A Facile Synthesis of 5,7-Dihydro-5-oxopyrido[3',2':5,6]pyrimido[1,2-*a*]benzimidazoles. A New Heterocyclic Ring System

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Received March 24, 1986

Reaction between 2-chloropyridine-3-carbonyl chloride and 1-alkyl-2-aminobenzimidazoles afforded the *N*-(1-alkylbenzimidazole-2-yl)-2-chloropyridine-3-carboxamides, which were cyclized to 5,7-dihydro-5-oxopyrido[3',2':5,6]pyrimido[1,2-*a*]benzimidazoles. The assigned structures of these hitherto unknown heterocyclic compounds were confirmed by their ir and ^{1}H nmr spectra and chemical evidence.

J. Heterocyclic Chem., **23**, 1833 (1986).

In previous papers we reported the synthesis of some 11*H*-indolo[3,2-*c*][1,8]naphthyridines I [1a-c], 6*H*-indolo-[2,3-*b*][1,8]naphthyridines II [2] and 3-substituted quino-[3,2-*c*][1,8]naphthyridines III [3a,b]. Some [1,8]naphthyrido[3,2-*c*][1,8]naphthyridines IV were also prepared in our laboratories [4].

A wide range screening was carried out with some of the above compounds, in order to assay their microbiological and pharmacological properties. Some compounds I were effective in inhibiting the reactions of delayed hypersensitivity. The intriguing question of the interaction between the indolonaphthyridines I and II and the benzodiazepine receptors was also examined [5].

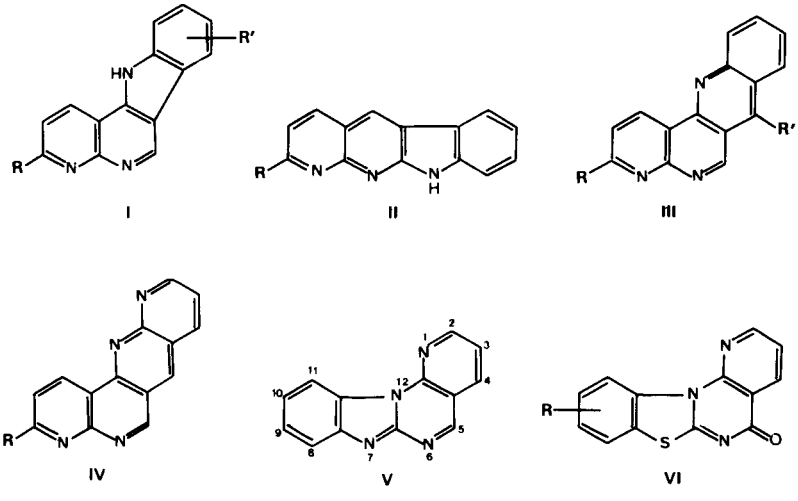
Pursuing our interest in heteropolycyclic substances which might exhibit biological activity because of their structural resemblance with the above compounds, we describe here the synthesis of some pyrido[3',2':5,6]pyrimido-[1,2-*a*]benzimidazoles V, which represent a new heterocyclic ring structure.

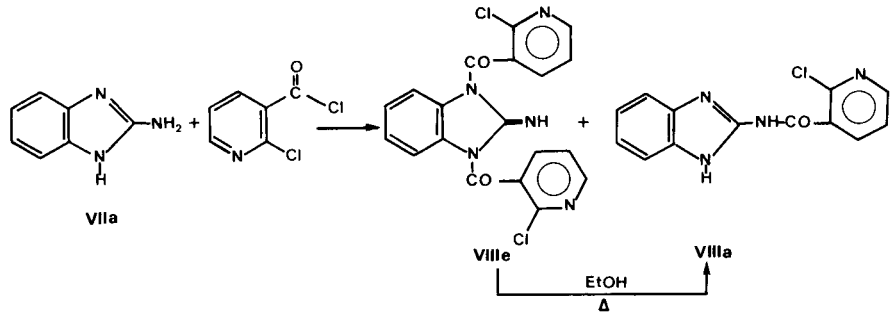
To the best of our knowledge, only one report on an analogous ring system, the pyrido[3',2':5,6]pyrimido[2,1-*b*]-[1,3]benzothiazole (VI), is found in the literature [6].

The target compounds, 5,7-dihydro-5-oxopyrido[3',2':-5,6]pyrimido[1,2-*a*]benzimidazoles Xa-d, were synthesized as shown in Scheme I.

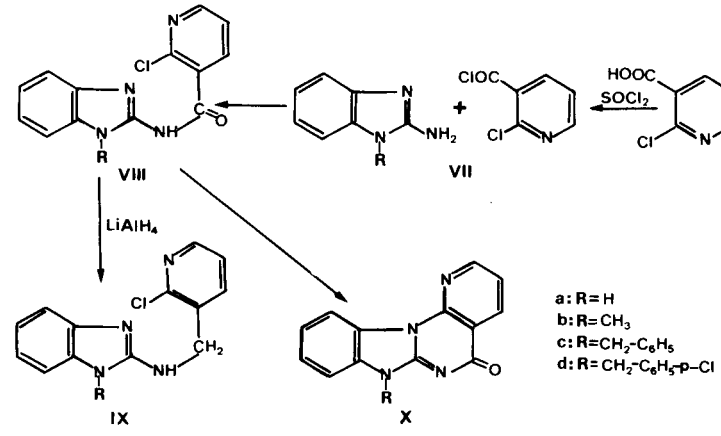
The preparation of the starting 1-alkylbenzimidazoles VIIb,c has already been described [7a,b]. We have found that the alkylation reaction, if carried out in potassium hydroxide-ethanol solution, gives the desired products in very good yield. In this way the unknown 1-*p*-chlorobenzyl-2-aminobenzimidazole (VIId) was obtained in 75% yield.

The *N*-(1*H*-benzimidazol-2-yl)-2-chloropyridine-3-carboxamides VIIIb-d were synthesized by reaction of VIIb-d and 2-chloropyridine-3-carbonyl chloride in benzene in presence of triethylamine at room temperature. At reflux of the solvent a mixture of carboxamides VIIIb-d and tetracyclic compounds Xb-d was instead obtained. In the case of the reaction of 2-aminobenzimidazole (VIIa) with





Scheme I



2-chloropyridine-3-carbonyl chloride, carried out in benzene at room temperature, a mixture (1.4:1) of the 1,3-diacyl-2-iminobenzimidazole VIIIe and of the 2-acyl derivative VIIIa was obtained. This behaviour is in agreement with data already reported in literature [8].

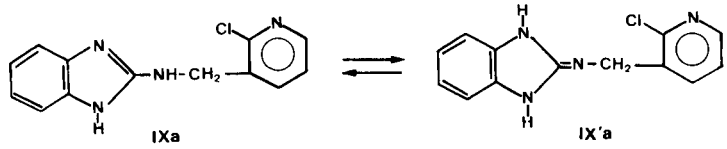
Compound VIIIe, refluxed in ethanol for 1 hour, afforded the corresponding 2-acylderivative VIIIa (total yield 43%). The structures of compounds VIII were confirmed by their analytical, ir and ^1H nmr spectral data (see Table I).

Table I

Physical, Analytical and Spectral Data of Compounds VIIIa-e

Compound	Yield [a] %	MP (°C) (Solvent)	IR (nujol, cm^{-1}) NH	IR (nujol, cm^{-1}) C=O	^1H NMR (Trifluoroacetic acid) (ppm)	Analysis, % Calcd./(Found) C	H	N
VIIIa	43	> 300 (DMF)	3250	1670	9.2-8.9 (m, 2H, Ar-H), 8.5-8.1 (m, 1H, Ar-H), 8.1-7.6 (m, 4H, Ar-H)	57.25 (56.94)	3.30 (3.34)	20.55 (20.35)
VIIIb	62	191-193 dec (Ethanol)	3320	1630	9.2-8.9 (m, 2H, Ar-H), 8.4-8.1 (m, 1H, Ar-H), 8.1-7.7 (m, 4H, Ar-H), 4.2 (s, 3H, CH_3)	58.64 (58.89)	3.84 (3.61)	19.55 (19.31)
VIIIc	48	140-143 (DMF/water)	3290	1610	9.2-8.7 (m, 2H, Ar-H), 8.3-7.2 (m, 10H, Ar-H), 5.9 (s, 2H, CH_2)	66.21 (65.95)	4.14 (4.02)	15.45 (15.24)
VIIId	76	200-205 dec (DMF/water)	3290	1620	9.2-8.7 (m, 2H, Ar-H), 8.4-7.1 (m, 9H, Ar-H), 5.9 (s, 2H, CH_2)	60.45 (60.35)	3.53 (3.48)	14.11 (13.96)
VIIIe	27	155 dec (Benzene)	3250	1710	8.9-8.1 (m, 3H, Ar-H), 7.8-7.0 (m, 7H, Ar-H) [b]	55.34 (55.62)	2.67 (2.79)	16.99 (16.64)

[a] Yield of crude products. [b] DMSO-d_6.



Moreover they were reduced with lithium aluminum hydride to the correspondent amines IXa-d. In the ^{1}H nmr spectra of IXb-d the signal due to the methylene group obtained by reduction of the amide function, appears as a doublet which coalesces to give a single peak after exchange with deuterium oxide.

The ^{1}H nmr spectrum of IXa does not fit this pattern and shows a single peak for the methylene group. This finding suggests that IXa exists predominantly in the imine form IX'a as previously reported for 2-methylaminobenzimidazole [9].

These behaviours agree with the proposed structures of compounds IX and confirmed that the aroylation of 2-aminobenzimidazoles yielded only the corresponding carboxamides VIII in the above reported conditions.

Analytical, ir and ^{1}H nmr data of compounds IXa-d are collected in Table II.

The cyclization reaction VIII → X is effected in good yields by refluxing compounds VIII in pyridine for 20-60 hours. The substances X, thus obtained, are high melting crystalline solids, slightly soluble in usual organic solvents.

The patterns of aromatic protons in the ^{1}H nmr spectra of Xa-d are closely similar.

A shift of three protons downfield about 1 ppm from the multiplet containing the other four aromatic protons was observed. These protons are assigned as H-2, H-4, H-11. The H-4 proton is shifted downfield by the deshielding effect of the 5-oxo function [10], while the H-11 proton is deshielded by the nonbonded electron pair of N-1 [11].

Analytical, ir and ^{1}H nmr data of compounds Xa-d are collected in Table III.

EXPERIMENTAL

Melting points were determined on a Köfler and are uncorrected. Ir spectra were taken with a Perkin-Elmer 197 spectrophotometer. The ^{1}H nmr spectra were recorded on a Varian EM 360A using tetramethylsilane as an internal standard.

1-(*p*-Chlorobenzyl)-2-aminobenzimidazole (VIId).

To a solution of 2-aminobenzimidazole (VIIa) (3.0 g, 0.023 mole) and potassium hydroxide (1.9 g) in ethanol (100 ml), 3.9 g (0.024 mole) of *p*-chlorobenzyl chloride were added. The mixture was stirred at room temperature for 1 hour and then the solid (potassium chloride) was filtered off. The solvent was evaporated off under reduced pressure and the residue was treated with water, collected and washed with benzene. The title compound was recrystallized from benzene to give 4.35 g (75%) of VIId, mp 191-193°; ir: 3440, 3350, 1630, 740 cm^{-1}; ^{1}H nmr (deuteriochloroform): ppm 7.6-6.8 (m, 8H, Ar-H), 5.3 (s, 2H, CH_2).

Anal. Calcd. for $C_{14}H_{12}ClN_3$: C, 65.24; H, 4.66; N, 16.31. Found: C, 65.20; H, 4.54; N, 16.05.

N-(1-Alkylbenzimidazole-2-yl)-2-chloropyridine-3-carboxamides VIIIb-d.

General Procedure.

A mixture of 2-chloropyridine-3-carboxylic acid (1.6 g, 0.01 mole) and thionyl chloride (8 ml, 0.11 mole) was heated at reflux for 16 hours. Excess thionyl chloride was distilled off under reduced pressure, benzene (10 ml) was added and the last traces of thionyl chloride were distilled off with the solvent. The 2-chloropyridine-3-carbonyl chloride thus obtained was suspended in dry benzene (40 ml) and treated with the appropriate 1-substituted-2-aminobenzimidazole VIIb-d (0.01 mole) and triethylamine (1.6 ml, 0.011 mole).

The mixture was stirred at room temperature for 16 hours, and then the solvent was distilled *in vacuo*. The residue was collected, washed with water to eliminate the triethylamine hydrochloride and purified by re-

Table II

Physical, Analytical and Spectral Data of Compounds IXa-d

Compound	Yield [a] %	MP (°C) (Solvent)	IR (nujol, cm^{-1})	^{1}H NMR (DMSO-d_6) (ppm)	Analysis, % Calcd./(Found) C	H	N
IXa	40	192-195 (Ethyl acetate)	1600, 1580, 1560, 1400, 1060	8.5-8.3 (m, 1H, A...), 8.0-7.8 (m, 1H, Ar-H), 7.6-6.8 [m, 7H, Ar-H and NH (exchangeable with deuterium oxide)], 4.7 (s, 2H, CH_2)	60.35 (60.15)	4.25 (4.34)	21.66 (21.73)
IXb	63	230-232 dec (Ethanol)	1610, 1580, 1470, 1410, 1380, 1240	8.0-7.8 (m, 1H, Ar-H), 7.7-7.5 (m, 1H, Ar-H), 7.2-6.6 (m, 5H, Ar-H), 4.6 (d, 2H, CH_2), 3.6 (s, 3H, CH_3), 3.3 (s, 1H, NH, exchangeable with deuterium oxide)	61.65 (61.30)	4.77 (4.70)	20.55 (20.79)
IXc	20	92-96 (Ethanol)	1610, 1590, 1570, 1540, 1410, 1400, 1060	8.5-8.3 (m, 1H, Ar-H), 7.9-6.7 (m, 11H, Ar-H), 5.4 (s, 2H, CH_2), 4.8-4.6 (d, 2H, $NHCH_2$), 3.4 (s, 1H, NH, exchangeable with deuterium oxide)	65.48 (65.45)	5.18 (5.12)	15.27 (15.07)
IXd	52	80-83 (Ethanol/H_2O)	1610, 1580, 1560, 1410, 1400, 1070	8.5-8.3 (m, 1H, Ar-H), 7.9-6.8 (m, 10H, Ar-H), 5.4 (s, 2H, CH_2), 4.9-4.6 (d, 2H, $NHCH_2$), 3.4 (s, 1H, NH, exchangeable with deuterium oxide)	62.66 (62.40)	4.18 (4.33)	14.62 (14.47)

[a] Yield of crude products.

Table III

Physical, Analytical and Spectral Data of Compounds Xa-d

Compound	Reaction time (hours)	Yield [a] %	MP (°C) (Solvent)	IR (nujol, cm^{-1}) C=O	^1H NMR (Trifluoroacetic acid) (ppm)	Analysis, % Calcd./(Found) C	H	N
Xa	16	74	> 300 (DMSO)	1670 + 1630	9.4-9.1 (m, 2H, Ar-H), 9.1-8.9 (dd, 1H, Ar-H), 8.1-7.7 (m, 4H, Ar-H)	66.10 (66.36)	3.39 (3.51)	23.73 (23.82)
Xb	50	64	280-290 dec (DMSO)	1640	9.4-9.2 (m, 2H, Ar-H), 9.2-8.9 (dd, 1H, Ar-H), 8.2-7.7 (m, 4H, Ar-H), 4.3 (s, 3H, CH_3)	67.20 (67.21)	4.00 (4.12)	22.40 (22.24)
Xc	60	74	242-246 dec (DMSO)	1640	9.5-9.2 (m, 2H, Ar-H), 9.1-8.9 (dd, 1H, Ar-H), 8.1-7.8 (m, 4H, Ar-H), 7.5 (s, 5H, Ar-H), 5.9 (s, 2H, CH_2)	73.62 (73.65)	4.29 (4.31)	17.18 (17.04)
Xd	60	73	> 300 (DMSO)	1630	9.5-9.3 (m, 2H, Ar-H), 9.2-8.9 (dd, 1H, Ar-H), 8.1-7.8 (m, 4H, Ar-H), 7.5 (s, 4H, Ar-H), 5.9 (s, 2H, CH_2)	66.57 (66.24)	3.61 (3.67)	15.53 (15.37)

[a] Yield of crude products.

crystallization. Yields and crystallization solvents are listed in Table I.

N-(1*H*-Benzimidazole-2-yl)-2-chloropyridine-3-carboxamide (VIIIa).

The acylation reaction of 2-aminobenzimidazole VIIa with 2-chloropyridine-3-carbonyl chloride was carried out as described for the preparation of the carboxamides VIIIb-d. From the crude reaction mixture the triethylamine hydrochloride was filtered off and the solution, washed with water and dried on $MgSO_4$, was evaporated to dryness. The residue oil was treated with ether and the obtained solid was collected and extracted with hot benzene. The insoluble part (0.47 g, yield 19%) was crystallized from DMF to give VIIIa.

From the benzene solution, concentrated to a small volume, 1.0 g, of VIIIe was obtained. The product was refluxed in ethanol for 1 hour to give an additional amount of VIIIa (total yield 43%). From the ethanolic solution an oil, identified as the ethyl ester of the 2-chloropyridine-3-carboxylic acid, was isolated by concentration.

2-(2-Chloropyridine-3-yl)-methylamino-1-alkylbenzimidazoles IXa-d.

General Procedure.

To a stirred ice cooled mixture of lithium aluminium hydride (0.013 mole) in dry ether (50 ml) was added under nitrogen in small portions the appropriate carboxamide VIII (0.0033 mole). The reaction mixture was refluxed for 4 hours and then the complex decomposed with ice-cooled water. The precipitate salts were filtered and extracted with hot ethanol. The ethereal solution was concentrated under reduced pressure and the residue was extracted with boiling ethanol. The combined extracts were evaporated to dryness and the product purified by recrystallization (see Table II).

5-Oxopyrido[3',2':5,6]pyrimido[1,2-*a*]benzimidazoles Xa-d.

General Procedure.

A suspension of carboxamides VIIIa-d (0.0013 mole) in pyridine (10 ml) was refluxed for some hours. The resulting solution was concentrated and, after cooling, the solid was collected and purified by recrystallization from DMSO (see Table III).

Acknowledgement.

This work was supported by a grant from M.P.I. and Italian CNR (Roma).

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