluble material

was filtered off and the solid washed with anhydrous acetone ($4 \times 3 \text{ cm}^3$). The acetone from the filtrate was removed under reduced pressure yielding the product which was purified by recrystallization. Melting points, recrystallization solvents, yields, elemental analyses and spectral data of the products **15** and **16** are given in the Tables 1 and 2.

Table 1. Preparation of the Compounds 7-16

Compound (Formula)	Melting point [°C] (Recryst. solvent)	Yield ^a [%]	Analysis		
			Found [%]		
			(Calculated [%])		
			C	H	N
7 (C ₇ H ₅ N ₃ O)	288-290 (subl.) (acetic acid - water 1 : 1) lit. ³⁰ m.p. 300	63	57.17 (57.14)	3.67 (3.43)	28.58 (28.56)
8 (C ₇ H ₅ N ₃ O)	288-290 (subl.) (acetic acid - water 1 : 1) lit. ³¹ m.p. 292-293	75	57.07 (57.14)	3.61 (3.43)	28.60 (28.56)
9 (C ₈ H ₇ N ₃ O)	196-198 (acetone) lit. ³² m.p. 192	55	59.60 (59.62)	4.55 (4.38)	25.79 (26.07)
10 (C ₈ H ₇ N ₃ O)	180-182 (methanol)	61	59.39 (59.62)	4.32 (4.38)	26.03 (26.07)
11 (C ₁₀ H ₉ N ₃ O)	82-84 (hexane - acetone 9 : 1)	28	64.13 (64.16)	4.90 (4.85)	22.32 (22.45)
12 (C ₁₀ H ₉ N ₃ O)	72-73 (hexane)	59	64.54 (64.16)	4.91 (4.85)	22.51 (22.45)
13 (C ₁₄ H ₁₁ N ₃ O)	144-146 (water - methanol 6 : 4)	30	70.56 (70.87)	4.68 (4.67)	17.56 (17.71)
14a (C ₁₄ H ₁₁ N ₃ O)	159-161 (methanol)	38	70.92 (70.87)	4.77 (4.67)	17.58 (17.71)
14b (C ₁₄ H ₁₁ N ₃ O)	285-287 (dec.) (methanol)	17	70.57 (70.87)	4.69 (4.67)	17.65 (17.71)
15 (C ₁₁ H ₁₁ N ₃ O ₃)	139.5-141.5 (ethyl acetate)	69	56.65 (56.65)	4.80 (4.75)	18.04 (18.02)
16 (C ₁₁ H ₁₁ N ₃ O ₃)	140.5-142 (anhydrous ethanol)	68	56.83 (56.65)	4.88 (4.75)	18.23 (18.02)

^aYields are given on pure products and are not optimised.

Table 2. Spectral Data of the Compounds 7-16

Compound	IR [cm ⁻¹]	NMR [δ, ppm; J, Hz]
7	1680 (C=O) 2700-3700 (N-H) ^c	¹ H: 13.3 (1H, br s, N-H), 9.4 (1H, dd, J=1.5 and 4.5, 2-H), 8.6-8.9 (2H, m, 4- and 5-H), 8.2 (1H, dd, J=4.5 and 8.5, 3-H) ^{b,f}
8	1670 (C=O) 2400-3700 (N-H) ^c	¹ H: 13.3 (1H, br s, N-H), 9.7 (1H, s, 5-H), 9.3 (1H, d, J=5.5, 7-H), 8.8 (1H, s, 4-H), 8.4 (1H, d, J=5.5, 8-H) ^{b,f}
9	1665 (C=O) ^d	¹ H: 9.1 (1H, dd, J=1.5 and 3.5, 2-H), 8.1-8.5 (2H, m, 4- and 5-H), 7.8 (1H, dd, J=4 and 8, 3-H), 3.9 (3H, s, Me-H) ^{b,e}
10	1665 (C=O) ^d	¹ H: 9.2 (1H, s, 5-H), 9.0 (1H, d, J=5.5, 7-H), 8.3 (1H, s, 4-H), 8.2 (1H, d, J=5.5, 8-H), 3.8 (3H, s, Me-H) ^{b,e}
11	1670 (C=O) ^d	¹ H: 9.1 (1H, dd, J=1.5 and 4.5, 2-H), 8.0-8.4 (2H, m, 4- and 5-H), 7.7 (1H, dd, J=4 and 8, 3-H), 5.7-6.5 (1H, m, CH-H), 5.0-5.5 (2H, m, CCH ₂ -H), 4.9 (2H, d, J=5.5, NCH ₂ -H) ^{b,e}
12	1670 (C=O) ^d	¹ H: 9.2 (1H, s, 5-H), 9.0 (1H, d, J=5, 7-H), 8.4 (1H, s, 4-H), 8.2 (1H, d, J=5.5, 8-H), 5.7-6.5 (1H, m, CH-H), 5.1-5.6 (2H, m, CCH ₂ -H), 4.9 (2H, d, J=5, NCH ₂ -H) ^{b,e}
13	1670 (C=O) ^d	¹ H: 9.1 (1H, dd, J=1.5 and 4.5, 2-H), 7.9-8.3 (2H, m, 4- and 5-H), 7.1-7.8 (6H, m, 3- and Ph-H), 5.4 (2H, s, CH ₂ -H) ^{b,e}
14a	1665 (C=O) ^d	¹ H: 9.35 (1H, s, 5-H), 9.01 (1H, d, J=5.2, 7-H), 8.64 (1H, s, 4-H), 8.12 (1H, d, J=5.2, 8-H), 7.24-7.41 (5H, m, Ph-H), 5.36 (2H, s, NCH ₂ -H) ^{a,f} ¹³ C: 157.3, 151.2, 150.3, 136.8, 136.7, 132.0, 128.4, 127.8, 127.4, 123.7, 118.2, 54.0 (NCH ₂ -C) ^{a,f}
14b	1605, 1560, 1465 (C=C, C=N) ^c	¹ H: 9.42 (1H, s, 4-H or 5-H), 9.37 (1H, s, 4-H or 5-H), 8.99 (1H, d, J=5.5, 7-H), 7.98 (1H, dd, J=0.8 and 5.5, 8-H), 7.49-7.59 (2H, m, Ph-H), 7.35-7.47 (3H, m, Ph-H), 5.53 (2H, s, OCH ₂ -H) ^{a,f} ¹³ C: 166.6, 152.4, 151.5, 134.4, 132.6, 130.5, 128.8, 128.62, 128.58, 124.8, 118.0, 66.9 (OCH ₂ -C) ^{a,f}
15	1745 (C=O ester) 1680 (C=O ring) ^d	¹ H: 9.11 (1H, dd, J=1.4 and 4.5, 2-H), 8.21 (1H, s, 5-H), 8.12 (1H, dd, J=1.4 and 8.0, 4-H), 7.77 (1H, dd, J=4.4 and 8.0, 3-H), 5.04 (2H, s, NCH ₂ -H), 4.25 (2H, q, J=7.1, OCH ₂ -H), 1.29 (3H, t, J=7.1, Me-H) ^{a,e} ¹³ C: 167.7, 158.8, 154.3, 143.8, 136.8, 134.6, 127.8, 126.3, 61.7 (OCH ₂ -C), 52.9 (NCH ₂ -C), 14.2 (Me-C) ^{a,e}
16	1750 (C=O ester) 1675 (C=O ring) ^d	¹ H: 9.18 (1H, d, J=1.1, 5-H), 9.00 (1H, d, J=5.2, 7-H), 8.31 (1H, s, 4-H), 8.21 (1H, d, J=5.2, 8-H), 4.98 (2H, s, NCH ₂ -H), 4.27 (2H, q, J=7.1, OCH ₂ -H), 1.30 (3H, t, J=7.2, Me-H) ^{a,e} ¹³ C: 167.5, 158.2, 151.5, 149.6, 136.2, 132.8, 124.3, 119.0, 61.8 (OCH ₂ -C), 53.0 (NCH ₂ -C), 14.2 (Me-C) ^{a,e}

Spectra were recorded: ^aon a Varian Gemini 300 spectrometer, ^bon a Tesla BS-467 spectrometer, ^cin KBr, ^din CHCl₃, ^ein CDCl₃, ^fin DMSO-d₆.

ACKNOWLEDGEMENTS

This work was supported by Grant-in-Aid for Scientific Research (No. 3 TO9A 041 09) from the Polish Committee for Scientific Research (KBN) that is gratefully acknowledged.

REFERENCES

- (a) Przyborowski, L. Leki działające na układ krążenia. In *Chemia leków*; Pawełczyk, E. Ed.; PZWL: Warszawa, 1978; pp. 256, 257. (b) Cherkez, S.; Herzig, J.; Yellin, H. *J. Med. Chem.* **1986**, 29, 947 and references within. (c) Eguchi, Y.; Sasaki, F.; Takashima, Y.; Nakajima, M.; Ishikawa, M. *Chem. Pharm. Bull.* **1991**, 39, 795 and references within. (d) *The Merck Index*; Budavari, S. Ed.; Merck & Co., Inc.: Rahway, 1989; pp. 222, 223 (no. 1457) and references within.
- (a) *The Merck Index*; Budavari, S. Ed.; Merck & Co., Inc.: Rahway, 1989; p. 145 (no. 922) and references within. (b) Scheffler, G.; Engel, J.; Kutscher, B.; Sheldrick, W. S.; Bell, P. *Arch. Pharm. (Weinheim, Ger.)* **1988**, 321, 205. (c) Engel, J.; Scheffler, G. *Ger. Offen. DE 3,813,531*, 1988; *Chem. Abstr.* **1989**, 110, 192838p. (d) Szelenyi, I.; Achterrath-Tuckermann, U.; Schmidt, J.; Minker, E.; Paegelow, I.; Werner, H. *Agents Actions Suppl.* **1991**, 34, 295.
- (a) Yamaguchi, M.; Kamei, K.; Koga, T.; Akima, M.; Kuroki, T.; Ohi, N. *J. Med. Chem.* **1993**, 36, 4052. (b) Yamaguchi, M.; Kamei, K.; Koga, T.; Akima, M.; Maruyama, A.; Kuroki, T.; Ohi, N. *ibid.* **1993**, 36, 4061.
- (a) Bavin, E. M.; Drain, D. J.; Seiler, M.; Seymour, D. E. *J. Pharm. Pharmacol.* **1952**, 4, 844. (b) Buu-Hoi, N. P.; Welsch, M.; Dechamps, G.; Le Bihan, H.; Binon, F.; Mentzer, C. *C. R. Hebd. Seances Acad. Sci.* **1952**, 234, 1925 and references within.
- (a) Nagakura, M.; Ota, T.; Shimizu, N. *Japan. Kokai* **74 31,683**, 1974; *Chem. Abstr.* **1974**, 81, 120670n. (b) Rothger, E. F.; Schroeder, H. A. *U.S.* **4,139,622**, 1979; *Chem. Abstr.* **1979**, 90, 168637v. (c) Bediar, H.; Lamphon, R. Q. *J. Prakt. Chem.* **1987**, 329, 675. (d) Abd El-Fattah, B.; Al-Ashmawi, M. I.; El-Feky, S.; Röder, E. *Egypt. J. Pharm. Sci.* **1987**, 28, 383. (e) Abdel-Fattah, B.; Al-Ashmawi, M. I.; El-Feky, S.; Roder, E. *Egypt. J. Pharm. Sci.* **1988**, 29, 259. (f) Joshi, H. D.; Upadhyay, P. S.; Baxi, A. J.; Parikh, A. R. *J. Inst. Chem. (India)* **1991**, 63, 149. (g) Rahman, S. A.; Latif, G. A.; Assy, M. G.; Shahin, A. A. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **1994**, 33B, 491; *Chem. Abstr.* **1994**, 121, 108672b.
- (a) Sugimoto, A.; Tanaka, H.; Eguchi, Y.; Ito, S.; Takashima, Y.; Ishikawa, M. *J. Med. Chem.* **1984**, 27, 1300. (b) Sugimoto, A.; Sakamoto, K.; Fujino, Y.; Takashima, Y.; Ishikawa, M. *Chem. Pharm. Bull.* **1985**, 33, 2809. (c) Morinaka, Y.; Iseki, K.; Kanayama, T.; Watanabe, T.; Nishi, H. *Eur. Pat. Appl. EP 159,652*, 1985; *Chem. Abstr.* **1986**, 104, 75039u. (d) Eguchi, Y.; Sasaki, F.; Takashima, Y.; Nakajima, M.; Ishikawa, M. *Chem. Pharm. Bull.* **1991**, 39, 795. (e) Uenishi, K.; Kosegi, K.; Asaumi, Y.; Ishizuka, Y.; Yaginuma, H. *Jpn. Kokai Tokkyo Koho JP 03,106,872 [91,106,872]*, 1991; *Chem. Abstr.* **1991**, 115, 256195q. (f) Uenishi, K.; Asaumi, Y.; Kosegi, K.; Ishizuka, Y.; Yaginuma, H. *Jpn. Kokai Tokkyo Koho JP 03,106,873 [91,106,873]*, 1991; *Chem. Abstr.* **1991**, 115, 256196r. (g) Uenishi, K.; Kosegi, K.; Yaginuma, H. *Jpn. Kokai Tokkyo Koho JP 03,106,874 [91,106,874]*, 1991; *Chem. Abstr.* **1991**, 115, 183338b. (h) Uenishi, K.; Kosegi, K.; Asaumi, Y.; Ishizuka, Y.; Yaginuma, H. *Jpn. Kokai Tokkyo Koho JP 03,106,875 [91,106,875]*, 1991; *Chem. Abstr.* **1991**, 115, 256197s. (i) Ohi, N.; Kuroki, T.; Yamaguchi, M.; Akima, M.; Koga, T.; Kamei, K. *PCT Int. Appl. WO 91 12,251*, 1991; *Chem. Abstr.* **1991**, 115, 256193n. (j) Iwase, N.; Morinaka, Y.; Tamao, Y.; Kanayama, T.; Yamada, K. *Eur. Pat. Appl. EP 534,443*, 1993; *Chem. Abstr.*, **1993**, 119, 249963t.
- (a) *The Merck Index*; Budavari, S. Ed.; Merck & Co., Inc.: Rahway, 1989; pp. 1208, 1209 (no. 7565) and references within. (b) Mylari, B. L.; Larson, E. R.; Beyer, T. A.; Zembrowski, W. J.; Aldinger, C. E.; Dee, M. F.; Siegel, T. W.; Singleton, D. H. *J. Med. Chem.* **1991**, 34, 108 and references within. (c) Mylari, B. L.; Beyer, T. A.; Scott, P. J.; Aldinger, C. E.; Dee, M. F.; Siegel, T. W.; Zembrowski, J.

- J. Med. Chem.* **1992**, 35, 457 and references within. (d) Collonges, F.; Dumas, H.; Durbin, P.; Guerrier, D. *PCT Int. Appl. WO 93 07,109*, 1993; *Chem. Abstr.* **1993**, 119, 160308k. (e) Mylari, B. L. U.S. US **5,304,557**, 1994; *Chem. Abstr.* **1994**, 121, 134137a.
8. (a) Campbell, S. F.; Danilewicz, J. C.; Ham, A. L.; Stubbs, J. K. *Eur. Pat. Appl.* **17,441**, 1980; *Chem. Abstr.* **1981**, 94, 156955s. (b) Campbell, S. F.; Danilewicz, J. C.; Ham, A. L.; Stubbs, J. K. U.S. US **4,370,328**, 1983; *Chem. Abstr.* **1983**, 98, 179397h. (c) Bristol, J. A.; Chorvat, R. J. *Cardiotonic Agents*. In *Cardiovascular Drugs*; Bristol, J. A. Ed.; John Wiley & Sons, Inc.: New York, 1986; pp. 279, 280 and references within. (d) Moro, K.; Kuromaru, O.; Takagi, M. *Jpn. Kokai Tokkyo Koho JP 03,246,292* [91,246,292], 1991; *Chem. Abstr.* **1992**, 116, 128949x.
 9. Grobelny, D. W. *PCT Int. Appl. WO 93 18,006*, 1993; *Chem. Abstr.* **1994**, 120, 324202v.
 10. For representative patents, see, inter alia:
 - (a) Noguchi, Y.; Sekikawa, N.; Sashihara, K.; Masuda, T. *Ger. Offen.* **2,449,252**, 1975; *Chem. Abstr.* **1976**, 84, 37303m. (b) Kobayashi, H.; Yano, Y.; Endo, I. *Ger. Offen.* **2,702,919**, 1977; *Chem. Abstr.* **1978**, 89, 34144c. (c) Ikenoue, S.; Katsuyama, H.; Masuda, T. *Ger. Offen.* **2,728,627**, 1977; *Chem. Abstr.* **1978**, 89, 34153e. (d) Ikenoue, S.; Masuda, T.; Sakawaki, S. U.S. **4,207,112**, 1980; *Chem. Abstr.* **1981**, 94, 9988b. (e) Ashai Chemical Industry Co., Ltd. *Jpn. Kokai Tokkyo Koho JP 57,200,032* [82,200,032], 1982; *Chem. Abstr.* **1984**, 100, 148540e. (f) Akashi, H.; Akiyama, M.; Shiga, T.; Matsui, T.; Hayashi, Y.; Kimura, T.; Kobayashi, H. *Jpn. Tokkyo Koho JP 61 45,817* [86 45,817], 1986; *Chem. Abstr.* **1987**, 106, 129392r.
 11. Dimroth, P. *Ger. Offen.* **2,521,437**, 1976; *Chem. Abstr.* **1977**, 86, 74399j.
 12. Shitachi, A.; Komata, K. *Jpn. Kokai Tokkyo Koho JP 04 89,407* [92 89,407], 1992; *Chem. Abstr.* **1993**, 118, 96274w.
 13. (a) Oka, Y.; Omura, K.; Miyake, A.; Itoh, K.; Tomimoto, M.; Tada, N.; Yurugi, S. *Chem. Pharm. Bull.* **1975**, 23, 2239 and references within. (b) Oka, Y.; Itoh, K.; Miyake, A.; Tada, N.; Omura, K.; Tomimoto, M.; Yurugi, S. *ibid.* **1975**, 23, 2306. (c) Yurugi, S.; Kikuchi, S. *Japan. Kokai 74 35,397*, 1974; *Chem. Abstr.* **1975**, 82, 4281h. (d) Nishikawa, K.; Shimakawa, H.; Inada, Y.; Shibouta, Y.; Kikuchi, S.; Yurugi, S.; Oka, Y. *Chem. Pharm. Bull.* **1976**, 24, 2057 and references within. (e) Mizuta, E.; Nishikawa, K.; Omura, K.; Oka, Y. *ibid.* **1976**, 24, 2078 and references within. (f) Omura, K.; Tada, N.; Tomimoto, M.; Usui, Y.; Oka, Y.; Yurugi, S. *ibid.* **1976**, 24, 2699 and references within. (g) Inada, Y.; Nishikawa, K.; Nagaoka, A.; Kikuchi, S. *Arzneim.-Forsch.* **1977**, 27, 1663. (h) Inada, Y.; Shibouta, Y.; Shimakawa, H.; Nishikawa, K.; Kikuchi, S. *ibid.* **1978**, 28, 1105 and references within. (i) Inada, Y.; Shimakawa, H.; Shibouta, Y.; Nishikawa, K.; Kikuchi, S.; Shimamoto, K. *Takeda Kenkyushoho 1978*, 37, 57; *Chem. Abstr.* **1979**, 90, 115247m. (j) Shida, M.; Nishikawa, K.; Kikuchi, S. *Arzneim.-Forsch.* **1979**, 29, 807 and references within.
 14. (a) Matsuura, I.; Yoneda, F.; Nitta, Y. *Chem. Pharm. Bull.* **1966**, 14, 1010. (b) Tišler, M.; Stanovnik, B. *Azolo- and Azinopyridazines and Some Oxa and Thia Analogs*. In *Condensed Pyridazines Including Cinnolines and Phthalazines*; Castle, R. N. Ed.; John Wiley & Sons, Inc.: New York, 1973; pp. 968-1012 and references within. (c) Heider, J.; Kutter, E.; Eberlein, W.; Austel, V.; Kadatz, R.; Daemmgen, J. *Ger. Offen.* **2,708,187**, 1978; *Chem. Abstr.* **1978**, 89, 180049s. (d) Tanabe, M.; Fujiki, C.; Inada, Y.; Hirata, M. *Takeda Kenkyushoho 1978*, 37, 49; *Chem. Abstr.* **1979**, 90, 115248n. (e) Kuczynski, L.; Mrozikiewicz, A.; Banaszekiewicz, W.; Respond, S. *Pol. J. Pharmacol. Pharm.* **1982**, 34, 223.
 15. Moriya, N.; Nakagawa, S.; Inada, Y.; Sugino, H.; Kakinuma, A. *Takeda Kenkyushoho 1979*, 38, 193; *Chem. Abstr.* **1980**, 93, 37214u.
 16. (a) Mylari, B. L.; Zembrowski, W. J. U.S. US **4,954,629**, 1990; *Chem. Abstr.* **1991**, 114, 62105u. (b) Mylari, B. L.; Zembrowski, W. J. *Eur. Pat. Appl. EP 401,981*, 1990; *Chem. Abstr.* **1991**, 114, 164264n. (c) Bru-Magniez, N.; Launay, M.; Teulon, J. M. *Fr. Demande FR 2,647,676*, 1990; *Chem. Abstr.* **1991**, 115, 71627p. (d) Mylari, B. L.; Zembrowski, W. J.; Beyer, T. A.; Aldinger, C. E.; Siegel, T. W. *J. Med. Chem.* **1992**, 35, 2155 and references within.
 17. (a) Faith, W. C.; Campbell, H. F.; Kuhla, D. E.; Studt, W. L.; Barnes, J. L. *PCT Int. Appl. WO 89 00,567*, 1989; *Chem. Abstr.* **1989**, 111, 153838q. (b) Societa Italiana Medicinali e Sintetici S.p.A. (SIMES) *Jpn. Kokai Tokkyo Koho JP 02 73,084* [90 73,084], 1990; *Chem. Abstr.* **1990**, 113, 97617u.

18. Hewett, R.; Pettit, S. N.; Smith, P. *Can. Pat. Appl. CA 2,086,898*, 1993; *Chem. Abstr.* **1994**, 121, 9415p.
19. Wilhelm, R. S.; Loe, B. E.; Devens, B. H.; Alvarez, R.; Martin, M. G. *PCT Int. Appl. WO 93 07,146*, 1993; *Chem Abstr.* **1993**, 119, 180830c.
20. Epsztajn, J.; Brzeziński, J. Z.; Czech, K. *Monatsh. Chem.* **1993**, 124, 549.
21. (a) Körmendy, K.; Kovács, T.; Szulágyi, J.; Ruff, F.; Kövesdi, I. *Acta Chim. Hung.* **1981**, 108, 167. (b) Körmendy, K.; Kovács, T.; Ruff, F.; Kövesdi, I. *ibid.* **1983**, 112, 487. (c) Dunn, A. D. *J. Heterocycl. Chem.* **1984**, 21, 961. (d) Dunn, A. D. *ibid.* **1984**, 21, 965.
22. (a) Dunet, A.; Willemart, A. *Bull. Soc. Chim. Fr.* **1948**, 1081. (b) Lechat, P. *C. R. Hebd. Seances Acad. Sci.* **1958**, 246, 2771. (c) Ismail, M. F.; Enayat, E. I.; El-Bassiouny, F. A. A.; Younes, H. A. *Gazz. Chim. Ital.* **1990**, 120, 677.
23. (a) Zaugg, H. E. *Synthesis* **1984**, 85. (b) Zaugg, H. E. *ibid.* **1984**, 181. (c) Speckamp, W. N.; Hiemstra, H. *Tetrahedron* **1985**, 41, 4367. (d) Goto, T.; Utsunomiya, S.; Aiba, H.; Hayasaka, H.; Endo, M.; Watanabe, R.; Ishizaki, T.; Sato, R.; Saito, M. *Bull. Chem. Soc. Jpn.* **1991**, 64, 1901.
24. (a) de Boer, J. J. J.; Speckamp, W. N. *Tetrahedron Lett.* **1975**, 4039. (b) Mali, R. S.; Yeola, S. N. *Synthesis* **1986**, 755. (c) Goto, G.; Saji, Y. *Jpn. Kokai Tokkyo Koho JP 61,130,290 [86,130,290]* 1986; *Chem. Abstr.* **1987**, 106, 33014t.
25. (a) Epsztajn, J.; Jóźwiak, A.; Czech, K.; Szcześniak, A. K. *Monatsh. Chem.* **1990**, 121, 909. (b) Epsztajn, J.; Bieniek, A.; Kowalska, J. A. *Tetrahedron* **1991**, 47, 1697. (c) Epsztajn, J.; Bieniek, A.; Kowalska, J. A.; Ścianowski, J. *Monatsh. Chem.* **1992**, 123, 1125. (d) Epsztajn, J.; Jóźwiak, A.; Szcześniak, A. K. *Tetrahedron* **1993**, 49, 929. (e) Epsztajn, J.; Jóźwiak, A.; Krysiak, J. A. *ibid.* **1994**, 50, 2907. (f) Epsztajn, J.; Jóźwiak, A.; Szcześniak, A. K. *Synth. Commun.* **1994**, 24, 1789.
26. Epsztajn, J.; Bieniek, A.; Płotka, M. W. *J. Chem. Res. (M)* **1986**, 442.
27. Computer program: C-13 NMR Module version 1.0 for ChemWindow version 3.0.2; SoftShell International Ltd. 1990-1994.
28. (a) Saleh, R. M.; Soliman, F. M. A.; Souka, L. M.; Abd El-Ghaffar, N. F. *Rev. Roum. Chim.* **1993**, 38, 1109. (b) Soliman, F. M. A.; Souka, L. M.; Abd El-Ghaffar, N. F. *ibid.* **1994**, 39, 827.
29. (a) Vogel, A. I. *Vogel's Textbook of Practical Organic Chemistry*, Longman Scientific & Technical: London, 1989; pp. 406, 407. (b) Vogel, A. I. *ibid.*; pp. 409, 410.
30. Bottari, F.; Carboni, S. *Gazz. Chim. Ital.* **1956**, 86, 990.
31. Matsuura, I.; Okui, K.; *Chem. Pharm. Bull.* **1969**, 17, 2266.
32. Kakimoto, S.; Tanooka, S. *Bull. Chem. Soc. Jpn.* **1967**, 40, 153.

(Received 25 September 1995; accepted 21 November 1995)