One Pot Synthesis of 6,12-Dihydro-1,3,7,9-tetramethyl-5*H*,11*H*-dipyrido[1,2-*a*:1',2'-*d*]pyrazine-2,8-dione by Hilbert-Johnson Reaction of 2-Chloromethyl-3,5-dimethyl-4-methoxypyridine [1]

Marina Orešić, Aleksandar Danilovski, and Miljenko Dumić*

PLIVA d.d., Research and Development, Prilaz baruna Filipovića 25, HR-10000 Zagreb, Croatia

Nada Košutić-Hulita

Department of Chemistry, Laboratory of General and Inorganic Chemistry, Faculty of Science, University of Zagreb, Ulica kralja Zvonimira 8, HR-10000 Zagreb, Croatia

Received November 3, 2000

By heating 2-chloromethyl-3,-5-dimethyl-4-methoxypyridine (**1**) either neat or in solution methoxy group cleavage was achieved, followed by dimerisation to poorly soluble 6,12-dihydro-1,3,7,9-tetramethyl-5*H*,11*H*-dipyrido[1,2-*a*:1',2'-*d*]pyrazine-2,8-dione (**3**) in almost quantitative yield with methyl chloride evolution. To our knowledge this is the first example of such Hilbert-Johnson preparation of dipyridopyrazinediones. Recrystallization of **3** from the hydrochloric acid yielded 6,12-dihydro-2,8-dihydroxy-1,3,7,9-tetramethyl-dipyrido[1,2-*a*:1',2'-*d*]pyrazinediylium dichloride (**4**), neutralization of which gave back the pyrazine-2,8-dione **3**. The molecular structures of both compounds **3** and **4** have been unambiguously confirmed by single crystal X-ray structure analysis.

J. Heterocyclic Chem., **38**, 785 (2001).

Introduction.

2-Chloromethyl-3,5-dimethyl-4-methoxypyridine (**1**) is a well known reagent for the synthesis of pharmacologically active substances bearing [(3,5-dimethyl-4-methoxy-2-pyridinyl)methyl] pattern [2], however no data about its stability have been reported. In this paper we would like to report thermal self condensation of **1** leading to the formation of novel derivatives in the dipyrido[1,2-*a*:1',2'-*d*]-pyrazine series.

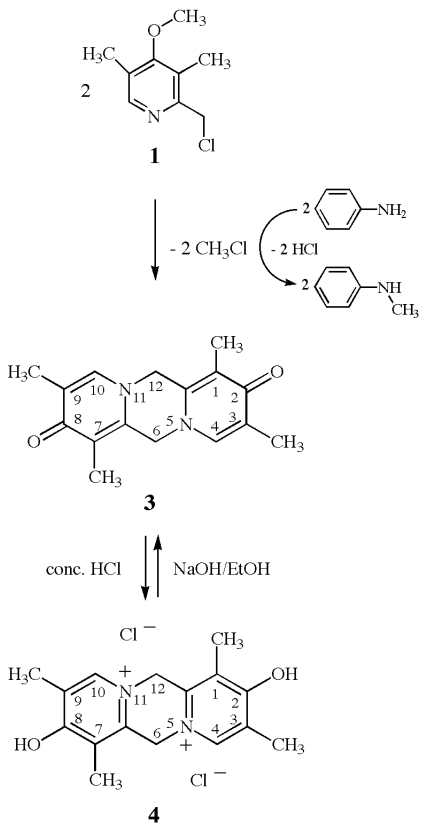
Results and Discussion.

As a continuation of our research into the dioxepino-[5,6-*b*]azirine hypoglycemics [3], **1** was used as reagent bearing pyridylmethyl functionality. It was observed that by refluxing **1** in toluene the solution became red, while after 5 hours small quantity of poorly soluble product precipitated.

In addition, by repeating the same procedure under stronger reaction conditions, *i.e.*, refluxing of **1** in xylene for 5 hours crude precipitate was isolated, m.p. > 300 °C. According to its ir spectral data, no methoxy group band was observed at 1087 cm^{-1}, while a new band at 1645 cm^{-1} appeared, indicating the presence of a keto group. Pure product recrystallized from methanol, showed the identical ir spectrum as that of the crude product. Therefore, one might conclude that **3** was formed by thermal cleavage of the methoxy group.

Although **3** has a very low solubility in most common organic nonpolar and polar solvents, including even dimethylsulfoxide, nmr data of its methanol solution showed no existence of methoxy group. On the other hand, mutual long range splitting of ring protons at 7.95 ppm and methyl protons at 2.05 ppm of ~ 0.8 Hz in ^{1}H nmr, as well as a singlet at ~ 180 ppm in the ^{13}C nmr indicating the presence of the 4-pyridone moiety. Finally, esi-ms [methanol] data of 271.2 $(M+H)^+$ gave conclusive evidence to confirm the structure of **3** as 6,12-dihydro-1,3,7,9-tetramethyl-5*H*,11*H*-dipyrido[1,2-*a*:1',2'-*d*]-pyrazine-2,8-dione (Scheme 1). Recrystallization of **3**

Scheme 1



1 **3** **4**

from 50 % (v/v) aqueous methanol solution gave its hexahydrate, the structure of which has been clearly confirmed by X-ray crystallography. (Fig. 1).

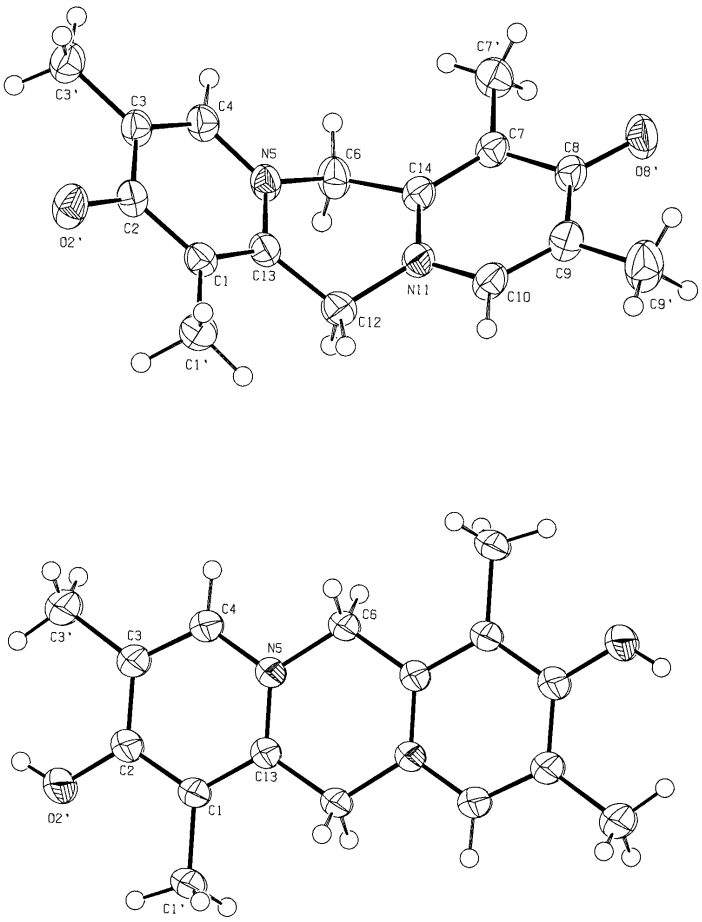


Figure 1. The X-ray molecular structures of **3** (up) and **4** (down) with the atomic numbering scheme. Non-hydrogen atoms are drawn at the 50% probability level, while hydrogen atoms are drawn as spheres of arbitrary radii. Water molecules, as well as chloride anions (**3** crystallizes as hexaxydrate, while **4** as dihydrate) are omitted for clarity.

Upon dissolving dipyridopirazinedione **3** in the hydrochloric acid 6,12-dihydro-2,8-dihydroxy-1,3,7,9-tetramethyl-dipyrido[1,2-*a*:1',2'-*d*]pyrazinediylium dichloride (**4**), was obtained, which by neutralization in ethanolic sodium hydroxide solution gave back **3** (Scheme 1).
The structure of **4** has been unambiguously confirmed by single crystal X-ray structure analysis (Figure 1) [4].

X-Ray Structural Investigation.

Up to now there are only a few representatives of 6,12-dihydro-dipyrido[1,2-*a*:1',2'-*d*]pyrazinediylium disalts [5] described in the literature, *e.g.* diperchlorate, dichloride, dibromide, diiodide and dipicrate analogues, while none of its 2,8-dihydroxy or 2,8-dione derivatives were known. Here, we report the unique 2,8-dione **3**, as well as 2,8-dihydroxy **4** derivatives of 6,12-dihydro-1,3,7,9-tetramethyl-dipyrido[1,2-*a*:1',2'-*d*]pyrazine scaffolds. Although first identified in late 1948 [6], dipyrido[1,2-*a*:1',2'-*d*]pyrazine ring systems have been relatively poorly studied [7] while its parent aromatic compound has been just recently characterized [5b].

Table 1

Summary and Comparison of some Essential Crystallographic Data for **3** and **4** [4]

Parameter	$3 \cdot 6H_2O$	$4 \cdot 2Cl^- \cdot 2H_2O$
Crystal system	Monoclinic	Triclinic
Space group	*I* 2/m	*P* $\bar{1}$
a / Å	11.255(15)	7.5934(3)
b / Å	6.8650(13)	11.1059(7)
c / Å	11.9530(12)	12.9432(7)
α / °	90	66.937(7)
β / °	104.15(2)	77.927(9)
γ / °	90	77.168(9)
V / Å^3	895.5(12)	970.08(14)
Z	2	2
D_x / gcm^{-3}	1.407	1.296
μ (Mo$K\alpha$) / mm^{-1}	0.385	0.103

Table 2

Atom Coordinates and Equivalent Isotropic Thermal Parameters (Å^2) for non-Hydrogen Atoms of **3**

Atom	x	y	z	U(eq)
O2'	0.29866(18)	-0.12563(11)	0.57868(9)	0.0425(4)
O8'	0.36649(19)	0.53698(11)	-0.15746(10)	0.0438(4)
N5	0.14229(18)	0.21668(12)	0.32468(11)	0.0305(4)
N11	0.18918(19)	0.22220(12)	0.10679(11)	0.0318(4)
C1	0.2131(2)	-0.01938(14)	0.39423(13)	0.0291(4)
C1'	0.2333(3)	-0.15101(16)	0.38187(16)	0.0376(5)
C2	0.2521(2)	-0.01826(14)	0.49836(13)	0.0297(4)
C3	0.2366(2)	0.10875(15)	0.50778(13)	0.0307(5)
C3'	0.2784(3)	0.11494(18)	0.61367(15)	0.0394(6)
C4	0.1831(2)	0.22059(15)	0.42094(13)	0.0314(5)
C6	0.0738(3)	0.34005(16)	0.23466(14)	0.0356(5)
C7	0.2298(2)	0.44966(14)	0.03375(13)	0.0301(4)
C7'	0.2085(3)	0.58073(16)	0.04685(17)	0.0398(6)
C8	0.3138(2)	0.43801(14)	-0.07315(13)	0.0313(5)
C9	0.3393(2)	0.30936(16)	-0.08146(14)	0.0367(5)
C9'	0.4338(4)	0.2888(2)	-0.18837(19)	0.0584(8)
C10	0.2754(2)	0.20724(16)	0.00849(14)	0.0353(5)
C12	0.1087(3)	0.11315(16)	0.20000(15)	0.0374(5)
C13	0.1585(2)	0.09852(14)	0.31124(13)	0.0291(4)
C14	0.1692(2)	0.34126(14)	0.12028(13)	0.0292(4)
O1W	0.0385(3)	0.60048(16)	0.33032(14)	0.0599(6)
O2W	0.2694(2)	0.49112(16)	-0.49435(16)	0.0571(6)
O3W	0.4163(2)	0.79962(15)	-0.20831(13)	0.0573(5)
O4W	0.2590(3)	-0.05007(18)	-0.07037(19)	0.0743(7)
O5W	0.0461(3)	-0.14640(19)	0.14059(16)	0.0695(7)
O6W	0.4224(2)	0.61366(13)	-0.38899(12)	0.0501(5)

Essential crystallographic data, atomic coordinates with equivalent isotropic thermal parameters for **3**, are reported in Tables 1 and 2, respectively. The molecular structure of **3** is depicted in Figure 1.

One can see that the central pyrazine ring of **3** adopts an eclipsed boat conformation as a part of the folded conformation in general, with the dihedral angle between the outer pyrido rings of 136.38(7)°, similar to the values of *cca.* 140° found in the 6,12-dipyrido[1,2-*a*:1',2'-*d*]pyrazinediylium dibromide methanol solvate [5b] and in the folded 9,10-dihydroanthracene systems [8]. Conversely, the 1,2,3-trisubstituted pyrido groups in **4** are symmetrically constrained and therefore perfectly coplanar [4].

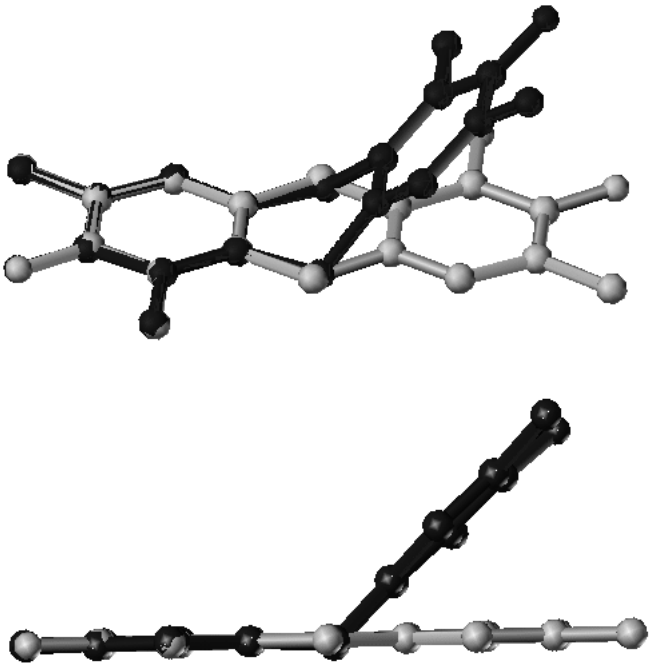


Figure 2. Overlap diagrams; top wiew (up) and side wiew (down) of molecular structures **3** (gray) and **4** (black). Hydrogen atoms are omitted for clarity.

The values of geometrical parameters are generally lying within expected ranges. It should only be pointed out that bond lengths have corroborated well with the existence of the 6,12-dihydro-5*H*,11*H*-dipyrido[1,2-*a*:1',2'-*d*]pyrazine-2,8-dione moiety and the sp^3 hybridized C6 and C12 atoms. Considering the sp^3 hybridization of atoms C6 and C12 the folded conformation of **3** was anticipated, unlike the extended and planar conformation of **4** (Figure 2).

Molecule **3** forms complex three-dimensional hydrogen-bond network (Figure 3). Keto moieties are linked with two water molecules, at each side, *via* intermolecular O8'(O2')…H-O3W(O6W) hydrogen bond forming pseudo-eight-membered ring patterns. Also, by combining ring patterns, chains along [0 $\bar{1}$ 1] direction are formed. Additionally by utilizing numerous intermolecular OW(n)-H···OW(n) (n = 1-6) hydrogen bonds the complete hydrogen-bond network is constructed.

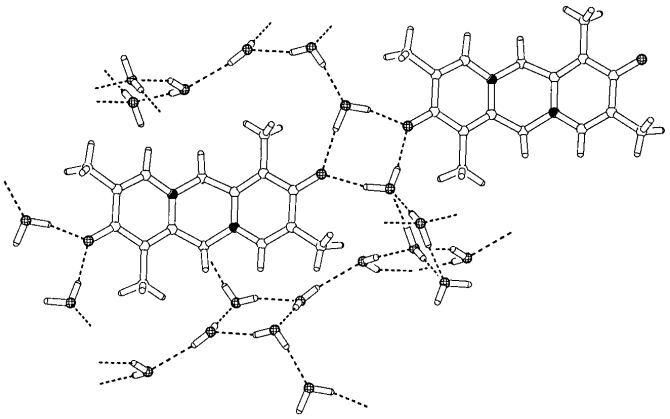


Figure 3. Packing diagram of **3**. Nitrogen atoms are solid while oxygen atoms are hatched. Hydrogen bonds are shown as dashed lines.

Mechanism of Cyclisation.

According to the literature condensation procedures for 2-halomethyl nitrogen containing heterocycles toward the formation of the 6,12-dihydro-dipyrido[1,2-*a*:1',2'-*d*]-pyrazine scaffold has been expected [6,7]. Isolation of the keto **3** and not the methoxydipyridopyrazinium dichloride **2** could be attributed to the hydrolysis of the expected intermediate **2**, during the course of reaction by air humidity. These findings, corroborate well with known hydrolytic cleavage of 4-methoxypyridinium salts to 4-pyridones [9].

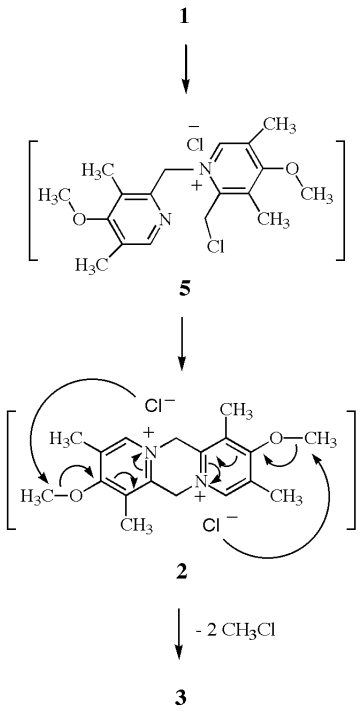
However, detailed study of reaction, performed in the absence of air and humidity, indicated, that heating of **1** in neat led to the methoxy group cleavage and dimerisation to the poorly soluble 6,12-dihydro-1,3,7,9-tetramethyl-5*H*,11*H*-dipyrido[1,2-*a*:1',2'-*d*]pyrazine-2,8-dione (**3**), under subsequent methyl chloride evolution (Scheme 1). The methyl chloride released during the course of cyclisation was trapped in aniline. *N*-Methylaniline was isolated (Scheme 1) and characterized by spectroscopic methods, and its ir spectrum was identical to the spectrum of the authentic sample [10].

Formation of the methyl chloride could be a consequence either of a radical or an ionic mechanism. In order to clarify this mechanistic dilemma, gas stream evolving during the reaction was analyzed by the gc for the presence of ethane, as an indicator of the possible radical pathway. Moreover, epr measurments of **1** in neat up to 140 °C was used as another radical species detector. Preliminary results did not show any trace of ethane, also epr radical patterns were not detected. Additionally, the thermal cyclization pathway of **1** was monitored by ^{1}H nmr experiments in dimethylsulfoxide-d_6 solution at 120 °C. Unfortunately, they were unsuccessful due to the precipitation of poorly soluble product **3**. No compound(s) was(were) perceived that could indicate formation of intermediate dimethoxy derivative **2,** as well.

Therefore, it might be concluded that according to the mentioned results one can rule out the radical process and propose an ionic mechanism of methyl chloride elimination and direct formation of pyrazine-2,8-dione **3** starting from **1**.

Although these initial experiments yielded no methoxy derivative **2**, one can propose that dimerisation of **1** represent the extension of Hilbert-Johnson reaction, known from pyrimidine [11] and pyridazine [12] nucleosides chemistry. Typically, treatment of an alkoxy- or trialkylsiloxy pyrimidines or pyridazines with alkyl- (glycosyl-) halides affords a quaternary salt, which readily loses the alkyl or trialkylsilyl halide to furnish a *N*-alkyl- (glycosyl) pyrimidinone or pyridazinone. It should be noted that dimerisation of **1** is a specific case of such reaction, where quaternization of pyridine nitrogen atoms leads formation of the dipyridopyrazinedione **3**.

Scheme 2



Initial formation of **5** and its subsequent cyclisation should lead to intermediate **2**. The next step most likely involves facile cleavage of a dimethoxydipyridopyrazinediylium salt **2** that probably occurs by immediate nucleophilic attack of chloride ions, yielding dipyridopyrazinedione **3**.

It is well known that alkyl aryl or alkyl heteroaryl ether group cleavage proceeds in the presence of the hydrohalic acids [13], where halide ions are strongly solvated, and less nucleophilic. However, cleavage conditions reported here are quite different, *i. e.* chloride ions are less solvated, and therefore more nucleophilic, so they can easily cleave methoxy group. The driving force for this reaction could be the precipitation of insoluble dipyridopyrazinedione **3**, as a product.

In general, concerted nature of any reaction is the source of great debate, even in the case of Diels-Alder reactions, which are commonly considered as concerted [14]. This is the reason why concerted mechanism of presented reaction might be excluded from further consideration.

To our knowledge the reaction pathway that has been discussed represents the first example of specific Hilbert-Johnson reaction variant, the significance and scope of which is still under investigation.

EXPERIMENTAL

Chemistry.

General Information.

Melting points were determined using a Fischer-Johns apparatus, and are uncorrected. Infrared spectra (ir) were recorded on a Nicolet Magna-IR 760 Spectrometer and the bands are given in cm^{-1}. Nuclear magnetic resonance spectra ^1H nmr and ^{13}C nmr were recorded in methanol-d_4 solution with tetramethylsilane as internal standard on Bruker Avance DPX 300 spectrometer. Chemical shifts (δ) are given in ppm relative to tetramethylsilane (δ = 0), and coupling constants (J) in Hz; with methanol-d_4 as a solvent. Mass spectrum was determined in the electronspray mode on Micromass Platform LCZ with capillary voltage of 3.5 kV and cone voltage of 35 V. Combustion analyses were performed in our laboratory. TLC was performed using Merck Kieselgel 60 F_{254} silica plates and components were visualized using UV light and iodine vapor. Solvents were *p.a.* grade and were used without further purification. 2-Chloromethyl-3,5-dimethyl-4-methoxypyridine (**1**) used was prepared by carefully neutralization of its hydrochloride, obtained from commercial sources, and its purity was checked by HPLC. Chemical yields were not optimized.

6,12-Dihydro-1,3,7,9-tetramethyl-5*H*,11*H*-dipyrido[1,2-*a*:1',2'-*d*]-pyrazine-2,8-dione (**3**).

Method A.

2-Chloromethyl-3,5-dimethyl-4-methoxypyridine (**1**) (7.5 g; 50.1 mmol) was refluxed in xylene (90 mL) (~ 140 °C) for 5 hours. After cooling, the solid precipitate was filtered by suction, washed with xylene and dried *in vaccuo* (~2.0 kPa) at 50 °C for 3 hours yielding crude, chromatographically pure dipyridopyrazinedione **3** (2.8 g; 42 %; m.p. > 300 °C). An analytical sample was obtained by recrystallization from methanol; ir (potassium bromide): 3433, 3011, 2925, 1649, 1559, 1492, 1372, 1279, 1115; ^1H nmr (300 MHz, methanol-d_4): δ 7.95 (d, 2H, J = 0.8 Hz, H-C4 & H-C10), 5.29 (s, 4H, H-C6 & H-C12), 2.18 (s, 6H, CH_3-C1 & CH_3-C7) and 2.06 (d, 6H, J = 0.8 Hz, CH_3-C3 & CH_3-C9); ^{13}C nmr (75 MHz, methanol-d_4,): δ ppm 179.90 (s, C1 and C8), 141.75 (s, C6a and 12a), 139.48 (d, C4 and C10), 122.77 (s, C1 and C7), 51.16 (t, C6 and C12), 14.39 (q, CH3-C1 and CH3-C7), 11.06 (q, CH3-C3 and CH3-C9); esi-ms [methanol] $C_{16}H_{18}N_2O_2$ M_r(calcd) = 270.30, M_r(found) = 271.2 $(M+H)^+$.

Anal. Calcd. for $C_{16}H_{18}N_2O_2$: C 71.09, H 6.73, N 10.37. Found: C 71.07, H 6.75, N 10.34.

Method B.

2-Chloromethyl-3,5-dimethyl-4-methoxypyridine (**1**) (7.8 g; 52 mmol) was charged in a 3-necked flask equipped with thermometer and a nitrogen inlet pipe and connected to four traps; empty, filed with 15.00 g aniline, empty and filed with 15 mL of 1.0 *M* NaOH). **1** was heated in the air-free atmosphere which was accomplished by slow, bulb-to-bulb nitrogen flow. Once 50 °C was reached the nitrogen flow was stopped. At about 120 °C solid precipitation and gas generation started, and over 130 °C both processes are considerable faster. Heating was continued for about 2 hours and ended at 160 °C. After cooling, the solid residue in the flask was crude, chromatographically pure dipyridopyrazinedione **3** (5.42 g; 77 %; m.p. > 300 °C). Its ir spectrum was identical to the spectrum of authentic sample (Method A).

The aniline trap mixture was resolved by column chromatography (methylene chloride:ethyl acetate = 98:2) to give *N*-methylaniline (1.56 g; 31.8 %). Its ir spectrum was identical to the spectrum of the authentic sample [10].

Method C.

6,12-Dihydro-2,8-dihydroxy-1,3,7,9-tetramethyl-dipyrido [1,2-*a*:1',2'-*d*]pyrazinediylium dichloride dihydrate (**4**) (0.34 g, 1 mmol) was dissolved in solution of sodium hydroxide (80 mg; 2 mmol) in 20 mL of ethanol. The mixture was stirred at room temperature for 2 hours. Solvent was evaporated under reduced pressure and solid residue was macerated in 3 mL of water. The obtained crystals were filtered off, washed with water and dried *in vaccuo* (~2 kPa) at 50 °C for 3 hours. Pure dipyridopyrazinedione 3 was obtained (0.25 g, 94 %; m.p. > 300 °C). Its ir spectrum was identical to the spectrum of the authentic sample (Method A).

6,12-Dihydro-2,8-dihydroxy-1,3,7,9-tetramethyl-dipyrido-[1,2-*a*:1',2'-*d*]pyrazine-diylium Dichloride Dihydrate (**4**).

Pyrazine-2,8-dione **3** (0.6 g; 2.2 mmol) was dissolved in 7 mL of 50 % aqueous methanol and 0.55 mL of hydrochloric acid. Mixture was stirred at room temperature for 15 minutes and another 8 mL of aqueous methanol was added. Big, colorless crystals of **4** precipitated from solution and were filtered off (0.5 g, 65 %, m.p. > 300 °C). ir (potassium bromide): 3306, 3023, 1644, 1495, 1434, 1322, 1275, 1109, 1035, 984; ^{1}H nmr (300 MHz, methanol-d_4): δ 8.76 (s, 2H, H-C4 & H-C10), 5.96 (s, 4H, H-C6 & H-C12), 2.48 (s, 6H, CH_3-C1 & CH_3-C7) and 2.37 (s, 6H, CH_3-C3 & CH_3-C9); ^{13}C nmr (75 MHz, methanol-d_4): δ 170.89 (s, C2 and C8), 145.07 (s, C6a and C12a), 144.31 (d, C4 and C10), 125.47 (s, C3 and C9), 123.90 (s, C1 and C7), 53.45 (t, C6 and C12), 14.46 (q, CH_3-C3 and CH_3-C9), 11.80 (q, CH_3-C1 and CH_3-C7); esi-ms [methanol] $C_{16}H_{20}Cl_2N_2O_2$ M_r(calcd) = 343.22, M_r(found) = 271.1 (M-H & -2Cl)$^+$.

Anal. Calcd. for $C_{16}H_{20}Cl_2N_2O_2$: C 55.99, H 5.89, N 8.16. Found: C 55.95, H 5.91, N 8.15.

X-ray Diffraction

The X-ray diffraction data for compound **3** were collected on PHILIPS PW1100 automatic four-circle diffractometer (Stoe/Cie upgrade) using graphite monochromatized MoKa radiation (λ = 0.71069 Å), at room temperature. The measured intensity data were corrected for Lorentz and polarization effects, but not for absorption. The molecular and crystal structure was solved by direct methods and refined on F^2 with anisotropic displacement parameters for all non-hydrogen atoms. All hydrogen atoms were located in the difference Fourier maps and refined isotropically. Refinement parameters converged as follows; $R(F)$ = 0.047 and $w(R_F^2)$ = 0.150.

Acknowledgment.

We thank Mrs. Zorica Veksli, Ph.D. and Mr. Boris Rakvin, Ph.D. Ruđer Bošković Institute, Zagreb for epr measurement, Mrs. Sanda Telen, B. Sc., INA Oil Industry, Division for Strategic Development and Research, Zagreb, Croatia for the gc ethane analysis, Professors Alan R. Katritzky , University of Florida, USA, Henk Van der Plas, University Wageningen, The Netherlands, Branko Stanovnik and Miha Tišler, University of Ljubljana, Slovenia for helpful discussions, and the Ministry of Science and Technology of the Republic of Croatia for partially supporting this work (grants: #006243 and #119420).

REFERENCES AND NOTES

[1] Presented at 8th Blue Danube Symposium on Heterocyclic Chemistry, Bled, Slovenia, Sept. 2000.

[2a] E. Cereda, M. Turconi, A. Ezhaya, E. Bellora, A. Brambilla, F. Pagani and F. Donetti, A. *Eur. J. Med. Chem*. **22**(6), 527 (1987); [b] Geun-jho Lim,Dong-sung Kim and Nung-min Yoon, Dong-A Pharmaceutical Co., Ltd., PCT WO Appl. 0027841 A1 (May 18, 2000); *Chem. Abstr.* **132**, 334462g (2000); [c] B. Tarbit, Seal Sands Chemical Limited, PCT WO Appl. 9910326 A1 (Mar. 04, 1999); *Chem. Abstr.* **130**, 196579r (1999); [d] Sung-Hwa Yoon, Seung Ki Seo, Young Hee Lee, Sung Kwan Hwang, and Dong Yeon Kim, Bioorg. *Med. Chem. Lett.* **8**(14), 1909 (1998); [e] Masami Muraoka, Katsuhisa Ioriya, Naohito Ohashi and Hideki Yagi, Sumitomo Pharmaceuticals Company, Limited, PCT WO Appl. WO 9823615 A1 (June 04, 1998); *Chem. Abstr.* **129**, 41083e (1998); [f] Pyeong-Uk Park, Sungsoo Pyo, Suk-Kwan Lee, Jin Heung , Wie Jong Sung, Wie Jong Kwak, Hwa-Kun Park, Yong-Baik Cho, Geun-Ho Ryu and Taek Soo Kim, Sunkyang Industries Co., Ltd., PCT WO Appl. 9518131 A1 (July 06, 1995); *Chem. Abstr.* **123**, 314213x (1995); [g] H. F. Deng, Y. Z. Jiang and Z. Z. Zhao, *Yaoxue Xuebao* **30**(5), 347 (1995), *Chem. Abstr.* **123**, 340706e (1995); [h] Hong Feng Deng, Yun Zhen Jiang and Zhi Zhong Zhao *Chin. Chem. Lett.* **5**(4), 271 (1994); *Chem. Abstr.* **121**, 180087g (1994); [i] Minoru Uchida, Seiji Morita and Masatoshi Chihiro, Otsuka Pharmaceutical Co., Ltd., Jpn. Kokai Tokkyo JP 62061978 A2 (Mar. 18, 1987); *Chem. Abstr.* **107**, 39827c (1987); [j] U. K. Junggren, S. E. Sjoestrand, Aktiebolag Haessle, CA 1129417 A2 (Aug 10, 1982); *Chem. Abstr.* **98**, 16689r (1983).

[3a] M. Dumić, D. Filić, M.Vinković, B. Jamnicky and B. Kamenar, *Tetrahedron Lett.*, **34**, 3639 (1993); [b] M. Dumić. M. Vinković, D. Filić, B. Jamnicky, M. Eškinja and B. Kamenar, *J. Med. Chem*., **38**, 3034 (1995);
[c] D. Filić, M. Vinković, B. Jamnicky and M. Dumić, *Croat. Chem. Acta.*, **69**, 631 (1996).

[4] N. Košutić-Hulita, A. Danilovski, M. Malešević, M. Orešić, M. Dumić, *Acta Cryst*., C**56**, 1144 (2000).

[5a] J. G. Eaves, D. Parker and N. Rudgewick-Brown, *Can. J. Chem*., **64**, 1711 (1986), [b] M. R. Bruce, J. G. Eaves, D. Parker, J. A. K. Howard and O. Johnson, *J. Chem. Soc., Perkin Trans. 2*, 433 (1985), [c] P. Jandik, U. Deschler and H. Schmitbaur, *Fresenius' Z. Anal. Chem.*, **305**, 347 (1981), [d] G. G. Abbot, D. Leaver and K. C. Mathur, *J. Res. Synops. (S)*, 224 (1978), [e] G. Buchmann, H. Franz and H. Krueger, Ger (East) Patent 55860 (May 5, 1967); *Chem. Abstr.* **67**, 116068r (1967).

[6] F. Šorm, L. Šedivy, *Collect. Czech. Chem. Commun.*, **13**, 289 (1948).

[7a] G. A. Abbot, D. Leaver, K. C. Mathur, *J. Res. Synops. (M)*, 2846 (1978), [b] E. E. Glover, G. H. Morris, *J. Chem. Soc.*, 3366 (1964) and references citied therein, [c] E. E. Glover, G. H. Morris, *J. Chem. Soc.*, 3885 (1965) and references citied therein; [d] A. L. Black, L. A. Summers, *Chem. Commun.*, 482 (1970).

[8a] F. H. Herbstein, M. Kapon, G. M. Reisner, *Acta Cryst.*, B**42**, 181 (1986), [b] J. P. Reboul, Y. Oddon, C. Caranoni, J. C. Soyfer, J. Barbe, G. Pepe, *Acta Cryst.*, C**43**, 537 (1987).

[9] D. L. Comins, *J. Heterocyclic Chem.*, **36**, 1491 (1999) and references citied therein.

[10] *The Aldrich Library of FT-IR Spectra*; Edition II, Aldrich, USA, 1997, Vol. **2**. 2024D.

[11a] J. Pliml, M. Prystaš The Hilbert-Johnson Reaction of 2,4-Dialkpxypyrimidines with Halogens, in Advances in Heterocyclic Chemistry, Vol. **8**, A. R. Katritzky, A. J. Boulton, eds, Academic Press, New York, 1967, pp 115 -142 and reference cited therein; [b] D. J. Brown, S. F. Mason, The Pyrimidines, in The Chemistry of Heterocyclic Compounds, Vol. **16**, A. Weisberger ed, John Wiley & Sons, New York, 1962, p.p. 227-271 and reference cited therein; [c] D. J. Brown, The Pyrimidines, in The Chemistry of Heterocyclic Compounds, Vol. **52**, E. C. Taylor, A. Weisberger, eds, John Wiley & Sons, New York, 1994 and reference cited therein.

[12a] J. W. Mason, D. L. Aldous, The Pyridazinones, Alkoxy- and Aryloxypyridazines, and Related Compounds, R. N. Castle, ed, Pyridazines in The Chemistry of Heterocyclyc Compounds, Vol. **28**, A. Weisberger, E. C. Taylor, eds, John Wiley & Sons, New York, 1973, p.p. 23-218 and references cited therein, [b] D. J. Brown, The Pyridazines in The Chemistry of Heterocyclyc Compounds, Supplement I, Vol **57**, E. C. Taylor, P. Wipf, eds, John Wiley & Sons, New York, 2000, p.p. 289 -290 and references cited therein.

[13a] H. Meerwin, in Houben-Weyl Methoden der Organischen Chemie, Band VI/3, E. M¸ller, ed, Georg Thieme Verlag, Stuttgart, 1965, 1-198, [b] The Chemistry of Functional Groups, S. Patai, ed.; John Wiley & Sons: Chichester, 1967 and references citied therein.

[14] J. Sauer and R. Sustmann, *Angew. Chem. Int. Ed. Engl.*, **19**, 779 (1980).