20. Photochemical Rearrangement of *N*-Substituted 2-Methyl-5-nitro-1*H*-imidazoles in the Presence of Water

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The photochemical behaviour of 2-methyl-5-nitro-1*H*-imidazoles **1** in water-containing solutions has been studied. In a first reaction step, the photorearrangement of **1** yields 2-methyl-2-imidazoline-4,5-dione-4-oximes **2**. Hydrolysis of **2** and subsequent elimination of water from a supposed intermediate **5** leads to 5-methyl-1,2,4-oxadiazole-3-carboxamides **4**. The basic structure of **4** was determined by X-ray analysis of the derivative **4e**. Further irradiation destroys the products **4** in part by light-induced hydrolysis.

1. Introduction. – Several 2-methyl-5-nitro-1*H*-imidazoles **1** exhibit anti-amebic and antiprotozoal activities. They are listed in the *Table* together with their generic names. Originally colourless aqueous solutions of **1a** became slightly yellow, when they were exposed to daylight. This observation led us to study the photochemical behaviour of **1a** and of the related compounds **1b–f** (see the *Table*).

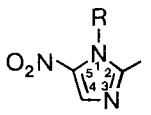

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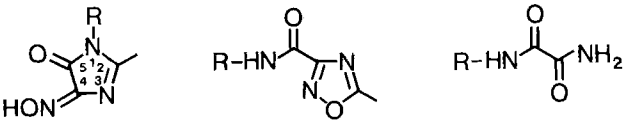
Table. *Compounds of Which the Photochemical Behaviour Has Been Studied*

Substrate	R	Generic Name	Preparation, Therapeutic Activities
1a	$ClCH_2CH(OH)CH_2$	Ornidazole	[1]
1b	$CH_3CH(OH)CH_2$	Secnidazole	[2]
1c	$CH_3CH(OAc)CH_2$	–	–
1d	$HOCH_2CH_2$	Metronidazole	[2]
1e	CH_3	Dimetridazole	[2] [3]
1f	H	–	[2]

2. Results. – Because **1a–f** are sparingly soluble in H_2O, we performed the irradiation experiments using a mixture of H_2O/1,4-dioxane 9:1. By irradiation with daylight, *ca.* 40% **1a** was consumed within 6 weeks. Light of a 150-W high-pressure Hg lamp accelerated the photoreaction considerably without changing the product distribution. In contrast to **1a–e**, compound **1f** (R=H) did not react photochemically. During the photoreactions of **1a–e**, the appearance of an intermediate could be detected by TLC. For trapping such intermediates, we used as solvent Et_2O with a H_2O content of 0.3–0.4%.



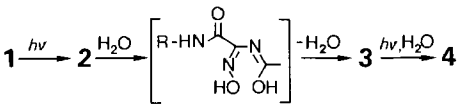
2 **3** **4**

Nevertheless, we only succeeded in isolating the very labile intermediates **2a** and **2e**. From their spectroscopic data, the carbonyl and hydroximino groups could not be assigned reliably. Therefore, structure **2** was proposed in analogy to the examples given below. The intermediates **2** react with H_2O yielding 1,2,4-oxadiazoles **3**, which are the main products of the light-induced reactions of **1a–e**. The general structure **3** was deduced from an X-ray analysis of **3e** (see *Exper. Part*).

The light absorption of **3** formed in the course of the reaction competes with the light absorption of **1** and causes a hydrolysis of **3** to give **4**. This assumption explains the relatively low yields (30–40%) of **3** and is supported by the isolation of **4e** from the reaction mixture of irradiated **3e**.

3. Discussion. – The transformation of **1** into **2** proceeds according to the general pattern of the photochemical rearrangement of nitro-olefins. The best known examples are: formation of 1-(phenylhydroximino)propan-2-one from β-methyl-β-nitrostyrene [4], the formation of 3-hydroximino-2-oxo-2,3-dihydrofuran from 2-nitrofuran [5], and the formation of 3-hydroximino-2-oxo-2,3-dihydropyrrole from 2-nitropyrrole [5]. The mechanism of this type of photoreaction involves in **1** initial rearrangement of the

Scheme



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5-nitro group to the nitrite followed by N–O bond cleavage and radical recombination at the 4-position yielding the 4,5-dione-4-oxime **2**. Subsequent hydrolysis opens the N(1)–C(2) bond of **2** enabling a rotation which brings the two OH groups in a position (see **5**) from which the 1,2,4-oxadiazole **3** can be formed by elimination of water. Light induced hydrolysis of **3** finally yields **4** *(Scheme)*.

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Experimental Part

1. *General.* M.p. (uncorrected): *Büchi SMP 20.* IR (cm^{-1}) in KBr: *Nicolet FT/IR 7199.* ^{1}H-NMR: *Bruker-Spectrospin HX-270* (270 MHz) and *WM250* (250 MHz), *Varian A 60 D* (60 MHz); δ in ppm and J in Hz. MS: *MS 9* from *AEI*, Manchester, updated with *ZAB* console and data system *3000*, *m/z* (rel. %). CI-MS: *VG 7070-DS-2050.*

2. *General Procedure.* Irradiation with a high-pressure Hg lamp (*TQ 150, Heraeus*, Hanau, FRG). *Method I:* Preparation of compounds **4** by irradiation of **1** dissolved in H_2O/1,4-dioxane 9:1 (250 ml). Workup: evaporation

of the solvent at 40° (*Rotavap*). *Lobar* chromatography, CH_2Cl_2/2-propanone 2:1 resp. 1:1 followed by crystallization. *Method 2:* Preparation of the intermediates **2** by irradiation of **1** dissolved in 250–360 ml Et_2O containing H_2O (0.3–0.4%). In both methods, the irradiations were performed under Ar, though similar but not quite the same results could be obtained under air. **Workup**: crystallization from the irradiated soln. which before was concentrated and dried ($MgSO_4$).

3. *5-Methyl-1,2,4-oxadiazole-3-carboxamides* **3**. N-*(3-Chloro-2-hydroxypropyl)-5-methyl-1,2,4-oxadiazole-3-carboxamide* (**4a**). *Method 1:* Irradiation of 2 g (9 mmol) of **1a** for 14 h. Crystallization from EtOH/hexane gave 0.73 g (36.5%) of crude product. Recrystallization from 2-propanone/petroleum ether 1:1 yielded 0.64 g (32%) of pure **3a**. M.p. 75.8. IR: 3330*m*, 3280*s*, 1673*s*, 1575*s*. ^{1}H-NMR ((D$_6$)DMSO, 270 MHz): 2,67 (*s*, CH_3); ~3.30, ~3.40 (2*dt*, J_{gem} = 13.5, J_{vic} = 6–7, *J*(C*H*, NH) ≈ 6, CH_2NH); 3.52, 3.63 (2*dd*, J_{gem} = 11.4, J_{vic} = 6 resp. 4.5, CH_2Cl); 3.88 (*m*, C*H*(OH)); 5.43 (*d*, *J* = 5, OH); 8.84 (*t*, *J* = 6, NH). MS: 176 (6, 1 Cl); 170 (5); 140 (30); 111 (11); 86 (15); 70 (12); 56 (26); 43 (100). CI-MS (NH_3): 237 (38, 1 Cl, [*M* + NH_4]$^+$), 220 (70, 1 Cl, [*M* + H]$^+$), 201 (15), 184 (100). Anal. calc. for $C_7H_{10}ClN_3O_3$ (219.63): C 45.40, H 5.99, N 22.69; found: C 45.46, H 5.98, N 23.13.

N-*(2-Hydroxypropyl)-5-methyl-1,2,4-oxadiazole-3-carboxamide* (**3b**). *Method 1:* A soln. of 2 g (10.8 mmol) of **1b** was irradiated for 26 h. Crystallization from 2-propanone/petroleum ether 1:1 at −70° yielded 0.62 g (31%) of **3b**. M.p. 85.5°. IR: 3420*m*, 3316*s*, 1668*s*, 1564*s*, 1142*s*. ^{1}H-NMR ((D$_6$)DMSO, 250 MHz): 1.05 (*d*, *J* = 6.3, CH_3–CH); 2.66 (*s*, CH_3–C(5)); 3.19 (*dt*, *J* = 6.6, 5.9, CH_2NH); 3.78 (*m*, C*H*(OH)); 4.80 (*d*, *J* = 4.9, OH); 8.72 (*t*, *J* ≈ 6, NH). MS: 186 (2, [*M* + H]$^+$), 141 (5), 111 (8), 99 (8), 86 (32), 85 (22), 70 (12), 56 (14), 43 (100), 30 (18). Anal. calc. for $C_7H_{11}N_3O_3$ (185.18): C 45.40, H 5.99, N 22.69; found: C 45.46, H 5.98, N 23.13.

1-[(5-Methyl-1,2,4-oxadiazol-3-ylcarbonylamino)methyl]ethyl Acetate (**3c**). Preparation of **1c** by acetylation of **1b** with Ac_2O/pyridine in the presence of 4-(dimethylamino)pyridine as catalyst. *Method 1:* A soln. of 2 g (8.8 mmol) of **1c** was irradiated for 22 h: colourless oil. B.p. 130°/0.1 Torr. Yield: 0.61 g (30.5%). IR: 3332*m*, 1737*s*, 1582*m*, 1541*s*, 1493*m*, 1245*s*. ^{1}H-NMR ((D$_6$)DMSO, 250 MHz): 1.16 (*d*, *J* = 6.4, CH_3–CH); 1.96 (*s*, CH_3–CO); 2.66 (*s*, CH_3–C(5)); 3.38 (*m*, CH_2NH); 4.97 (*m*, CH_3C*H*); 9.07 (*t*, *J* ≈ 6, NH). MS: 228 (9, [*M* + H]$^+$), 183 (6), 168 (7), 141 (47), 140 (9), 111 (11), 99 (12), 86 (45), 85 (27), 83 (11), 71 (6), 70 (17), 58 (11), 56 (32), 44 (9), 43 (100), 41 (14), 30 (21). Anal. calc. for $C_9H_{13}N_3O_4$ (227.22): C 47.57, H 5.77, N 18.49; found: C 47.64, H 5.87, N 18.36.

N-*(2-Hydroxyethyl)-5-methyl-1,2,4-oxadiazole-3-carboxamide* (**3d**). *Method 1:* A soln. of 2 g (11.6 mmol) of **1d** was irradiated for 18 h: colourless oil. Remaining traces of solvent were removed at r.t. *in vacuo* (10^{-3} Torr). Yield: 0.6 g (30%). IR: 3357*s*, 1680*s*, 1581*m*, 1559*m*, 1060*m*. ^{1}H-NMR ((D$_6$)DMSO, 250 MHz): 2.66 (*s*, CH_3–C(5)); 3.32, 3.50 (2*dt*, *J* = 6, 6.4, CH_2CH_2); 4.77 (*t*, *J* = 5.6, OH); 8.78 (*t*, *J* = 6.5, NH). MS: 172 (3, [*M* + H]$^+$), 140 (33), 111 (27), 86 (17), 70 (28), 56 (30), 43 (100), 40 (13). Anal. calc. for $C_6H_9N_3O_3$ (171.16): C 42.11, H 5.30, N 24.55; found: C 42.20, H 5.42, N 24.44.

N,*5-Dimethyl-1,2,4-oxadiazole-3-carboxamide* (**3e**). *Method 1:* A soln. of 1 g (7 mmol) of **1e** was irradiated for 12 h. Crystallization from 2-propanone/petroleum ether. Yield: 0.31 g (31%) of **3e**. M.p. 110.8°. IR: 3339*s*, 1681*s*, 1585*s*, 1555*s*. ^{1}H-NMR ($CDCl_3$, 60 MHz): 2.67 (*s*, CH_3–C(5)); 3.07 (*d*, *J* = 5, CH_3–NH); 7.03 (~*s*, NH). MS: 141 (2, M^+), 85 (14), 70 (12), 56 (10), 43 (100), 42 (18), 30 (19). Anal. calc. for $C_5H_7N_3O_2$ (141.13): C 42.55, H 5.00, N 29.77; found: C 42.63, H 5.00, N 29.58. *X-Ray Analysis of* **3e** (*Fig.*). *Crystal Data*[1]): Monoclinic $P2_1/a$; *a* = 7.832(3), *b* = 21.186(6); *c* = 8.051(3) Å, *β* = 106.19(3)°; *Z* = 8; *R* = 0.0457.

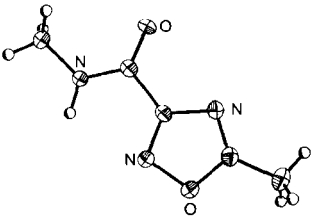

Figure. *Representation of* **3e** *with thermal ellipsoids*

[1]) The refinement has been performed using the SHELXTL package of the *R3m* system. Coordinates and thermal parameters have been deposited at the *Cambridge Crystallographic Data Centre*.

4. *Reaction Intermediates: 2-Methyl-5-oxo-2-imidazolin-4-one Oximes* **2**. *1-(3-Chloro-2-hydroxypropyl)-2-methyl-5-oxo-2-imidazoline-4-one Oxime* (**2a**). *Method 2:* Irradiation of 2 g (9 mmol) of **1a** for 10 h. Crystallization at −18° yielded 30 mg of **2a**, which, in contact with humid air, was slowly converted into **3a**. IR: 3433*s*, 1746*s*, 1642*s*, 991*m*, 941*m*. ^{1}H-NMR ($CDCl_3$, 270 MHz): 2.33 (*s*, CH_3–C(2)); 3.47–3.72 (4*dd*, detected in a spectrum with 10 Hz/cm, but not sufficiently separated to give *J*, CH_2CH_2); 3.87 (*m*, C*H*OH); 5.67 (*d*, *J* = 5.3, OH); 12.53 (*s*, NOH). MS: 219 (80, $M^{+\cdot}$), 184 (14), 170 (13), 134 (39), 128 (20), 99 (21), 96 (18), 83 (34), 71 (48), 67 (72), 57 (44), 56 (43), 55 (39), 44 (22), 43 (61), 42 (100), 41 (22), 29 (44).

1,2-Dimethyl-5-oxo-2-imidazoline-4-one Oxime (**2e**). *Method 2:* Irradiation of 0.5 g (3.5 mmol) of **1e** for 7 h. Three charges were combined and gave at −18° after 5 days 9 mg of crystalline **2e**, which, in contact with humid air, slowly converted into **3e**. IR: 3430*s*, 1748*s*, 1724*s*, 1646*s*, 993*m*, 979*m*. ^{1}H-NMR ($CDCl_3$, 250 MHz): 2.30 (*s*, CH_3–C(2)); 3.04 (*s*, CH_3N); 12.50 (*s*, NOH). MS: 141 (89, $M^{+\cdot}$), 111 (29), 83 (5), 69 (5), 67 (18), 57 (11), 56 (100), 43 (10), 30 (5).

5. *Light-Induced Hydrolysis. Methyloxamide* **4e**. Analogous to *Method 1:* Irradiation of 2 g (14 mmol) of **3e** for 30 h. Recovered: 0.9 g (45%) of **3e**. The relevant fractions were combined and concentrated. Isolation of **4e** was continued using repeated PLC. CH_2Cl_2/MeOH 8:2, crystallization from MeOH. After this difficult purification procedure, only 8 mg of **4e** remained, though TLC of the mixture showed that it was the main product. In the dark no hydrolysis of **3e** was observed. IR: 3388*s*, 3327*s*, 1652*s*, 1602*w*, 1556*m*. ^{1}H-NMR ((D_6)DMSO, 270 MHz): 2.65 (*d*, *J* = 5, C*H*$_3$NH); 7.74, 8.03 (2 br. *s*, NH_2); 8.67 (br. ~ *d*, CH_3N*H*). MS: 102 (51, $M^{+\cdot}$), 59 (51), 58 (100), 44 (62), 30 (17). Exact mass 102.09 (calc. for $C_3H_6N_2O_2$).

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