International Journal of Pharmaceutics, 49 (1989) 83–89
Elsevier

IJP 01647

Photochemical decomposition of midazolam. I. Isolation and identification of products

Riitta Selkämaa and Seija Tammilehto

Division of Pharmaceutical Chemistry, School of Pharmacy, University of Helsinki, Helsinki (Finland)

(Received 27 May 1988)
(Accepted 20 June 1988)

Key words: Midazolam [8-chloro-6-(2′-fluorophenyl)-1-methyl-4H-imidazo[1,5-a][1,4]-benzodiazepine]; Benzodiazepine; *N*-Desalkylflurazepam; 4-Phenylquinazoline; Benzophenone; Photochemical decomposition

Summary

Midazolam, 8-chloro-6-(2′-fluorophenyl)-1-methyl-4H-imidazo[1,5-a][1,4]-benzodiazepine (Dormicum), is easily decomposed photochemically in ethanolic solutions. TLC experiments revealed several degradation products after exposure to a high-pressure mercury lamp or to daylight. The 3 main decomposition products were isolated by flash chromatography and identified as 6-chloro-2-methyl-4-(2′-fluorophenyl)-quinazoline, *N*-desalkylflurazepam and 7-chloro-2-[(1-ethoxyethylimino)ethoxymethyl]-5-(2′-fluorophenyl)-3H-1,4-benzodiazepine. Several minor decomposition products were identified by GC-MS.

Introduction

Midazolam, an imidazobenzodiazepine, is used as a hypnotic in tablet form and in parenteral solutions. Very little information is available on the stability of the drug. In acid hydrolysis the azomethine bond is cleaved and the corresponding benzophenone is formed (Bhattacharrya and Grant, 1982; Schütz, 1985). The equilibrium of the reaction is affected by the pH of the solution with the open ring benzophenone predominating in more acidic milieu. Thermostability of the drug has not been reported, but our preliminary experiments showed midazolam to be thermostable in ethanolic solutions. Photochemical decomposition, by contrast, was found to occur readily; the drug was totally degraded after exposure to radiation from a high-pressure mercury lamp for about 5 h and after exposure to ordinary daylight for 3 months.

One source of the phototoxicity claimed for some benzodiazepines (Magnus, 1976) may be the photodegradation products. The few existing studies on the photochemical degradation of benzodiazepines have reported on chlordiazepoxide (Cornelissen et al., 1979; Field and Sternbach, 1968; Sternbach et al., 1962), diazepam (Cornelissen et al., 1978), flunitrazepam (Givens et al., 1986) and nitrazepam (Adomeit, 1970; Roth and Adomeit, 1969, 1973). The aim of the present study was to isolate the main photochemical decomposition products of midazolam and elucidate

Correspondence: R. Selkämaa, Division of Pharmaceutical Chemistry, School of Pharmacy, University of Helsinki, SF-00170 Helsinki, Finland.

their structures, and to use GC-MS in identifying some of the minor photodegradation products.

Experimental

Materials

Midazolam was kindly supplied by Hoffmann-La Roche (Basle, Switzerland). The identity and purity of the substance were verified by TLC and GC and by UV, IR, ^{1}H-NMR and ^{13}C-NMR spectra. Reference substances, *N*-desalkylflurazepam and 2-amino-5-chloro-2′-fluoro-benzophenone were also obtained from Hoffmann-La Roche and used as such. All other reagents and solvents were of analytical grade.

Apparatus

The radiation source was a high-pressure mercury lamp, Original Hanau TQ 150. Elemental analyses were performed by the Ilse Beetz Micro-analytical Laboratory (Kronach, F.R.G.). The melting points were determined with an Electro-thermal digital melting point apparatus and are uncorrected. The UV spectra were recorded in ethanol with a Philips PU 8700 series UV/vis spectrophotometer and the IR spectra were obtained with a Unicam SP 1000 infrared spectrometer (KBr-disc). ^{1}H-NMR and ^{13}C-NMR spectra were run on a Jeol JNM-FX 200 FT spectrometer using tetramethylsilane as internal standard. GC-MS spectra were recorded with a quadrupole mass spectrometer (HP 5970A) coupled to an HP 5890 gas chromatograph (ion source 70 eV). The analyses were carried out on a silica capillary column (SE-54) using the temperature program 159–275 °C/8 °C · min^{-1}, temperature of the injector 250 °C and temperature of the detector 300 °C. TLC experiments were carried out on precoated 0.25 mm silica gel 60 F_{254} aluminium plates with spots detected under UV light (254 nm). Solvent systems are listed in Table 1. The purity of the isolated decomposition products was also checked by silica capillary gas chromatography, performed on a Carlo Erba Fractovap 4200 instrument equipped with FID and a Merck Hitachi D-2000 Chromato-Integrator. The temperature program was the same as in the GC-MS analyses.

Photodegradation of midazolam

Midazolam was dissolved in ethanol (0.5%) and 10-ml aliquots of the solution were charged into clear glass ampoules. The ampoules were exposed to a high-pressure mercury lamp or to daylight on a windowsill.

Isolation of the main decomposition products

Flash chromatography technique (Still et al., 1978) was used in the isolation of the decomposition products **II**, **III** and **IV**. The irradiated ethanolic solution (10 ml) was evaporated to dryness under reduced pressure and the residue was dissolved in the eluent and transferred to a silica gel column (Sorbsil C-60, length 24 cm, diameter 2 cm). The column was first eluted with 50 ml of toluene : 2-propanol (9 : 1) and then with 150 ml of toluene : 2-propanol (7 : 3). The first 60 ml of eluate was discarded, after which 5-ml aliquots were

TABLE 1

R_f values in different solvent systems (length of run 15 cm)

Solvent system	Compound					Reference substance	
	I	II	III	IV	VI	Desalkyl-flurazepam	2-Amino-5-chloro-2′-fluoro-benzophenone
Toluene : 2-propanol (7 : 3)	0.22	0.55	0.48	0.30	0.60	0.49	0.60
Chloroform : acetone (9 : 1)	0.05	0.47	0.16	0.07	0.62	0.16	0.62
Ethyl acetate : methanol : diethylamine (9 : 0.5 : 0.5)	0.38	0.62	0.45	0.48	0.54	0.45	0.54

collected and analyzed by TLC. Compound **II** was found in fractions 2–5, compound **III** in fractions 6–12 and compound **IV** in fractions 16–25. Compounds **II** and **III** were further purified by the same technique using toluene : 2-propanol (9 : 1) as eluent, and compound **IV** was further purified with toluene : 2-propanol (7 : 3). The purity of the samples was checked by TLC and GC.

GC-MS analysis

GC-MS was used to identify 3 minor degradation products in the irradiated ethanolic solution of midazolam. The samples for the analysis were prepared by evaporating the irradiated solution to dryness with nitrogen stream and dissolving the residue in chloroform.

Isolated photodecomposition products

Compound II. 6-Chloro-2-methyl-4-(2′-fluorophenyl)-quinazoline, white to yellowish crystals from ethanol-water. Mol. wt. 272.7, m.p. 129 °C. Found C 65.80, H 4.01, Cl 12.77, N 10.06. Calc. for $C_{15}H_{10}ClFN_2$: C 66.06, H 3.70, Cl 13.00, N 10.27. R_f values in different solvent systems are listed in Table 1. $UV_{\lambda_{max}}$ ($\log\epsilon$): 206 (4.81), 230 (4.65), 326 (3.67) nm. $IR_{\nu_{max}}$: 3080, 2970, 2940, 2860, 1715, 1620, 1555, 1490, 1460, 1395, 1340, 1230, 1210, 1090, 840, 825, 805, 760 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 8.00–7.24 (m, 7H, aromatic), 2.95 (s, 3H, CH_3) ppm. ^{13}C-NMR ($CDCl_3$) δ: 164.3 and 163.8 (both s, C_2 and C_4 or vice versa), 159.7 (d, $C_{2'}$, $J_{CF} = 250.6$ Hz), 149.4 (s, C_{8a}), 134.9 (d, C_7), 132.6 (s, C_6), 132.0 (dd, $C_{4'}$, $J_{CF} = 7.3$ Hz), 131.4 (dd, $C_{6'}$, $J_{CF} = 2.9$ Hz), 129.8 (d, C_8), 125.5 (d, C_5), 124.8 (dd, $C_{5'}$, $J_{CF} = 2.9$ Hz), 122.4 (s, C_{5a}), 116.3 (dd, $C_{3'}$, $J_{CF} = 20.5$ Hz), 26.5 (s, CH_3) ppm. MS m/z (% rel. int.): 274 (20, M + 2), 273 (37), 272 (62, M), 271 (83, M − 1), 237 (100, M-Cl), 151 (23), 136 (16), 111 (16), 110 (42), 75 (43).

Compound III. *N*-Desalkylflurazepam, 7-chloro-5-(2′-fluorophenyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one. White crystals from diethyl ether. Mol. wt. 288.7, m.p. 206 °C. Found C 61.53, H 4.16, Cl 12.62, N 9.01, O 6.30. Calc. for $C_{15}H_{10}ClFN_2O$: C 62.40, H 3.49, Cl 12.28, N 9.70, O 5.54, R_f values in different solvent systems are listed in Table 1. $UV_{\lambda_{max}}$ ($\log\epsilon$): 230 (4.52), 318 (3.33) nm.$IR_{\nu_{max}}$: 3200, 3120, 3095, 2970, 1705 (C = O), 1615, 1485, 1450, 1395, 1365, 1330, 1260, 1220, 1105, 1020, 955, 830, 770, 750 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 9.54 (s, 1H, NH), 7.61–7.03 (m, 7H, aromatic), 4.38 (s, 2H, CH_2) ppm. ^{13}C-NMR ($CDCl_3$) δ: 171.2 (s, C_2), 166.6 (s, C_5), 160.4 (d, $C_{2'}$, $J_{CF} = 252.0$ Hz), 136.2 (s, C_{9a}), 132.3 (dd, $C_{4'}$, $J_{CF} = 8.8$ Hz), 132.0 (d, C_8), 131.4 (s, C_7), 129.4 (d, C_6 and $C_{6'}$), 129.3 (s, C_{5a}), 127.2 (d, $C_{1'}$, $J_{CF} = 11.7$ Hz), 124.4 (dd, $C_{5'}$, $J_{CF} = 2.9$ Hz), 122.6 (d, C_9), 116.3 (dd, $C_{3'}$, $J_{CF} = 22.0$ Hz), 56.7 (t, CH_2) ppm. MS m/z (% rel. int.): 290 (21, M + 2), 289 (32), 288 (68, M), 287 (69), 269 (25), 262 (35), 261 (57), 260 (95, M–CO), 259 (100, M–CHO), 225 (18), 177 (16), 170 (15), 169 (16), 163 (18), 138 (17), 112 (25), 107 (15), 102 (29), 98 (18), 75 (26), 63 (16), 51 (16).

Compound IV. 7-Chloro-2[(1-ethoxyethylimino)ethoxymethyl]-5-(2′-fluorophenyl)-3H-1,4-benzodiazepine. Almost white crystals from diethyl ether. Mol. wt. 415.9, m.p. 172 °C. Found C 63.64, H 5.74, Cl 9.01, N 9.49. Calc. for $C_{22}H_{23}ClFN_3O_2$: C 63.61, H 5.54, Cl 8.43, N 10.12. R_f values in different solvent systems are listed in Table 1. $UV_{\lambda_{max}}$ ($\log\epsilon$): 211 (4.58) nm. $IR_{\nu_{max}}$: 3090, 2990, 2940, 2880, 1640, 1610, 1490, 1460, 1400, 1360, 1315, 1255, 1215, 1150, 1125, 1085, 1060, 1030, 1010, 885, 825, 780, 765 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 7.75–6.93 (m, 7H, aromatic), 5.18 (s, 1H, CH), 4.59 (d, 1H in 7-ring CH_2, J = 11.2 Hz), 4.07–3.71 (m, 2H, $CHOCH_2CH_3$), 3.46–3.62 (m, 2H, OCH_2), 3.29 (d, 1H in 7-ring CH_2, J = 11.2 Hz), 1.84 (s, CH_3), 1.30 (t, 3H, CH_3 in OCH_2CH_3, J = 7.3 Hz), 1.22 (t, 3H, CH_3 in OCH_2CH_3, J = 7.3 Hz) ppm. ^{13}C-NMR ($CDCl_3$) δ: 165.0 (s, C_5), 161.8 (s, C_2), 160.6 (d, $C_{2'}$, $J_{CF} = 250.5$ Hz), 137.8 (s, C aromatic), 135.6 (s, C aromatic), 134.5 (s, C aromatic), 132.0 (dd. $C_{4'}$, $J_{CF} = 8.8$ Hz), 131.6 (d, C aromatic), 131.4 (d, C aromatic), 131.1 (d, C aromatic), 129.0 (d, C_9), 127.5 (d, $C_{1'}$, $J_{CF} = 13.2$ Hz), 124.3 (dd, $C_{5'}$, $J_{CF} = 2.9$ Hz), 115.9 (dd, $C_{3'}$, $J_{CF} = 22.0$ Hz), 111.5 (s, C), 98.9 (d, CH), 65.5 (t, CH_2), 58.1 (t, CH_2), 54.1 (dd, CH_2 in 7-ring), 15.7 (q, CH_3), 15.1 (q, 2 × CH_3 in OCH_2CH_3) ppm. MS m/z (% rel. int.): 415 (2, M), 386 (7), 370 (6), 340 (5), 317 (8), 285 (5), 273 (11), 259 (6), 140 (7), 109 (10), 99 (46), 86 (6), 70 (20).

Decomposition products identified by GC-MS

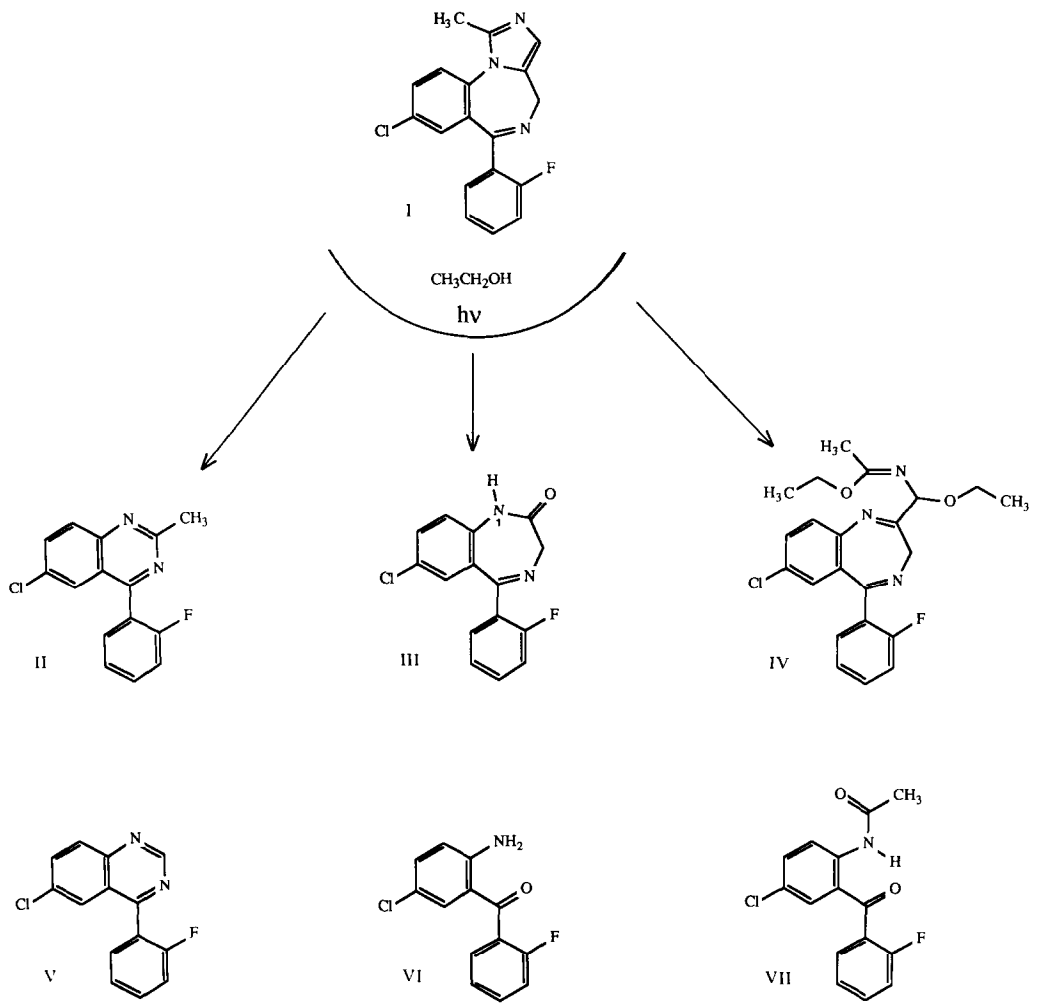
Compound V. 6-Chloro-4-(2′-fluorophenyl)-quinazoline. MS m/z (% rel. int.): 260 (26, M + 2), 259 (38), 258 (70, M), 257 (100), 223 (100), 195 (16), 136 (16), 111 (17), 110 (40), 100 (16), 75 (45), 74 (18).

Compound VI. 2-Amino-5-chloro-2′-fluorobenzophenone. R_f values in different solvent systems are listed in Table 1. MS m/z (% rel. int.): 251 (31, M + 2), 250 (41), 249 (100, M), 248 (91), 232 (24), 230 (27), 154 (44), 126 (38), 123 (69), 99 (26), 95 (52), 75 (28), 63 (24).

Compound VII. 2-Acetamido-5-chloro-2′-fluorobenzophenone. MS m/z (% rel. int.): 291 (23, M), 251 (27), 250 (30), 249 (81), 248 (74), 230 (26), 229 (20), 154 (22), 126 (17), 123 (39), 95 (30), 43 (100).

Results and Discussion

The photodegradation of midazolam was studied in 0.5% ethanolic solutions (Scheme 1). Several decomposition products were detected on TLC plates, 3 of them present in major quantities analyzed by GC. Total degradation of the parent compound was achieved in about 5 h on exposure to a high-pressure mercury lamp (Fig. 1) and in 3 months on exposure to ordinary daylight.



Scheme 1. Photochemical decomposition of midazolam.

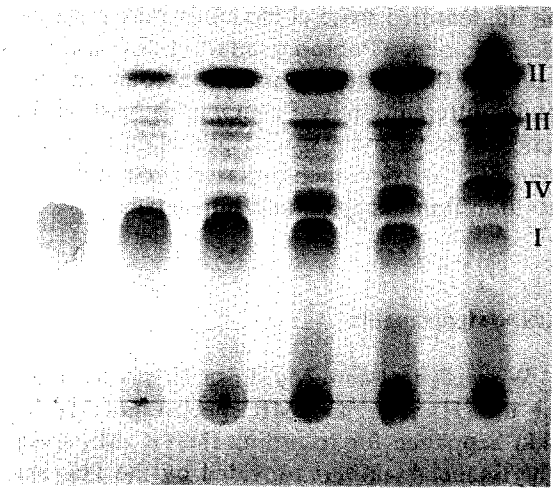


Fig. 1. Photodegradation of midazolam. TLC studies after 0, 1, 2, 3, 4 and 5 h exposure to a high-pressure mercury lamp (length of run 7 cm).

The midazolam solutions were irradiated in clear glass ampoules to allow only wavelengths above 300 nm to pass through the samples. Oxygen was not removed from the ampoules before irradiation. To study the effect of the radiation source the samples were exposed both to a high-pressure mercury lamp and to ordinary daylight. The same degradation products were observed in both cases, in agreement with the observation of Cornelissen et al. (1978, 1979) that the wavelength does not determine the character of the products but only the amount formed. The identity of the 3 main products was confirmed by IR spectra of the isolated compounds.

The main degradation products were isolated by flash chromatography (Still et al., 1978), a method that was simple, inexpensive and fast.

The IR spectrum of compound **II** showed aromatic and aliphatic structure elements. The ^{1}H-NMR spectrum revealed only 7 aromatic and 3 aliphatic protons (CH_3). ^{13}C-NMR confirmed the presence of only 14 aromatic and one aliphatic carbon. The typical values of the coupling constants between fluorine and carbon atoms were observed, as earlier for fludiazepam (Kuwayama and Yashiro, 1985) and flunitrazepam (Haran and Tuchagues, 1980; Finner et al., 1984). The mass spectrum showed the molecular ion peak at 272 m/z and a M + 2 peak at 274 m/z, confirming the presence of one chlorine atom. The even number of the molecular ion proved the compound to have an even number of nitrogen atoms. The spectral data indicated the loss of the imidazole moiety and contraction of the 7-ring to a 6-ring. Further evidence that the degradation product was 6-chloro-2-methyl-4-(2′-fluorophenyl)-quinazoline was obtained by comparing its mass spectrum with that of 6-chloro-2-methyl-4-phenylquinazoline (Maurer and Pfleger, 1987). The two spectra showed almost identical mass fragmentation, the photodegradation product only differing by carrying a fluorine atom.

The IR spectrum of compound **III** showed a very strong C = O absorption a little above 1700 cm^{-1} and a NH absorption at 3200 cm^{-1}. In the mass spectrum the molecular ion at 288 m/z corresponded to the formula $C_{15}H_{10}ClFN_2O$. The ^{13}C-NMR spectrum showed a carbonyl carbon at 171.2 ppm, 13 carbon atoms in the aromatic region and an aliphatic CH_2. The ^{1}H-NMR spectrum gave further evidence of a NH proton (9.54 ppm, the signal disappeared on addition of D_2O) and of a CH_2 group with equivalent protons. Evidently the imidazole ring of midazolam had disappeared and an oxygen atom was attached to C-2, indicative that the degradation product was *N*-desalkylflurazepam. Comparison with an authentic sample of desalkylflurazepam by TLC and GC confirmed the identification. The R_f values of the two samples were identical in all 3 solvent systems studied (Table 1), and the GC retention time of the isolated compound was exactly the same as that of pure desalkylflurazepam (7.59 min).

An increase in molecular weight of 90 mass units in compound **IV** indicated the addition of two ethoxy groups to the parent molecule. Alcohols have been reported to be active solvents in photochemical reactions (Moore, 1987). Since hydroxylation of the imidazole ring is possible (Hofmann, 1953) and since the addition of a solvent molecule to an unsaturated carbon atom can cause allylic rearrangement (Sykes, 1975), it seemed clear that the ethoxy groups were attached to the imidazole ring and the bond between C-1 and the 7-ring N was broken. All spectral data and the

results of the elemental analysis pointed to the identification of **IV** as 7-chloro-2-[(1-ethoxyethylimino)ethoxymethyl]-5-(2′-fluorophenyl)-3H-1,4-benzodiazepine. The very low relative intensities in the mass spectrum suggested the molecule to be branched. The IR absorption in the aliphatic area was more pronounced than in the spectrum of midazolam and the etheral band was seen around 1080 cm^{-1}. The ^{1}H-NMR spectrum revealed, in addition to the protons of the benzodiazepine skeleton, a methine-proton at 5.18 ppm and the protons of 2 methylene and 3 methyl groups. These structural assignments were supported by the ^{13}C-NMR spectrum. The protons of one of the CH_2 groups formed a very complex multiplet in ^{1}H-NMR, due to coupling with the proton of an asymmetric C atom adjacent to the group (Günther, 1983). The other OCH_2 signal showed a splitting pattern similar to what one would expect with an adjacent CH_3 group.

The minor photodegradation products of the irradiated midazolam solution were identified by GC-MS and through reference to the literature: compound **V** as 6-chloro-4-(2′-fluorophenyl)-quinazoline (Maurer and Pfleger, 1987) (an analogue without fluorine), compound **VI** as 2-amino-5-chloro-2′-fluorobenzophenone (Schütz, 1982) and compound **VII** as 2-acetamido-5-chloro-2′-fluorobenzophenone (Maurer and Pfleger, 1987). Final proof of the identity of compound **VI** was obtained by comparing its R_f values in 3 solvent systems with those of an authentic sample of 2-amino-5-chloro-2′-fluorobenzophenone (Table 1). Also co-injection in GC confirmed these compounds to be identical.

Comparison with the photochemical degradation of other benzodiazepines showed a degree of resemblance between the decomposition of midazolam and diazepam. Benzophenones, 4-phenylquinazolinones, 4-phenylquinazolines and glycine were formed in the decomposition of diazepam (Cornelissen et al., 1978), whereas the most obvious products in the decomposition of midazolam were phenylquinazolines, desalkylflurazepam, a solvent addition product and benzophenones. In contrast to the decomposition of diazepam (Cornelissen et al., 1978) dechlorinated degradation products were not observed though some of the unidentified trace compounds may have been dechlorinated. Photodegradation of chlordiazepoxide, flunitrazepam and nitrazepam produces totally different kinds of compounds because these materials have some special photolabile structure elements: *N*-oxide in chlordiazepoxide and a nitro group in flunitrazepam and nitrazepam.

Acknowledgements

We wish to thank Ms. Liisa Heino for recording the ^{1}H- and ^{13}C-NMR spectra and Ms. Tuulikki Seppänen for recording the GC-MS spectra. The financial support provided by the Pharmacal Research Foundation, Finland, is gratefully acknowledged.

References

Adomeit, M., *Zur Photochemie des Nitrazepams und nitroaromatischer Modelle*, Dissertation, Bonn, 1970, 87 pp.

Bhattacharrya, P. and Grant, A., Simultaneous determinations of a monofluorinated imidazo[1,5-a][1,4]benzodiazepine and the corresponding benzophenone as a function of pH and in aqueous formulations by fluorine-19 nuclear magnetic resonance spectrometry. *Anal. Chim. Acta*, 142 (1982) 249–257.

Cornelissen, P.J.G., Beijersbergen van Henegouwen, G.M.J. and Gerritsma, K.W., Photochemical decomposition of 1,4-benzodiazepines. Diazepam. *Int. J. Pharm.*, 1 (1978) 173–181.

Cornelissen, P.J.G., Beijersbergen van Henegouwen, G.M.J. and Gerritsma, K.W., Photochemical decomposition of 1,4-benzodiazepines. Chlordiazepoxide. *Int. J. Pharm.*, 3 (1979) 205–220.

Field, G.F. and Sternbach, L.H., Quinazolines and 1.4-benzodiazepines. XLII. Photochemistry of some *N*-oxides. *J. Org. Chem.*, 33 (1968) 4438–4440.

Finner, E., Zeugner, H. and Milkowski, W., Conformational equilibria in flunitrazepam due to sp^2–sp^2 carbon–carbon single bond rotational isomerism. *Arch. Pharm.*, 317 (1984) 1050–1053.

Givens, R.S., Gingrich, J. and Mecklenburg, S., Photochemistry of flunitrazepam: a product and model study. *Int. J. Pharm.*, 29 (1986) 67–72.

Günther, H., *NMR-Spektroskopie. Eine Einführung in die Protonenresonanz-Spektroskopie und ihre Anwendungen in der Chemie*. Thieme, Stuttgart, 1983, p. 191.

Haran, R. and Tuchagues, J.P., Carbon-13 and proton NMR studies of 1,4-benzodiazepines. *J. Heterocycl. Chem.*, 17 (1980) 1483–1488.

Hofmann, K., *The Chemistry of Heterocyclic Compounds. Imidazole and its Derivatives. Part I*, Interscience, New York, 1953, p. 288.

Kuwayama, T. and Yashiro, T., The behavior of 1,4-benzodiazepine drugs in acidic media. IV. Proton and carbon-13 nuclear magnetic resonance spectra of diazepam and fludiazepam in acidic aqueous solution. *Chem. Pharm. Bull.*, 33 (1985) 5503–5510.

Magnus, I.A., *Dermatological Photobiology*, Blackwell, London, 1976.

Maurer, H. and Pfleger, K., Identification and differentiation of benzodiazepines and their metabolites in urine by computerized gas chromatography-mass spectrometry. *J. Chromatogr.*, 422 (1987) 85–101.

Moore, D., Principles and practice of drug photodegradation studies. *J. Pharm. Biomed. Anal.*, 5 (1987) 441–453.

Roth, H.J. and Adomeit, M., Photochemische Reduktion des 7-Nitro-5-phenyl-2,3-dihydro-1H-1,4-benzodiazepin-2-on und der drei isomeren -Acetyl-nitraniline. *Tetrahedron Lett.*, 37 (1969) 3201–3204.

Roth, H.J. and Adomeit, M., Photochemie des Nitrazepams. *Arch. Pharm.*, 306 (1973) 889–897.

Schütz, H., *Benzodiazepines*, Springer, Heidelberg, 1982, pp. 55 and 107.

Schütz, H., Analytische Daten des neuen Benzodiazepinderivates Midazolam (Dormicum) und seiner Metaboliten. *Z. Rechtsmed.*, 94 (1985) 197–205.

Sternbach, L.H., Koechlin, B.A. and Reeder, E., Quinazolines and 1,4-benzodiazepines (VIII). The photoisomerization of 7-chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine 4-oxide. *J. Org. Chem.*, 27 (1962) 4671–4672.

Still, W.C., Kahn, M. and Mitra, A., Rapid chromatographic technique for preparative separations with moderate resolution. *J. Org. Chem.*, 43 (1978) 2923–2925.

Sykes, P., *A Guidebook to Mechanism in Organic Chemistry*. Clay, Bungay, 1975, p. 109.