PHOTOCHEMICAL REARRANGEMENTS OF 3-METHYLISOXAZOLOPYRIDINES

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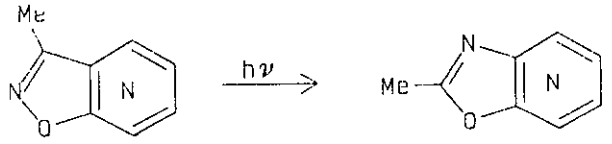
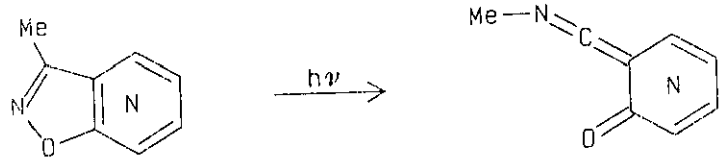
Abstract — Irradiation in water-saturated ethyl ether of isoxazolopyridines 1a,e, beside the corresponding oxazolopyridines 2a,e, leads to N-methylcarboxamides 3a,e via 1-2 shift of the methyl group. The isoxazolopyridine 5, bearing a hydrazino group in 4-position, rearranges only to 1-aminopyrazolopyridine 6.

The molecular photorearrangement of aromatic isoxazolopyridines **A** to the corresponding oxazolopyridines **B** is a quite general process. In fact, it was reported that uv-irradiation of isoxazolo[4,5-c]- and [5,4-b]pyridines gives the corresponding oxazolo[4,5-c]- and[5,4-b]pyridines, respectively[1,2]. Afterwards we found the



A B

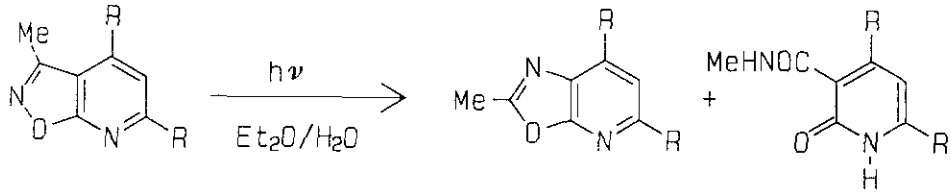
same photoreactivity in the case of isoxazolo[4,5-b]- and [5,4-c]pyridines[3,4]. Previous knowledges in the field of isoxazoles and benzoisoxazoles photochemistry[5,6], suggesting also the possibility of formation of the ketenimines C via 1,2-methyl shift, prompted us to a further investigation of the photochemical



A C

behaviour of the title compounds, focusing the attention on the occurrence of such intermediate

Uv irradiation of isoxazolo[5,4-b]pyridines **1a,b** in water-saturated ethyl ether yielded both the expected oxazolopyridines **2a,b** and a small amount of two new products, identified as 3-(N-methylcarbamoyl)-2-pyridones **3a,b**, respectively, on the basis of the analytical and spectral data. In particular, both show in ^{1}H-nmr spectra signals attributable to the -NHMe moiety (a doublet near 3.00 ppm, which gives a singlet on deuterium exchange and an exchangeable broad signal at low field).



1a, b 2a, b 3a, b

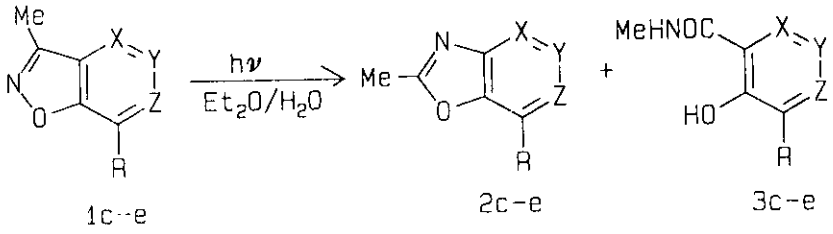
a) R= H b) R= Cl

The same behaviour was found in the case of the other aromatic isoxazolopyridines **1c-e** considered, which gave, on irradiation in moist ether, the oxazoles **2c-e** and the corresponding N-methylcarboxamides **3c-e** in a 5-10% yield.

TABLE 1 - *PHOTOREACTIVITY OF 3-METHYLISOXAZOLOPYRIDINES 1a-e*

Compound	Irradiation time (h)	Conversion (%)	Separation conditions	Products (yield %)[a]
1a	24	45	c	**2a**[7] (55) **3a** (8)
1b	15[b]	65	c	**2b**[3] (52) **3b** (6)
1c	14[b]	45	d	**2c**[3] (65) **3c** (10)
1d	24	30	c	**2d**[1] (55) **3d** (9)
1e	16	35	c	**2e**[3] (70) **3e** (4)

([a]) Based on converted isoxazolopyridine. ([b]) When the photoreaction was carried out to a larger conversion (80 - 90%), also the amides **4b,c**, respectively, were obtained in 4 - 5 % yield. ([c]) Column was eluted first with light petroleum:ether 2:1 and after with chloroform:methanol 95:5 (order of mobility 1 - 2 - 3). Compound **3e** was identified in the crude reaction mixture by comparison (t.l.c. and ^{1}H-nmr spectrum) with an authentic sample, prepared as above (Experimental). ([d]) *Column was eluted with light petroleum:ether 1:1 (order of mobility* **1c-3c-2c**).

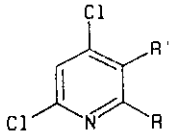


1c-e 2c-e 3c-e

c) X= N, Y= CCl, Z= CH, R= Cl
d) X= CCl, Y= N, Z= CCl, R= H
e) X= CH, Y= CH, Z= N, R= H

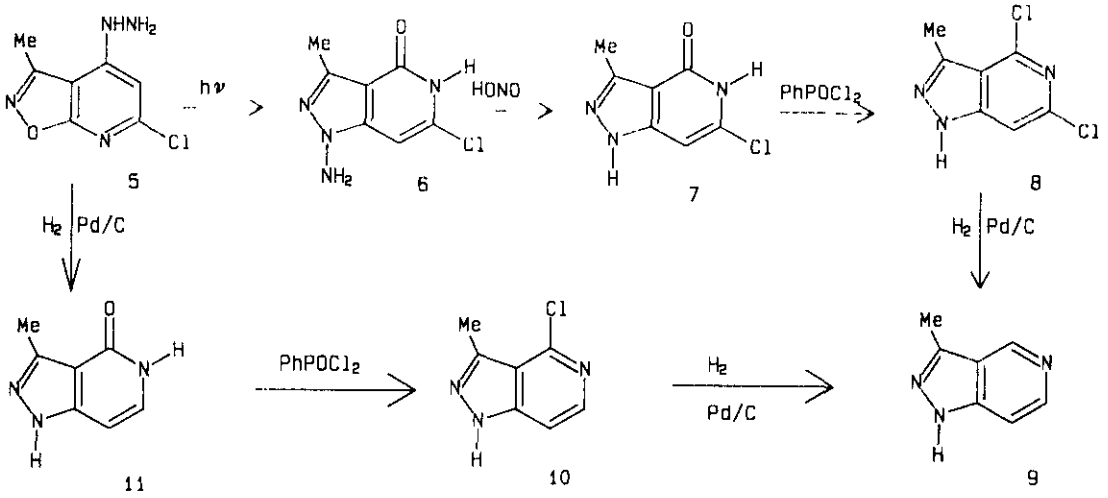
Water addition on photochemically generated ketenimines **C** accounts for the formation of **3a-e**. It is to be noting that our previous experiments[1,3,4] were carried out in anhydrous ether or ethanol: as a consequence, the ketenimines **C** or the corresponding imino ethers were lost during irradiation and/or chromatographic separations. An attempt to evidence ketenimine infrared absorption by irradiation of the isoxazolopyridine **1a** in a low temperature infrared cell gave unconclusive results.

The above photorearrangements were carried out to about half transformation of the starting materials, in order to reduce the by-products formation, due to irradiation of the primary photoproducts. In fact,acetamidopyridines **4b,c** were also obtained in low yields by prolonged irradiation of dichloroisoxazolopyridines **1b,c**, as a consequence of water addition on the oxazoles **2b,c**.



4b) R= OH, R'= NHAc
4c) R= NHAc, R'= OH

A different photochemical behaviour was found when the isoxazolopyridine system have a suitable substituent at the 4-position . Thus, irradiation of the hydrazine **5** gave 1-amino-6-chloro-3-methylpyrazolo[4,3-c] pyridin-4(5H)-one **6** in good yield, whereas no products arising from 1,2-methyl shift were found. The structure of **6** was assigned on the basis of chemical considerations. Thus, deamination of **6** with nitrous acid gave 6-chloro-3-methylpyrazolo[4,3-c]pyridin-4(5H)-one **7**, which was chlorinated by phenylphosphonic dichloride to 4,6-dichloro-3-methylpyrazolo-[4,3-c]pyridine **8**. Catalytic hydrogenation of the latter compound afforded the parent ring system **9**, which was also prepared, in an unambiguous way, from compound **5** by catalytic hydrogenation to **11**[8], chlorination to 4-chloro-3-methylpyrazolo[4,3-c]pyridine **10** and, finally, catalytic dehalogenation by hydrogen.



As a conclusion, the 1-2 methyl shift is confirmed as a possible mechanism also in the isoxazolopyridine photorearrangements. However, some particular substituents, opening easier pathways, may reduce or suppress the occurrence of such mechanism. This and previous our studies demonstrate the synthetic interest of the isoxazolopyridine photochemistry: in fact, according to the presence and the nature of 4-substituents, *easy entry towards functionalized monocyclic or condensed* pyridines could be achieved.

EXPERIMENTAL

Melting points were determined on a Reichert Kofler block and are uncorrected. ^{1}H-Nmr spectra were recorded on a Perkin Elmer R 600 instrument; chemical shifts (J in Hz) are in ppm (δ) from internal tetramethylsilane. Ir spectra were recorded for KBr discs on a Perkin Elmer 782 spectrophotometer. Photochemical reactions were carried out with a water cooled low pressure mercury immersion lamp (6W); nitrogen was constantly bubbled through the irradiated solution. Column chromatography were carried out on silica gel (40-63 μ). Light petroleum refers to that fraction boiling in the range 40-70 °C).

Irradiation of the Isoxazolopyridines (**1a-e**)

A solution of **1a-e** (3 mmol) in water saturated ether (peroxides free) (120 ml) was irradiated for 14-24 hours. Solvent was removed *in vacuo* and the residue was column chromatographed to give, as reported in the Table 1, starting materials, the oxazolopyridines **2a-e** and the methylamides **3a-e**. Physical and analytical data of the latter compounds are listed in the Table 2.

3-Hydroxy-N-methylisonicotinamide (3e)

Methyl 3-hydroxypyridine-4-carboxylate [9] (0.306 g, 2.0 mmol) in dioxane (5 ml) was saturated with anhydrous methylamine and the solution was heated in a sealed tube at 90-100 °C (3 h). After cooling, solid material was filtered, washed with ether and dissolved in water. Extraction with dichloromethane of the acidified (pH 5) solution afforded, on evaporation of the organic layer, compound **3e** (0.25 g, 82%).

Irradiation of 6-Chloro-4-hydrazino-3-methylisoxazolo[5,4-b]pyridine (5)

A solution of **5** (0.5 g, 2.5 mmol) in anhydrous ethanol (120 ml) was irradiated for 48 h. During the reaction, an insoluble material was periodically collected by filtration and identified as 1-amino-6-chloro-3-methylpyrazolo[4,3-c]pyridin-4(5H)-one **6** (0.3 g, 60%): mp 280-282 °C (dimethyl sulfoxide/water). Anal. Calcd for $C_7H_7ClN_4O$: C, 42.32; H, 3.56; N, 28.21. Found: C,42.70; H, 3.62; N, 27.95. ^{1}H-Nmr (DMSO - d_6): 2.40 (s, Me), 6.32 (exch. s, NH_2),6.45 (s, H_7), 11.63 (exch, br s, NH/OH). Ir: 3300,3200 (NH_2), 3100 - 2500 (NH), 1690,1660 (CO).

Compound **6** by refluxing with benzaldehyde in methanol afforded the corresponding benzalderivative in quantitative yield, mp 320 °C (methanol). Anal. Calcd for $C_{14}H_{11}ClN_4O$: C, 58.64; H, 3.87; N, 19.54. Found: C, 58.53; H, 3.96; N, 17.32.

Deamination of 1-Aminopyrazolopyridine (6)

A solution of **6** (0.14 g, 0.7 mmol) in 6N hydrochloric acid (5 ml) was treated with sodium nitrite (0.05 g, 0 7 mmol). Sodium hydroxide was then added (pH 5) and 6-chloro-3-methylpyrazolo[4,3-c]pyridin-4(5H)-one **7** was collected by filtration (0.11 g, 86%): mp 316-319 °C (dimethylsulfoxide/water). Anal. Calcd for $C_7H_6ClN_3O$: C, 45.79; H, 3.30; N, 22.89. Found: C, 45.53; H, 3.19; N, 22.67. ^{1}H-Nmr (DMSO-d_6): 2.48 (s, Me), 5.80 (exch, br s, 2 NH), 6.46 (s, H_7). Ir: 3150 (NH), 3100 - 2200 (NH), 1680 (CO) cm^{-1}.

Hydrogenation of 6-Chloro-4-hydrazino-3-methylisoxazolo[5,4-b]pyridine (5)

A solution of **5** (0.4 g, 2 mmol) in ethanol (200 ml) was shaked in a Parr apparatus in presence of 10% Pd-C (0.2 g) under a hydrogen pressure of 2.5 atm for 3 h. Catalyst was removed by filtration, solvent was evaporated and the residue, dissolved in 6N sodium hydroxide, was neutralized to precipitate 3-methylpyrazolo-[4,3-c]pyridin-4(5H)-one **11**, (0.25 g, 84%): mp 310-312 °C. Anal. Calcd for $C_7H_7N_3O.1/2\ H_2O$): C, 53.16; H, 5.10; N, 26.57 Found: C, 53.45; H, 4.97; N, 26.38. ^{1}H-Nmr (DMSO-d_6): 2.48 (s,Me), 6 12 (d, J = 6.8, H_7), 7.23 (d, J = 6.8, H_6), 8.00, 11.92 (exch, br s, 2 NH). Ir: 3350 - 2400 (NH), 1660 (CO) cm^{-1}.

4,6-Dichloro-3-methylpyrazolo[4,3-c]pyridine (8)

Compound **7** (0.11 g, 0.6 mmol) and phenylphoshonic dichloride (1 ml) were heated at 150 °C (1 h). The solution was poured into ice, neutralized with solid $NaHCO_3$ and extracted with dichloromethane. Solvent was then evaporated and the residue sublimed at 120 °C (0.03 mm Hg) to afford compound **8** (0.055 g, 45%): mp 172-174 °C (in a sealed tube). Anal. Calcd for $C_7H_5Cl_2N_3$): C, 41.61; H, 2.49; N,

TABLE 2 - ANALYTICAL AND SPECTRAL DATA OF THE AMIDES **3a-e** and **4b,c**

	mp °C	Anal,% [a] (calcd)			IR ν (cm^{-1})	^{1}H-NMR ($CDCl_3$) δ(ppm)
		C	H	N		
3a	196-9[d]	55.42 (55.25)	5.34 (5.31)	18.19 (18.41)	3290(NH), 3200-2400(OH/NH), 1665(CO)	3.01(d,s with D_2O,J=5.0,Me), 6.55(t,$J_{4,5}=J_{5,6}$=6.7,H_5), 7.59(dd,$J_{5,6}$=6.7,$J_{4,6}$=2.0,H_6), 8.66(dd,$J_{4,5}$=6.7,$J_{4,6}$=2.0,H_4), 9.50(exch.br,NH)
3b	192-3[b]	38.30 (38.03)	3.05 (2.74)	12.46 (12.68)	3280(NH) 3250-2200(OH/NH), 1660(CO)	3.05(d,s with D_2O,J=4.8,Me) 6.89(s,H_5) 7.55(exch.br,NH), 10.00(exch.br,NH/OH)
3c	198-9[b]	38.42 (38.03)	2.71 (2.74)	12.82 (12.68)	3410(NH) 3100-2250(OH/NH), 1660(CO)	3.02(d,s with D_2O,J=5.2,Me), 7.46(s,H_5),7.82(exch br,NH), 12.95(exch.br,OH)
3d	156-8[d]	37.83 (38.03)	2.73 (2.74)	12.40 (12.68)	3390(NH), 3350-2300(OH/NH) 1645(CO)	3.06(d,s with D_2O,J=4.8,Me), 6.90(s,H_5),7.76(exch.br,NH), 8.30(exch.br,OH/NH)
3e	142-3[d]	55.21 (55.25)	5.24 (5.31)	18.64 (18.41)	3120(NH), 3100-2000(OH), 1660(CO)	3.02(d,s with D_2O,J=4.8,Me), 7.75,8.04(AB,$J_{5,6}$=4.8,H_5,H_6), 8.33(s,H_2),8.56(exch.br q, J=4.8,NH),10.05(exch.br,OH)
4b	225-7[c]	38.34 (38.03)	2.90 (2.74)	12.83 (12.68)	3245(NH), 3200-2300(OH/NH), 1665(CO)	2.22(s,Me),6.69(s,H_5),7.38 (exch.br,NH/OH)
4c	125-7[d]	38.37 (38.03)	2.78 (2.74)	12.38 (12.68)	3290(NH), 3100-2100(OH/NH), 1665(CO)	2.31(s,Me),7.22(s,H_5), 7.52(exch.br, NH), 9.86(exch.br, OH)

([a]) Calculated values in parenthesis. ([b]) From benzene. ([c]) From benzene-methanol. ([d]) Sublimed in vacuo.

20.80. Found: C, 41.91; H, 2.56; N, 20.72. ^{1}H-Nmr ($CDCl_3$): 2.76 (s, Me), 7.31 (s, H_7). Ir: 3200 (NH).

4-Chloro-3-metnylpyrazolo[4,3-c]pyridine (10)

Operating as above from compound **11** (0.26 g, 1.74 mmol) and phenylphosphonic dichloride (5 ml), chloroderivative **10** was obtained (0.16 g, 55%): mp 197-198 °C (in a sealed tube). Anal. Calcd for $C_7H_6ClN_3$): C, 50.16; H, 3.62; N,25.08. Found: C, 50.33; H, 3.78; N, 25.36. ^{1}H-Nmr ($CDCl_3$): 2.79 (s, Me), 7.27 (d, J = 5.8, H_7), 8.15 (d, J = 5.8, H_6), 10.24 (exch, br s, NH). Ir: 3130 (NH).

3-Methylpyrazolo[4,3-c]pyridine (9)

A solution of **8** (0.05 g ,0.25 mmol) and triethylamine (0.1 ml) in ethanol (10 ml) was shaked under hydrogen at atmospheric pressure in presence of 10% Pd-carbon (0.02 g). The catalyst was filtered off, and the filtrate was evaporated. The residue was treated with 1N NaOH (2 ml). Extraction with ether gave, on evaporation, compound **9**, which was crystallized from cyclohexane (0.024 g, 72%): mp 165-167 °C (in a sealed tube). Anal. Calcd for $C_7H_7N_3$): C, 63.13; H, 5.31; N, 31.56. Found: C, 62.88; H, 5.42; N, 31 86. ^{1}H-Nmr (DMSO-d_6): 2.58 (s, Me), 7.42 (dd, $J_{6,7}$ = 5 6, $J_{4,7}$ = 1.0, H_7), 8.30 (d, $J_{6,7}$ = 5.6, H_6), 9.05 (d, $J_{4,7}$ = 1.0, H_4), 12.9 (exch. br s, NH). Ir: 3300-2500 (NH). The same compound (ir and ^{1}H-nmr spectra) was obtained (80 % yield) by catalytic hydrogenation of chloropyrazolopyridine **10**, operating as above.

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Received, 22th March, 1988