Formation of α-(Acylamino)butyramide Oximes from 5-Substituted 3-(1-Aminopropyl)-1,2,4-oxadiazoles: An Astonishing Hydrolytic Transformation

Erzsébet M. Bakó, Károly Horváth, Endre Pálosi, and Dezső Korbonits*

Chinoin Pharmaceutical and Chemical Works, Ltd.,
Budapest, P.O.B. 110, H-1325, Hungary

Received October 19, 1987

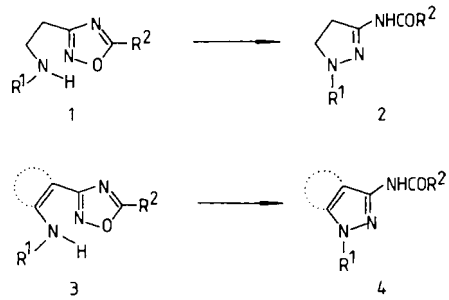
α-Aminobutyramide oxime (**6**), obtained from α-aminobutyronitrile (**5**) with hydroxylamine, reacted with esters in the presence of sodium ethoxide to furnish 5-substituted 3-(1-aminopropyl)-1,2,4-oxadiazoles **7**. α-(Acylamino)butyramide oximes **8** were formed from the compounds **7** by the action of dilute aqueous sodium hydroxide at ambient temperature. This astonishing reaction presumably proceeds by nucleophilic ring fission.

Synthese von α-(Acylamino)butyramidoximen aus 5-substituierten 3-(1-Aminopropan-1-yl)-1,2,4-oxadiazolen: Eine überraschende hydrolytische Umwandlung

Die Reaktion von α-Aminobutyramidoxim (**6**), hergestellt aus α-Aminobutyronitril (**5**) mit Hydroxylamin, mit Estern in Gegenwart von Natriumethoxid führte zu 5-substituierten 3-(1-Aminopropyl)-1,2,4-oxadiazolen **7**. Bei der Reaktion von **7** mit verdünntem wäßrigem Natriumhydroxid bei Raumtemperatur wurden überraschend α-(Acylamino)butyramidoxime (**8**) gebildet. Diese Umwandlung läuft wahrscheinlich über eine nucleophile Ringspaltung.

Earlier we reported that 3-(2-aminoethyl)-1,2,4-oxadiazoles **1** and 3-(2-aminoaryl)-1,2,4-oxadiazoles **3** isomerize spontaneously or on heating into 3-(acylamino)pyrazole derivatives **2** and **4**, respectively[1].

Scheme 1



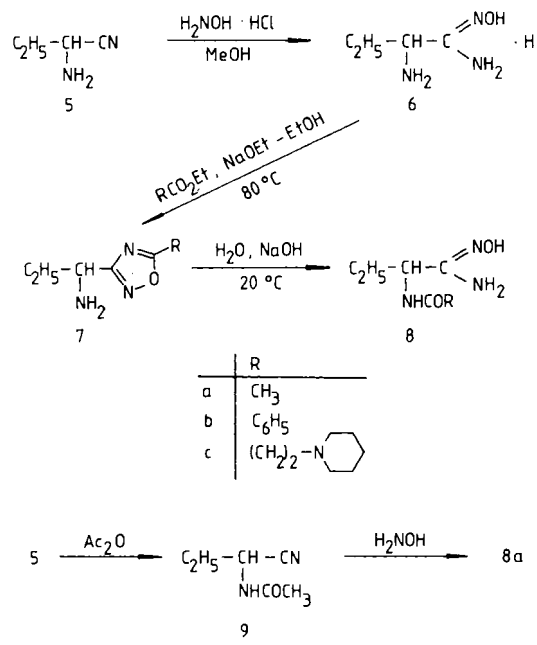
The homologues of **1**, 3-(3-aminopropyl)-1,2,4-oxadiazoles, under the conditions of the ring transformation **1**→**2** underwent no change not even by boiling in alkaline or in acidic aqueous media[2].

The question arises how would the stability of the 1,2,4-oxadiazole ring be affected by the decrease of the distance between the amino moiety and the ring.

Here we report the synthesis of 5-substituted 3-(1-aminopropyl)-1,2,4-oxadiazoles **7a–c** and their unexpected hydrolytic transformation.

Oxadiazoles **7** were synthesized from α-aminobutyramide oxime hydrochloride (**6**), obtained by the reaction of α-aminobutyronitrile (**5**)[3] with hydroxylamine hydrochloride, by ring closure reaction with esters in the presence of sodium ethoxide. Under the conditions of the transformations of **1** and **3** (heating in various organic solvents)[1] the compounds **7** proved to be stable which seemed to be in agreement with

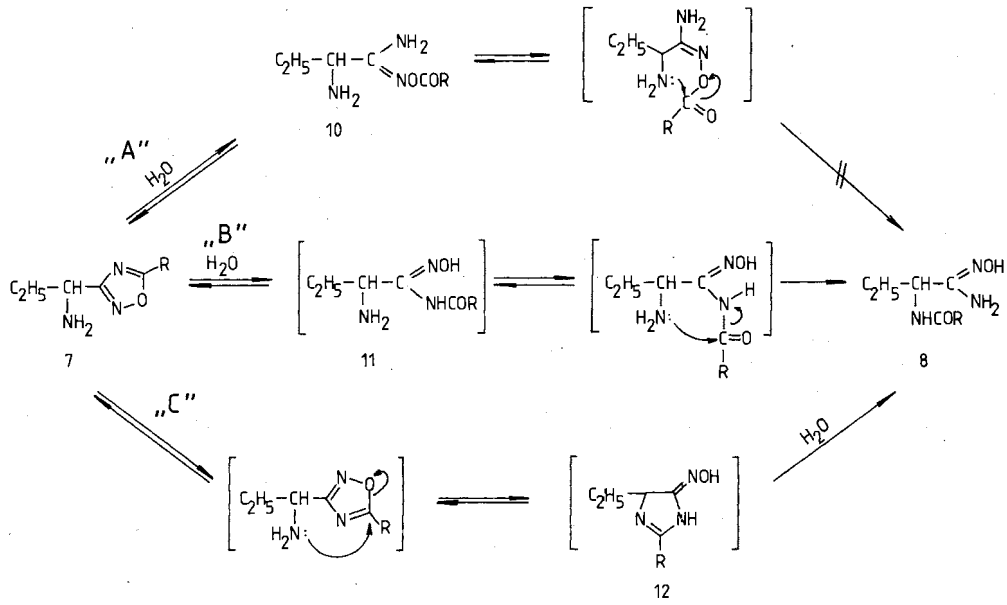
Scheme 2



our earlier finding that in the ring transformation reactions of 3-(2-aminoalkyl)-1,2,4-oxadiazoles the distance between the amino moiety and the ring is of decisive importance[2,4]. To our astonishment we have found that oxadiazoles **7** isolated as crystalline salts yield (acylamino)butyramide oximes **8** by the action of aqueous sodium hydroxide. For the purpose of structure proof we have synthesized **8a** by treating **9**, obtained by acetylation of **5**, with hydroxylamine. The unexpected transformation **7**→**8** occurs even under rather mild conditions. The most simple procedure is to cover the oxadiazoles with 4–8% aqueous sodium hydroxide. They

  0009–2940/88/0404–0723 $ 02.50/0

Scheme 3



go slowly into solution, then after standing for some weeks the amides **8** precipitate as crystals with good yields. This reaction goes as well in the presence of a catalytic amount of sodium hydroxide (0.05–0.1 mol equivalent), though the yields are fairly low.

It should be emphasized that 1,2,4-oxadiazoles bearing alkyl or aryl substituents in the positions 3 and 5 are stable against hydrolysis[5]. Moreover, 5-hydroxyoxadiazole derivatives are resistent even to boiling in 5% sodium hydroxide for several hours[6]. Ring opening or transformation may usually take place under relatively mild conditions if the oxadiazole compounds – as **1** and **3** – comply with the original or extended Boulton-Katritzky scheme of type 2[7,1b], where the third atom of the side-chain bearing a mobile proton attacks the azole ring. The reaction **7**→**8** is different from each of the latter transformations.

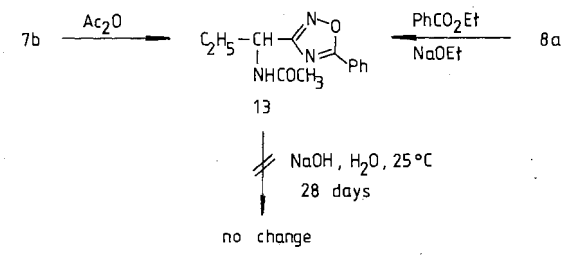
If the hydrolysis of the oxadiazole ring is the first step of the obviously complex process then the formation of *O*-acylamide oxime **10** seems to be the most likely from which the amide **8** can be formed by acyl migration (Scheme 3, path A). Since the aqueous alkaline hydrolysis of **10a**, obtained from the amide oxime hydrochloride **6** by selective *O*-acetylation, failed to produce even traces of **8a**, this route can be ruled out.

In another route the hydrolysis of **7** would result in the formation of *N*-acylamide oxime from which **8** could be formed by acyl migration (Scheme 3, path B) as well. On the basis of the literature data[5,6], however, this type of hydrolysis of 1,2,4-oxadiazoles seems to be rather unlikely.

Taking into consideration that the ring isomerization reactions **1**→**2** and **3**→**4** took place in many cases even at ambient temperature we suggest that in the reaction **7**→**8** a ring transformation step is also involved (Scheme 3, path C).

In contrast to the ring transformation depicted in Scheme 1 the attack of the amino nitrogen of oxadiazole **7** at the N-2 atom of the ring would lead to the formation of a sterically unfavourable four-membered ring. Therefore we assume that the nucleophilic amino nitrogen establishes a bond with the most electron deficient atom (C-5) of the ring[4], concomitantly with the fission of the C-5–O bond resulting in the formation of an imidazolin-4-one oxime derivative **12** which on hydrolysis gives **8**. The primary role of the free amino moiety in the ring opening of oxadiazole **7** is supported by the fact that 3-[1-(acetylamino)propyl]-5-phenyl-1,2,4-oxadiazole (**13**) obtained either by acetylation of **7b** or by ring closure with ethyl benzoate from **8a**, proved to be completely stable under the conditions of the transformations **7**→**8** (Scheme 4).

Scheme 4



The reaction **7**→**8** consisting of two or eventually more steps, in which the alkaline medium obviously plays an important role, according to the reaction path C in Scheme 3 shows two common features with the ring transformation **1**→**2**. As on the one hand in both reactions the crucial step is the attack of the aminoalkyl side chain leading to an azole→azoline transformation, and as on the other hand both reactions have the same driving force namely the potential formation of the thermodynamically stable amide moieties[1a,b] the discovery of this unique hydrolytic reaction

is completely in line with results obtained earlier in the field of aminoamide oxime derivatives[1,2,4,8].

Thanks are due to Mrs. *V. Kovács* and Dr. *G. Horváth* for recording the IR spectra and to Dr. *I. Remport* for the elemental analyses.

Experimental

IR spectra: Unicam SP-1000 and Zeiss UR-20, in KBr. – ^{1}H-NMR spectra: Bruker WP-80 DS at 80 MHz, TMS internal standard. – Melting points are not corrected.

2-Aminobutyramide Oxime Hydrochloride (**6**): A methanolic solution (200 ml) of α-aminobutyronitrile (**5**)[3] (21.03 g, 250 mmol) and hydroxylamine hydrochloride (17.37 g, 250 mmol) was allowed to stand at ambient temperature for 1 day. The reaction mixture containing already a crystalline precipitate was kept at 0°C for about 12 h in order to collect more product. The product was filtered off by suction, washed with ethyl acetate to give 30.2 g (78%) of **6**·HCl. M.p. 185–187°C (ethanol). – IR (KBr): 3420 cm^{-1}, 3300, 1672, 955. – ^{1}H NMR ([D$_6$]DMSO): δ = 0.89 (t, 3H, C*H*$_3$CH), 1.85 (quint, 2H, CH$_3$C*H*$_2$), 3.51 (t, 1H, CH), 5.8 (b, 2H, NH$_2$), 8.3 (b, 3H, NH$_3^+$), 9.4 (b, 1H, OH).

$C_4H_{12}ClN_3O$ (153.6) Calcd. C 31.27 H 7.88 Cl 23.08 N 27.35
Found C 31.38 H 8.03 Cl 22.98 N 27.28

3-(1-Aminopropyl)-5-methyl-1,2,4-oxadiazole Hydrochloride (**7a**·HCl): To a solution of **6** (6.14 g, 40 mmol) and ethyl acetate (9.96 g, 120 mmol) in ethanol (100 ml) was added a sodium ethoxide solution freshly prepared from 1.84 g (80 mmol) of sodium and 30 ml of ethanol, then the reaction mixture was heated to reflux for 6 h on a waterbath. After evaporation the residue was triturated with water, extracted with chloroform, dried, and converted to the salt with ethanolic hydrogen chloride 5.54 g (78%) of **7a** · HCl was obtained, m.p. 185–187°C (ethanol). – IR (KBr): 3400 cm^{-1}, 3300–2700 very intensive band, 1600. – ^{1}H NMR ([D$_6$]DMSO): δ = 0.85 (t, 3H, C*H*$_3$CH$_2$), 1.95 (m, 2H, CH$_3$C*H*$_2$), 2.65 (s, 3H, 5-CH$_3$), 4.43 (dd, 1H, CH), 9.1 (b, 3H, NH$_3^+$).

$C_6H_{12}ClN_3O$ (177.6) Calcd. C 40.55 H 6.82 Cl 19.99 N 23.63
Found C 40.68 H 6.95 Cl 19.95 N 23.52

3-(1-Aminopropyl)-5-phenyl-1,2,4-oxadiazole Hydrochloride (**7b**·HCl): As in the previous example but with ethyl benzoate (12.01 g, 80 mmol). Yield 8.24 g (86%) of **7b** · HCl, m.p. 258°C (70% ethanol). – IR (KBr): 3400 cm^{-1}, 3150–2750 very intensive band, 1600. – ^{1}H NMR ([D$_6$]DMSO): δ = 0.96 (t, 3H, C*H*$_3$CH$_2$), 2.13 (quint, 2H, CH$_3$C*H*$_2$), 4.57 (t, 1H, CH), 7.40–7.96 (m, 3H, Ar), 8.0–8.5 (m, 2H, Ar), 9.2 (b, 3H, NH$_3^+$).

$C_{11}H_{14}ClN_3O$ (239.7) Calcd. C 55.11 H 5.89 Cl 14.79 N 17.52
Found C 55.00 H 5.88 Cl 14.72 N 17.48

3-(1-Aminopropyl)-5-(2-piperidinoethyl)-1,2,4-oxadiazole Dihydrochloride (**7c** · 2HCl): As in the previous examples using ethyl 3-piperidinopropionate (14.82 g, 80 mmol) as ester component to give 9.59 g (77%) of **7c** · 2 HCl. M.p. 186–187°C (ethanol). – IR (KBr): 3300–2800 cm^{-1} strong band, 1595. – ^{1}H-NMR ([D$_6$]DMSO): δ = 0.89 (t, 3H, C*H*$_3$CH$_2$), 1.83 (m, 8H, 4 × CH$_2$), 3.10 (b, 5H, 2 × CH$_2$ + NH$^+$), 3.66 (m, 4H, 2 × CH$_2$), 4.45 (t, 1H, CH), 9.4 (b, 3H, NH$_3^+$).

$C_{12}H_{22}Cl_2N_4O \cdot H_2O$ (327.3)
Calcd. C 44.04 H 7.39 Cl 21.67 N 17.12
Found C 44.31 H 7.69 Cl 21.69 N 16.96

2-(Acetylamino)butyramide Oxime (**8a**)

a) A mixture of **7a** · HCl (1.77 g, 10 mmol) and 1 N NaOH (15 ml, 15 mmol) was allowed to stand for 4 weeks at ambient (20–22°C) temperature. The starting material became oily, then slowly went into solution, while the product formed precipitated in crystalline form. The product was removed by suction, thoroughly washed with water, dried, and recrystallized from ethanol to give 1.24 g (78.5%) of **8a**, m.p. 174–175°C. If a smaller quantity of sodium hydroxide is used or the precipitated crystals are removed earlier (after 10 days) the yield is lower.

b) A mixture of **5** (1.08 g, 10 mmol) and acetic anhydride (1.02 g, 10 mmol) was allowed to stand for 3 days at 20°C then stirred under cooling with 10 ml of 1 N NaOH. The oil formed was extracted with ether, the extract was dried and evaporated. To the yellow oily residue (crude 2-(acetylamino)butyronitrile) a solution of hydroxylamine base in 30 ml of methanol was added, and the mixture was heated to reflux for 24 h on a waterbath. [The hydroxylamine base was prepared by the reaction of hydroxylamine hydrochloride (2.78 g, 40 mmol) and sodium methoxide (2.16 g, 40 mmol) in methanol; the formed sodium chloride was removed by filtration.] The solvent was distilled off, the residue triturated with water, filtered off, and recrystallized from ethanol to give 1.12 g (70%) of **8a**, m.p. 174–175°C. – IR (KBr): 3450 cm^{-1}, 3300, 1695, 1642, 938. – ^{1}H NMR ([D$_6$]DMSO): δ = 0.81 (t, 3H, C*H*$_3$CH$_2$), 1.50 (m, 2H, CH$_3$C*H*$_2$), 1.82 (s, 3H, CH$_3$CO), 4.14 (q, 1H, CH), 5.25 (b, 2H, NH$_2$), 7.82 (d, 1H, NH), 8.96 (s, 1H, OH); $^3J_{NH,CH}$ = ca. 8 Hz.

$C_6H_{13}N_3O_2$ (159.2) Calcd. C 45.27 H 8.75 N 26.40
Found C 45.10 H 8.72 N 26.17

2-(Benzoylamino)butyramide Oxime (**8b**): A mixture of **7b** · HCl (1.2 g, 5 mmol), 2 N NaOH (10 ml, 20 mmol), and ethanol (30 ml) was allowed to stand for 21 days at 20–22°C, then the pH of the reaction mixture was adjusted to 7 with 2 N HCl. The product **8b** crystallized as the sodium salt. Yield 1.03 g (85%), m.p. 246–248°C (from water).

$C_{11}H_{14}NaN_3O_2$ (243.3) Calcd. C 54.31 H 5.80 N 17.28
Found C 54.27 H 6.04 N 17.00

From the aqueous solution of the sodium salt the free amide oxime **8b** is obtained by acidification to pH 3 with nearly quantitative yield. After drying at 110°C in a vacuum desiccator and recrystallizing from dry ethanol the substance obtained melts at 175–178°C. – IR (KBr): 3500 cm^{-1}, 3380, 1680, 1645, 920. – ^{1}H NMR ([D$_6$]DMSO): δ = 0.87 (t, 3H, C*H*$_3$CH$_2$), 1.69 (q, 2H, CH$_3$C*H*$_2$), 4.41 (q, 1H, CH), 5.39 (b, 2H, NH$_2$), 7.51 (m, 3H, Ar), 7.88 (m, 2H, Ar), 8.26 (d, 1H, NH); $^3J_{NH,CH}$ = ca. 9 Hz.

$C_{11}H_{15}N_3O_2$ (221.3) Calcd. C 59.71 H 6.83 N 18.99
Found C 59.94 H 6.87 N 19.01

2-[(3-Piperidinopropionyl)amino]butyramide Oxime (**8c**): A mixture of **7c** dihydrochloride (1.64 g, 5.0 mmol) and 2 N NaOH (10 ml, 20 mmol) was allowed to stand at 20–22°C for 2 weeks. After adjusting the pH to 8 the mixture was extracted with chloroform, the organic phase after drying was evaporated, the residue was triturated with petroleum ether and recrystallized from ethyl acetate to give 1.00 g (75%) of **8c**. M.p. 95–97°C. – IR (KBr): 3495 cm^{-1}, 3350, 1650, 920. – ^{1}H NMR (CDCl$_3$): δ = 0.98 (t, 3H, C*H*$_3$CH$_2$), 1.20–2.10 (m, 8H, 4 × CH$_2$), 2.20–3.10 (m, 8H, 4 × CH$_2$), 4.35 (q, 1H, CH), 4.99 (b, 2H, OH + 0.5 H$_2$O), 5.34 (b, 2H, NH$_2$), 8.93 (d, 1H, NH); $^3J_{NH,CH}$ = ca. 8 Hz.

$C_{12}H_{24}N_4O_2 \cdot 0.5\ H_2O$ (265.4) Calcd. C 54.31 H 9.50 N 21.11
Found C 54.51 H 9.64 N 21.30

O-Acetyl-2-aminobutyramide Oxime Hydrochloride (**10a** · HCl): To a mixture of **6** · HCl (3.07 g, 20 mmol) and ether (20 ml) acetic anhydride (2.04 g, 20 mmol) was added dropwise under cooling (20°C) and stirring. Then the mixture was stirred for an additional

16 h. The crystalline **10a** · HCl was filtered off by suction and thoroughly washed with ether to give 3.85 g (98%) of product. M.p. 166°C (dec.). – IR (KBr): 3380 cm^{-1}, 3310, 3200, 1732 1660. – ^1H NMR ([D_6]DMSO): δ = 0.90 (t, 3H, CH_3CH_2), 1.85 (m, 2H, CH_3CH_2), 2.10 (s, 3H, CH_3CO), 3.36 (b, 1H, OH), 3.66 (t, 1H, CH), 6.95 (b, 2H, NH_2), 8.60 (b, 3H, NH_3^+).

$C_6H_{14}ClN_3O_2$ (195.7) Calcd. C 36.83 H 7.21 Cl 18.12 N 21.47
Found C 36.58 H 6.95 Cl 18.08 N 21.45

No traces of **8a** could be detected after a treatment of **10a**·HCl with aqueous sodium hydroxide.

3-[1-(Acetylamino)propyl]-5-phenyl-1,2,4-oxadiazole (**13**)

a) An aqueous solution of **7b** · HCl (2.40 g, 10 mmol) was neutralized with 10% sodium carbonate solution, the precipitated oil was extracted with chloroform, the solution was dried and evaporated. The residue was dissolved in pyridine (5 ml) and treated with acetic anhydride (1.02 g, 10 mmol) at 20°C. Then the mixture was allowed to stand for 2 days at room temperature. After removal of the pyridine by distillation the residue was triturated with water to obtain 2.09 g (85%) of **13**, m.p. 102°C (from petroleum ether).

b) A mixture of **8a** (0.80 g, 5.0 mmol), ethyl benzoate (1.5 g, 10 mmol), sodium ethoxide (0.34 g, 5.0 mmol), and ethanol (60 ml) was heated to reflux for 5 h on a water bath. After evaporation the residue was triturated with water to give 0.99 g (89%) of **13**, identical with the product obtained according to a). The compound **13** proved to be stable under the condition of the reaction **7**→**8**. – IR (KBr): 3300 cm^{-1}, 3220, 3080, 1650. – ^1H NMR ([D_6]DMSO): δ = 0.93 (t, 3H, CH_3CH_2), 1.40–2.30 (m, 2H, CH_3CH_2), 1.90 (s, 3H, CH_3CO), 4.99 (q, 1H, CH), 7.66 (m, 3H, Ar), 8.11 (m, 2H, Ar), 8.47 (d, 1H, NH); $^3J_{NH,CH}$ = ca. 10 Hz.

$C_{13}H_{15}N_3O_2$ (245.3) Calcd. C 63.66 H 6.16 N 17.13
Found C 63.64 H 6.29 N 17.20

CAS Registry Numbers

5: 40651-89-6 / **6** · HCl: 67015-12-7 / **7a** · HCl: 111997-68-3 / **7b** · HCl: 111997-69-4 / **7c** · 2 HCl: 111997-70-7 / **8a**: 111997-71-8 / **8b**: 112021-09-7 / **8b** · Na: 111997-72-9 / **8c**: 111997-73-0 / **10a** · HCl: 111997-74-1 / **13**: 111997-75-2 / ethyl benzoate: 93-89-0 / ethyl 3-piperidinopropionate: 19653-33-9 / 2-(acetylamino)butyronitrile: 5990-99-8

[1] [1a] D. Korbonits, E. M. Bakó, K. Horváth, *J. Chem. Res.* **1979**, (S) 64; (M) 0801. – [1b] D. Korbonits, I. Kanzel-Szvoboda, K. Horváth, *J. Chem. Soc., Perkin Trans. 1*, **1982**, 759. – [1c] I. Bata, G. Héja, P. Kiss, D. Korbonits, *J. Chem. Soc., Perkin Trans. 1*, **1986**, 9.

[2] D. Korbonits, K. Horváth, Cs. Gönczi, J. Tamás, *Acta Chim. Hung.* **117** (1984) 239.

[3] [3a] N. Zelinsky, G. Stadnikoff, *Ber. Dtsch. Chem. Ges.* **41** (1908) 2061. – [3b] M. Freifelder, R. B. Hasbrouck, *J. Am. Chem. Soc.* **82** (1960) 696.

[4] K. Horváth, D. Korbonits, G. Náray-Szabó, K. Simon, *J. Mol. Struct. (Theochem.)* **136** (1986) 215.

[5] [5a] F. Tiemann, P. Krüger, *Ber. Dtsch. Chem. Ges.* **17** (1884) 1685. – [5b] L. B. Clapp, *Adv. Heterocycl. Chem.* **20** (1976) 65.

[6] K. Takács, K. Harsányi, *Chem. Ber.* **103** (1970) 2330.

[7] A. J. Boulton, A. R. Katritzky, A. Majid Hamid, *J. Chem. Soc. C*, **1967**, 2005.

[8] [8a] D. Korbonits, P. Kiss, K. Simon, P. Kolonits, *Chem. Ber.* **117** (1984) 3183. – [8b] D. Korbonits, K. Simon, P. Kolonits, *Tetrahedron Lett.* **24** (1983) 5763. – [8c] D. Korbonits, P. Kolonits, *J. Chem. Soc., Perkin Trans 1*, **1986**, 2163. – [8d] D. Korbonits, P. Kiss, I. Bata, G. Héja, K. Simon, P. Kolonits, *Chem. Ber.* **120** (1987) 1039.

[286/87]