Acta Poloniae Pharmaceutica – Drug Research, Vol. 56 No. 1 pp. 57–60, 1999

ISSN 0001-6837
Polish Pharmaceutical Society

SYNTHESIS OF 5–IMINO–5H–DIPYRIDO[1,2–a; 2',3'–d]PYRIMIDINES AS POTENTIAL ANTIALLERGY AGENTS (1)

ANDRZEJ RYKOWSKI[1] and WIESŁAW PUCKO[2]

[1]Institute of Chemistry, Agricultural and Pedagogical University,
54, 3 Maja Str., 08–110 Siedlce, Poland
[2]Pharmaceutical Institute, 8 Rydygiera Str., 01–793 Warsaw, Poland

Abstract: A novel route to 5–imino–5H–dipyrido[1,2–a; 2',3'–d]pyrimidines is described. The method is based on the Ullmann condensation of 2–chloro–3–cyano–5–nitropyridine with 2–amino–pyridine 1–oxides, followed by intramolecular cyclization of the resulting 2–(3–cyano–5–nitro–2–pyridylamino)pyridine 1–oxides with phosphorous trichloride.

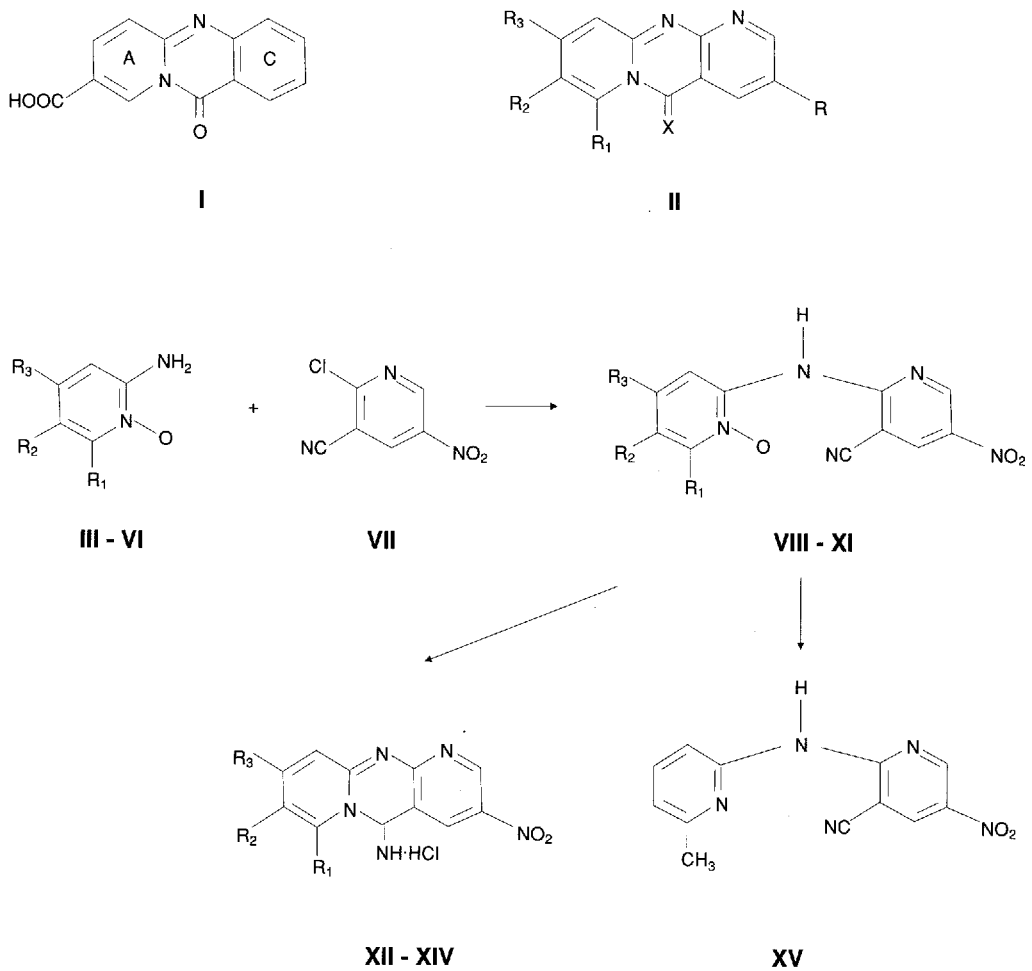
Keywords: 5–imino–5H–dipyrido[1,2–a; 2',3'–d]pyrimidines, antiallergy agents.

Since the pioneering work of Schwender (2) on the antiallergy activity of 11–oxo–11H–pyrido[2,1–b]quinazoline–8–carboxylic acid [**I**] many derivatives of this compound, including ring homologes, have been synthesized and examined as potential antiallergic and antiastmatic agents (3). The synthesis and antiallergy activity of compounds with additional hetero atoms in ring A or C, which may be regarded as sulfur or nitrogen isosters of **I**, have also been investigated (4–8). In the previous paper in this series a novel route to 5H–dipirydo[1,2a; 2',3'–d]pyrimidin–5–one [**II**] (X=0), which is a 4–aza analog of **I**, has been developed. The method is based on the Ullmann reaction of 2–chloronicotinic acid, or its 5–bromo derivative, with 2–aminopyridine 1–oxides, followed by intramolecular cyclization of the resulting 2–(3–carboxy–2–pyridylamino)pyridine 1–oxides with phosphorous trichloride (9). This procedure seems to be general and can be applied to the preparation of functionalized derivatives of **II** (X=0) with selected substituents (R=H, Br; R_1=R_2=R_3=H or CH_3) in fused pyridine rings (9). It was of interest, therefore, from the structure activity point of view, to synthesize and test for its biological activity the imino analogue of **II** (X=NH) in which the carbonyl oxygen is replaced by NH group. To our knowledge there has been no report discussing the effect of this substituent on the affinities for its antiallergy activity in dipyridopyrimidines.

This paper describes the synthesis of such derivatives by adopting a methodology developed for the preparation of dipyrido[1,2a; 2',3'–d]pyrimidin–5–ones [**II**]. In principle, a successful approach includes a nucleophilic displacement of chlorine in 2–chloro–3–cyano–5–nitropyridine [**VII**] by amino group in 2–aminopyridines [**III–VI**] and intramolecular cyclization of the resulting 2–(3–cyano–2–pyridylamino)pyridine 1–oxides [**VII–XI**] under the conditions previously reported (9).

Thus, the treatment of 2–chloro–3–cyano–5–nitropyridine (**VII**) with 2–aminopyridine 1–oxide (**III**) in N,N–dimethylformamide (DMF) at room temperature for 1 hr gave 2–(3–cyano–5–nitro–2–pyridylamino)pyridine 1–oxide (**VIII**) in excellent yield. The structure of **VIII** was proven by means of elemental analysis and by IR and 1H NMR spectra. The IR spectrum of **VIII** shows absorption bands at 3110 cm^{-1} (NH) and at 2220 cm^{-1} (CN), whereas the ^1H NMR spectrum shows signals attributed to aromatic protons in the 7.20–9.40 ppm region. The facile synthesis of the parent compound in this series led us to explore the preparation of its derivatives. The results of these reactions and spectroscopic characterization of the products [**VIII–XI**] are summarized in Table 1.

Compound **VIII**, when subjected to reaction with phosphorous trichloride in boiling ethyl acetate gave directly 5–imino–5H–dipyrido[1,2–a; 2',3'–d]pyrimidine hydrochloride [**XII**] in 88% yield. Analogous procedure was applied to prepare its methyl derivatives [**XIII–XIV**]. ^1H NMR, IR, MS and HRMS were used to determine the structure of the resulting compounds (see Table 2). However, it was found that the reaction of 2–(3–cyano–5–nitro–2–pyridylamino)–6–methylpyridine 1–oxide [**XI**] with phosphorous trichloride led to deoxygenated derivative **XV**. This result clearly shows that cyclization of the cyano derivatives of 2–(2–pyridylamino)pyridine 1–oxide [**VIII–XI**] into the corresponding 5–imino–5H–dipyrido[1,2–a;



Scheme 1.

2',3'–d]pyrimidines [**XII–XIV**] upon treatment with phosphorous trichloride is hindered by the presence of substituent at C–6 in the pyridine 1–oxide ring.

The procedure otulined above constitutes a general synthesis for imino analogues of **II**. A report on the biological properties of these compounds is in progress.

EXPERIMENTAL

Melting points are given without corrections. The purity of products and the course of chemical reactions were monitored by means of thin layer chromatography on silica gel using methanol – ethyl acetate (1:1) as a mobile phase. ^{1}H NMR spectra were recorded in DMSO – d_6 with Varian Gemini 200 MHz instrument using TMS as internal

No	R_1	R_2	R_3
VIII	H	H	H
IX	H	H	CH_3
X	H	CH_3	H
XI	CH_3	H	H
XII	H	H	H
XIII	H	H	CH_3
XIV	H	CH_3	H

Table 1. Physico–chemical properties and spectroscopic data of compounds **VIII–XI**

Compound	Formula Molecular mass	M.p. °C	Yield %	Analysis Calculated/Found C%	H%	N%	^{1}H NMR (δ ppm.) (DMSO–d_6)	IR cm^{-1}
VIII	$C_{11}H_7N_5O_3$ 257.206	257–258	89	51.36 51.32	2.74 2.77	27.23 27.09	7.20–7.28 (m, 1H), 7.53–7.62 (m, 1H), 8.50–8.54 (m, 1H) 8.64–8.67 (m, 1H), 9.21 (d, 1H, J=2.8 Hz), 9.38 (d, 1H, J=2.8 Hz)	3110 (NH) 2220 (CN)
IX	$C_{12}H_9N_5O_3$ 271.232	275–276	84	53.14 53.08	3.34 3.27	25.82 25.70	2.40 (s, 3H), 7.07 (dd, 1H, J_1=6.6 Hz, J_2=2.4 Hz), 8.40 (d, 1H, J=6.6 Hz), 8.49 (d, 1H, J=2.4 Hz), 9.20 (d, 1H, J=2.8 Hz), 9.39, (d, 1H, J=2.8 Hz)	3100 (NH) 2220 (CN)
X	$C_{12}H_9N_5O_3$ 271.232	251	91	53.14 53.15	3.34 2.29	25.82 25.71	2.29 (s, 3H), 7.41 (dd, 1H, J_1=8.6 Hz, J_2=1.2 Hz), 8.44 (d, 1H, J=1.2 Hz), 8.51 (d, J=8.6 Hz), 9.19 (d, 1H, J=2.8 Hz), 9.36, (d, 1H, J=2.8 Hz), 10.94 (s, 1H)	3130 (NH) 2220 (CN)
XI	$C_{12}H_9N_5O_3$ 271.232	249–250	84	53.14 53.17	3.34 3.26	25.82 25.68	2.48 (s, 3H), 7.29 (dd, 1H, J_1=7.9 Hz, J_2=1.3 Hz), 7.43–7.51 (m, 1H), 8.55 (dd, 1H, J_1=8.4 Hz, J_2=1.4 Hz), 9.21 (d, 1H, J=2.8 Hz), 9.38 (d, 1H, J=2.8 Hz), 11.30, (s, 1H)	3110 (NH) 2220 (CN)

Table 2. Physico–chemical properties and spectroscopic data of compounds **XII–XIV**

Compound	Formula Molecular mass	M.p. °C	Yield %	Analysis HR-MS Calculated/Found	^{1}H NMR[a] (δ ppm.) (DMSO-d_6)	IR[a] cm^{-1}
XII	$C_{11}H_7N_5O_2HCl$ 277.667	331-332	88	241.05997 / 241.05983 [M-HCl]	7.11-7.18 (m, 1H), 7.42-7.47 (m, 1H), 7.88-7.96 m, 1H), 9.12-9.15 (m, 1H), 9.43 (d, 1H, J=2.7 Hz), 9.63 (d, 1H, J=2.7 Hz), 10.75 (s, 1H)	3170 (C=NH)
XIII	$C_{12}H_9N_5O_2HCl$ 291.693	300	86	255.076 / 255.0756 [M-HCl]	2.60 (s, 3H), 7.47-7.51 (dd, 1H, J_1=7.3 Hz, J_2=1.7 Hz), 7.66 (s, 1H,), 9.35 (d, 1H, J=7.3 Hz), 9.55 (d, 1H, J=2.5 Hz 9.85 (d, 1H, J=2.5 Hz)	3220 (C=NH)
XIV	$C_{12}H_9H_5O_2HCl$ 291.693	306	89	255.0756 / 255.0753 [M-HCl]	2.34 (s, 3H), 7.39 (d, 1H, J=9.02 Hz), 7.79-7.84 (dd, 1H, J_1=9.02 Hz, J_2=1.97 Hz), 8.95 (s, 1H), 9.40 (d, 1H, J=2.7 Hz), 9.60 (d, 1H, J=2.7 Hz), 10.67 (s, 1H)	3290 (C=NH)

[a] – ^{1}H NMR and IR spectra of compounds **XII** and **XIV** were recorded for their hydrochloride salts. ^{1}H NMR and IR spectra of compound **XIII** was recorded for its free basis obtained by treatment of **XIII** HCl with sodium bicarbonate.

standard. IR spectra have been recorded with SP–200 spectrometer using the KBr pellets.

2–(3–cyano–5–nitro–2–pyridylamino)pyridine 1–oxides [**VIII–XI**]

General procedure. A mixture of 2–chloro–3–cyano–5–nitropyridine [**VII**], 0.01 mole, and appropriate 2–aminopyridine 1–oxide [**III–VI**], 0.011 mole, was stirred for 1 h. Crystals which separated upon cooling were filtered and recrystallized from ethanol–water.

5–imino–5H–dipyrido[1,2–a; 2',3'–d]pyrimidine hydrochlorides [**XII–IV**]

General procedure. A mixture of the corresponding 2–(3–cyano–5–nitro–2–pyridylamino)pyridine 1–oxides [**VIII–X**], 0.01 mole, and phosphorous trichloride, 0.03 mole in 30 cm^3 anhydrous ethyl acetate, was refluxed for 4 h. Crystals which separated upon cooling were filtered and washed with ethyl acetate.

2–(3–cyano–5–nitro–2–pyridylamino)–6–methylpyridine [**XV**]

A similar procedure as above using 2–(3–cyano–5–nitro–2–pyridylamino)–6–methylpyridine 1–oxide [**XI**] and phosphorous trichloride yielded compound **XV**. Yield 97%, m.p. 204–205°C; ^1H NMR ($CDCl_3$), δ: 2.52 (s, 3H). 6.96–7.00 (m, 1H), 8.11–8.15 (m, 2H), 8.63 (d, 1H, J=2.75), 9.28 (d, 1H, J=2.75); IR(KBr):3370 cm^{-1} (NH), 2220 cm^{-1} (CN). Analysis for $C_{12}H_9N_5O_2$ (255.232) – calcd.: 56.47%C, 3.55%H, 27.44%N; found: 56.49%C, 3.55%H, 27.18%N.

REFERENCES

1. Part 6 in chemistry of pyridine N–oxides. For part 5, see Rykowski A., Pucko W.: Polish J. Chem. 72, 2378 (1998).
2. Schwender C.F., Sunday B.R., Herzig D.J.: J. Med. Chem. 22, 14 (1979).
3. Schwender C.F., Sunday B.R., Herzig D.J., Kusner E.K., Schumann P.R., Gawlak D.L.: J. Med. Chem. 22, 748 (1979).
4. Schwender C.F., Sunday B.R., Kerbleski J.J., Herzig D.J.: J. Med. Chem. 23, 964 (1980).
5. Tinney F.J., Cetenko W.A., Kerbleski J.J., Connor D.T., Sorenson R.J.: J. Med. Chem. 24, 868 (1981).
6. Connor D.T., Sorenson R.J., Tinney F.J., Cetenko W., Kerbleski J.: J. Heterocyclic Chem. 19, 1185 (1982).
7. Connor D.T., Sorenson R.J., Cetenko W.A., Kerbleski J.J., Tinney F.J.: J. Med. Chem. 27, 528 (1984).
8. Huber I., Fulop F., Bernath G., Hermecz I.: J. Heterocyclic Chem. 24, 1473 (1987).
9. Rykowski A., Pucko W.: Acta Polon. Pharm. Drug Research: 54, 325 (1997).

Received: 15.10.1998