29. Cycloalkylations of *N*-(ω-Halogenoalkyl)-substituted Macrocyclic Imides

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With ω-halogenoalkyl isocyanates, 2-oxocyclododecane-1-carbonitrile is transformed under ring enlargement to 1-(ω-halogenoalkyl)-2,14-dioxo-1-azacyclotetradecane-3-carbonitriles. In the presence of base, these products undergo *O*- or *C*-alkylation leading to bicyclic compounds. The *C*-alkylation product **7** undergoes solvolysis to form a sixteen-membered ring compound.

In [1], we have presented the preliminary results of the one-step ring enlargement of 2-oxocycloalkane-1-carbonitriles and -1-carboxylates into macrocyclic imides. As substrates, *p*-toluenesulfonyl, aryl, and vinyl isocyanates were used, since it is known that electron-attracting groups may enhance the reactivity of the azomethine moiety of the isocyanate towards nucleophilic reagents [2]. To expand the synthetic scope of this new ring-enlargement reaction, we were interested in investigating the reactivity of 'unactivated' alkyl isocyanates.

We found that the sodium salt of 2-oxocyclododecane-1-carbonitrile (**1**) [3] reacted with benzyl isocyanate (**2a**) or butyl isocyanate (**2b**) at 20° for 1 h to give, after acidic workup, the *N*-substituted cyclic imides **3a** and **3b** in 75 and 72% yield, respectively *(Scheme 1)*. Under the same conditions, **1** reacted chemoselectively with 3-chloropropyl isocyanate (**4**) to give the corresponding ring-enlarged product **5** in 74% yield. The ease of formation of the imides **3a**, **3b**, and **5** indicates that alkyl isocyanates are sufficiently reactive substrates in the ring-enlargement reaction of 2-oxocycloalkane-1-carbonitriles.

It is known that cycloalkylation of ω-halogenoalkyl-substituted active methylene compounds proceeds under basic conditions, and is a convenient method for the preparation of carbo- and heterocycles [4–6]. Thus, the presence of the chloroalkyl side chain in the imide **5** would allow the initially formed sodium enolate of **5** to undergo such an intramolecular nucleophilic substitution. However, we could not detect any cycloalkylation products in the crude reaction mixture of **5**, probably because of the short reaction time. Therefore, **5** was treated with excess K_2CO_3 in DMSO [4] at 20° for 10 h, and the

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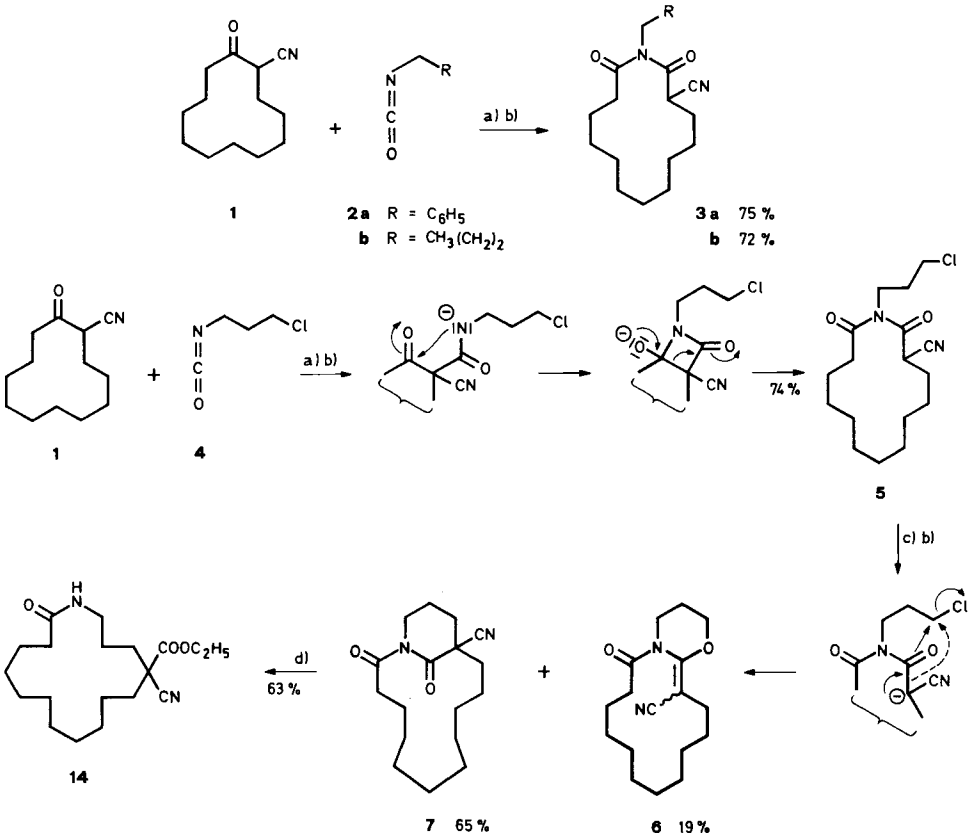
Scheme 1



a) NaH/THF. b) H_2O. c) K_2CO_3, DMSO, 20°. d) EtOH/46 h reflux.

expected products of *O*- and *C*-alkylation **6** and **7** were obtained in 19 and 65% yield, respectively *(Scheme 1)*.

On the other hand, when **1** was treated with the homologous 4-bromobutyl isocyanate (**8**) [7] at 20° for 1 h, **9** was obtained in 61% yield, together with small amounts of the *O*-alkylation product **10** *(Scheme 2)*. Unexpectedly, the cycloalkylation of **9** with K_2CO_3 in DMSO proceeded faster (3 h at 20°) than in the case of **5**, giving, however, only the *O*-alkylation product **10** in 79% yield. Similar selectivity was observed in the reaction of **1** with the homologous 2-chloroethyl isocyanate (**11**). Under the ring-enlargement conditions, imide **12** and the *O*-alkylation product **13** were obtained in 45 and 4% yield, respectively *(Scheme 2)*. Further treatment of **12** with K_2CO_3 in DMSO at 20° for 2 h gave again only **13** in 65% yield, without any traces of the corresponding *C*-alkylation product[2]).

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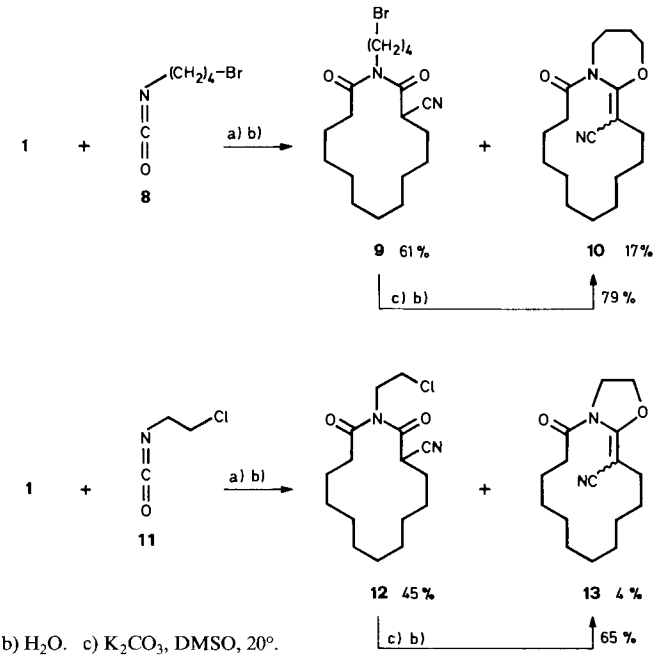
[2]) An analogous selective formation of *O*- or *C*-cycloalkylation products, depending on the length of the ω-halogenoalkyl side chain, was observed in the case of other enolizeable active methylene compounds [4].

Scheme 2



a) NaH/THF. b) H_2O. c) K_2CO_3, DMSO, 20°.

The reactivity of 2-oxocyclododecane-1-carbonitrile (**1**) towards ω-halogeno-substituted alkyl isocyanates has some resemblances to the so-called '*Michael*-initiated ring closure' principle [8] which represents a conjugate addition of a nucleophile to an α,β-unsaturated ester or ketone, followed by intramolecular alkylation of the intermediate enolate. In our case, the ring closure is preceeded by a ring enlargement induced by nucleophilic addition of **1** to the imino moiety of the isocyanate which forms the corresponding enolate (see *Scheme 1*). The observed reaction path could be explained with the faster formation of a four-membered cyclic intermediate *(cf. Scheme 1)* leading to ring enlargement as compared to the competitive intramolecular alkylation of the initially formed adduct of **1** and isocyanate.

The smooth preparation of the bicyclic compound **7**, possessing an imide function, prompted us to investigate its behavior towards nucleophilic reagents. Nucleophilic addition to the C=O group of the bridge could induce cleavage of the N–CO bond with formation of the ring-enlarged product [9]. Indeed, in a preliminary experiment, we found that the solvolysis [10] of **7** with absolute EtOH gave the 16-membered (ethoxycarbonyl)-substituted lactam **14** in 63% yield *(Scheme 1)*.

The results presented above show that the ring enlargement of 2-oxocycloalkane-1-carbonitriles into macrocyclic imides is not restricted to a specific structure of the isocyanate and may have more general synthetic application.

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Experimental Part

General. See [1].

1. *Reaction of 2-Oxocyclododecane-1-carbonitrile* (**1**) *with the Alkyl Isocyanates* **2a, 2b, 4, 8,** or **11**. To a suspension of NaH (6 mmol) in dry THF (50 ml) **1** (5 mmol) was added under stirring in small portions and the resulting mixture was stirred at 20° for 30 min. After dropwise addition of **2a, 2b, 4, 8,** or **11** (6 mmol), stirring was continued for 1 h at 20°, and the solvent evaporated. The residue was dissolved in H_2O (100 ml), extracted with Et_2O (3 × 30 ml) and the combined org. layers separated. The alkaline H_2O phase was acidified with dil. HCl and extracted with CH_2Cl_2 (3 × 30 ml). The combined org. extracts were washed with H_2O, dried, evaporated, and the residue was crystallized from a suitable solvent to give **3a, 3b, 5, 9,** or **12,** resp. Column chromatography (Et_2O/hexane 1:1) of the combined Et_2O extracts before acidic workup of **9** or **12** gave **10** or **13,** resp.

1-Benzyl-2,14-dioxo-1-azacyclotetradecane-3-carbonitrile (**3a**). Yield 75%. M.p. 67–69° (EtOH). IR: 2254, 1704, 1498. ^{1}H-NMR: 7.50–7.10 (*m*, 5 arom. H); 5.09, 4.85 (*AB*, *J* = 17, 2 H–C(1′)); 5.03 (*dd*, *J* = 9, 5, H–C(3)); 2.74 (*ddd*, *J* = 16, 10, 3, 1 H–C(13)); 2.38 (*ddd*, *J* = 16, 7, 3, 1 H–C(13)); 2.00–1.10 (*m*, 18 H). ^{13}C-NMR: 177.2 (*s*, C(2)); 170.3 (*s*, C(14)); 136.0 (*s*, 1 arom. C); 129.0, 127.9, 126.5 (3 *d*, 5 arom. C); 117.2 (*s*, CN); 48.0 (*t*, C(1′)); 40.4 (*d*, C(3)); 35.6, 30.0 (2 CH_2); 25.8 (2 *t*); 25.7, 25.1, 24.4, 24.1, 24.0, 23.6 (6 CH_2). CI-MS: 341 ([*M* + 1]$^+$). Anal. calc. for $C_{21}H_{28}N_2O_2$ (340.46): C 74.08, H 8.29, N 8.23; found: C 74.06, H 8.12, N 8.23.

1-Butyl-2,14-dioxo-1-azacyclotetradecane-3-carbonitrile (**3b**). Yield 72%. M.p. 50–51° (hexane). IR: 2250, 1692. ^{1}H-NMR: 4.93 (*dd*, *J* = 8, 5, H–C(3)); 3.67 (*t*, *J* = 8, 2 H–C(1′)); 2.80–2.40 (*m*, 2 H–C(13)); 2.30–1.20 (*m*, 22 H); 0.96 (*t*, *J* = 7, CH_3). ^{13}C-NMR: 176.9 (*s*, C(2)); 169.8 (*s*, C(14)); 117.3 (*s*, CN); 45.1 (*t*, C(1′)); 40.3 (*d*, C(3)); 35.1, 31.3, 29.9 (3 CH_2); 25.9 (2 CH_2); 25.7, 25.1, 24.3, 24.1, 24.0, 23.8, 20.0 (7 CH_2); 13.6 (*q*, CH_3). EI-MS: 306 (8, M^+), 251 (12), 209 (15), 153 (16), 142 (20), 112 (25), 98 (81), 83 (30, 55 (98), 41 (100). Anal. calc. for $C_{18}H_{30}N_2O_2$ (306.45): C 70.55, H 9.87, N 9.14; found: C 70.43, H 9.86, N 9.30.

1-(3′-Chloropropyl)-2,14-dioxo-1-azacyclotetradecane-3-carbonitrile (**5**). Yield 74%. M.p. 64–66° (CH_2Cl_2/EtOH). IR: 2250, 1704. ^{1}H-NMR: 4.94 (*dd*, *J* = 8, 4, H–C(3)); 3.86 (*t*, *J* = 8, 2 H–C(1′)); 3.61 (*t*, *J* = 6, 2 H–C(3′)); 2.80 (*ddd*, *J* = 16, 10, 3, 1 H–C(13)); 2.57 (*ddd*, *J* = 16, 6, 3, 1 H–C(13)); 2.20–1.00 (*m*, 20 H). ^{13}C-NMR: 176.7 (*s*, C(2)); 170.0 (*s*, C(14)); 117.1 (*s*, CN); 43.1, 42.0 (2 CH_2); 40.2 (*d*, C(3)); 35.2, 31.6, 29.8, 25.8, 25.7, 25.5, 25.1, 24.3, 24.0, 23.9, 23.7 (11 CH_2). CI-MS: 329, 327 ([*M* + 1]$^+$), 291 ([*M* – Cl]$^+$). Anal. calc. for $C_{17}H_{27}ClN_2O_2$ (326.86): C 62.47, H 8.33, N 8.57; found: C 62.34, H 8.39, N 8.71.

1-(4′-Bromobutyl)-2,14-dioxo-1-azacyclotetradecane-3-carbonitrile (**9**). Yield 61%. M.p. 62–64° (Et_2O/hexane). IR: 2255, 1698. ^{1}H-NMR: 4.93 (*dd*, *J* = 8, 5, H–C(3)); 3.71 (*t*, *J* = 8, 2 H–C(1′)); 3.44 (*t*, *J* = 6, 2 H–C(4′)); 2.74 (*ddd*, *J* = 14, 10, 3, 1 H–C(13)); 2.52 (*ddd*, *J* = 16, 8, 3, 1 H–C(13)); 2.10–1.10 (*m*, 22 H). ^{13}C-NMR: 176.7 (*s*, C(2)); 169.9 (*s*, C(14)); 117.2 (*s*, CN); 44.2 (*t*, C(1′)); 40.3 (*d*, C(3)); 35.2, 32.7, 29.9, 29.6, 27.7, 25.9, 25.8, 25.7, 25.1, 24.4, 24.0, 23.9, 23.8 (13 CH_2). EI-MS: 386, 384 (8, 8, M^+), 306 (48, [*M* – Br]$^+$), 127 (28), 113 (42), 99 (98), 83 (38), 70 (28), 56 (100), 42 (81). Anal. calc. for $C_{18}H_{29}BrN_2O_2$ (385.34): C 56.11, H 7.59, N 7.27; found: C 56.33, H 7.72, N 7.38.

1-(2-Chloroethyl)-2,14-dioxo-1-azacyclotetradecane-3-carbonitrile (**12**). Yield 45%. M.p. 98–99° (CH_2Cl_2/EtOH). IR: 2255, 1702. ^{1}H-NMR: 4.96 (*dd*, *J* = 9, 4, H–C(3)); 4.04 (*t*, *J* = 6, 2 H–C(1′)); 3.75 (*t*, *J* = 6, 2 H–C(2′)); 2.90 (*ddd*, *J* = 16, 10, 3, 1 H–C(13)); 2.62 (*ddd*, *J* = 16, 6, 3, 1 H–C(13)); 2.10–1.10 (*m*, 18 H). ^{13}C-NMR: 176.7 (*s*, C(2)); 170.3 (*s*, C(14)); 117.0 (*s*, CN); 46.5, 41.7 (2 CH_2); 40.3 (*d*, C(3)); 35.3, 30.0, 26.0, 25.8, 25.7, 25.0, 24.4 (7 CH_2); 24.0 (2 CH_2); 23.5 (CH_2). EI-MS: 314/312 (1/4, M^+), 277 (4, [*M* – Cl]$^+$), 188 (14), 149 (14), 126 (14), 112 (30), 98 (100), 84 (23), 69 (25), 56 (63), 42 (76). Anal. calc. for $C_{16}H_{25}ClN_2O_2$ (312.84): C 61.43, H 8.06, N 8.96; found: C 61.44, H 7.86, N 8.98.

2-Oxo-15-oxa-1-azabicyclo[12.5.0]nonadec-13-ene-13-carbonitrile (**10**). Yield 17%. M.p. 81–83° (hexane). IR: 2210, 1688, 1682, 1640. ^{1}H-NMR: 4.72 (*d*-like *m*, 1 H); 4.38–4.20 (*d*-like *m*, 1 H); 3.86 (*t*, *J* = 12, 1 H); 2.80–2.34 (*m*, 4 H); 2.20–2.02 (*m*, 1 H); 2.00–1.10 (20 H). ^{13}C-NMR: 172.2 (*s*, C(2)); 160.8 (*s*, C(14)); 118.6 (*s*, CN); 88.2 (*s*, C(13)); 69.8 (*t*, C(16)); 46.9 (*t*, C(19)); 31.8, 28.5, 26.7, 26.6, 26.2, 25.3, 25.2, 25.1, 24.6, 23.4 (10 CH_2); 23.1 (2 CH_2). CI-MS: 305 ([*M* + 1]$^+$). Anal. calc. for $C_{18}H_{28}N_2O_2$ (304.43): C 71.02, H 9.27, N 9.20; found: C 71.22, H 9.34, N 9.19.

2-Oxo-15-oxa-1-azabicyclo[12.3.0]heptadec-13-ene-13-carbonitrile (**13**). Yield 4%. M.p. 90–92° (Et_2O/hexane). IR: 2205, 1698, 1658. ^{1}H-NMR: 4.68 (*ddd*, *J* = 12, 8, 1.4, 0.5 H); 4.33 (*dt*, *J* = 8, 1.4, 1 H); 4.06–3.88 (*m*, 0.5 H); 3.84–3.36 (*m*, 1.5 H); 3.12 (*dt*, *J* = 14.6, 8.3, 0.5 H); 2.66–2.38 (*m*, 1 H–C(3)); 2.34–2.16 (*m*, 1 H–C(3)); 2.10–1.00 (*m*, 18 H). ^{13}C-NMR: 172.7 (*s*, C(2)); 158.9 (*s*, C(14)); 119.2 (*s*, CN); 75.4 (*s*, C(13)); 65.9 (*t*, C(16)); 45.8 (*t*, C(17)); 31.5, 26.1, 26.0, 25.3, 25.1, 24.0, 23.7, 23.1, 23.0, 22.6 (10 CH_2). EI-MS: 276 (10, M^+), 207 (6), 193 (4), 179 (26), 165 (11), 152 (9), 123 (100), 110 (14), 98 (70), 80 (22), 56 (21), 42 (33). Anal. calc. for $C_{16}H_{24}N_2O_2$ (276.38): C 69.53, H 8.75, N 10.14; found: C 69.42, H 8.89, N 10.19.

2. *General Procedure for Cycloalkylation of the Imides* **5**, **9**, *or* **12** *to the Bicyclic Compounds* **6**, **7**, **10**, *and* **13**. A mixture of **5**, **9**, or **12** (2 mmol), finely powdered anh. K_2CO_3 (8 mmol), and DMSO (2 ml) was stirred at 20° for the required time, and H_2O (50 ml) was added. The mixture was extracted with CH_2Cl_2 (3 × 10 ml), the combined org. phases were washed with H_2O, dried, and evaporated. The residue was purified by column chromatography or crystallized from a suitable solvent.

2-Oxo-15-oxa-1-azabicyclo[12.4.0]octadec-13-ene-13-carbonitrile (**6**) *and 2,7-Dioxo-1-azabicyclo[11.3.1]-heptadecane-13-carbonitrile* (**7**). Reaction time 10 h. Column chromatography with Et_2O/hexane 1:1 (**7** faster moving).

Data of **6**: Yield 19%. M.p. 61–63° (hexane). IR: 2210, 1688, 1644. ^{1}H-NMR: 4.49 (*dt*, *J* = 13, 9, 1 H); 4.34–4.18 (*m*, 1 H); 3.97 (*dt*, *J* = 5, 10, 1 H); 3.30–3.12 (*m*, 1 H); 2.91 (*ddd*, *J* = 14, 10, 7, 1 H); 2.57 (*ddd*, *J* = 14, 10, 4, 1 H–C(3)); 2.38 (*ddd*, *J* = 14, 10, 4, 1 H–C(3)); 2.22–2.00 (*m*, 3 H); 2.00–1.06 (*m*, 16 H). ^{13}C-NMR: 172.9 (*s*, C(2)); 158.7 (*s*, C(14)); 118.7 (*s*, CN); 87.5 (*s*, C(13)); 65.9 (*t*, C(16)); 40.2 (*t*, C(18)); 31.0, 26.7, 26.2, 25.6, 25.5, 24.7, 24.4, 24.1, 23.4, 22.9, 22.8 (11 CH_2). CI-MS: 291 ([*M* + 1]$^+$). Anal. calc. for $C_{17}H_{26}N_2O_2$ (290.41): C 70.31, H 9.02, N 9.65; found: C 70.38, H 9.06, N 9.56.

Data of **7**: Yield 65%. M.p. 112–113° (EtOH). IR: 2240, 1704. ^{1}H-NMR: 3.86–3.62 (*m*, 1 H–C(16)); 3.54–3.30 (*m*, 1 H–C(16)); 2.60–2.30 (*m*, 1 H–C(3)); 2.24–1.80 (*m*, 3 H); 1.70–1.10 (*m*, 20 H). ^{13}C-NMR: 176.9 (*s*, C(17)); 169.8 (*s*, C(2)); 120.0 (*s*, CN); 48.4 (*s*, C(13)); 45.1, 38.3, 37.8, 33.2, 26.2, 25.8 (6 CH_2); 25.5 (2 CH_2); 24.4, 23.3, 23.2, 22.2, 19.3 (5 CH_2). CI-MS: 291 ([*M* + 1]$^+$), 264 ([*M* – CN]$^+$). Anal. calc. for $C_{17}H_{26}N_2O_2$ (290.40): C 70.31, H 9.02, N 9.65; found: C 70.11, H 9.21, N 9.56.

Compound **10** *from* **9**. Yield 79%. Identical with **10** from *Exper. 1* (mixed m.p. without depression; spectra superimposable).

Compound **13** *from* **12**. Yield 65%. Identical with **13** from *Exper. 1* (mixed m.p. without depression; spectra superimposable).

3. *Ethyl 5-Cyano-16-oxo-1-azacyclohexadecane-5-carboxylate* (**14**). A soln. of **7** (1.16 g, 4 mmol) in dry EtOH (10 ml) was refluxed under N_2 for 46 h. Evaporation and crystallization of the residue from Et_2O/hexane gave **14** (0.85 g, 63%). M.p. 63–64°. IR: 3210, 3090, 2235, 1748, 1682. ^{1}H-NMR: 6.68 (br. *s*, NH, exchangeable with D_2O); 4.13 (*q*, *J* = 7, CH_3CH_2O); 3.54–3.24 (*m*, 2 H); 2.40–1.20 (*m*, 27 H), therein *t* at 2.30 (*J* = 7, 2 H) and *t* at 1.26 (*J* = 7, CH_3). ^{13}C-NMR: 173.8 (*s*, CO); 167.5 (*s*, CO); 120.6 (*s*, CN); 60.0 (*t*, CH_2O); 43.7 (*s*, C(13)); 42.0, 36.1, 34.3, 30.5 (4 CH_2); 29.3 (2 CH_2); 29.2, 29.1, 29.0, 28.9, 24.9, 24.5, 19.1 (7 CH_2); 14.2 (*q*, CH_3). CI-MS: 337 ([*M* + 1]$^+$), 291 ([*M* – OEt]$^+$). Anal. calc. for $C_{19}H_{32}N_2O_3$ (336.47): C 67.82, H 9.58, N 8.32; found: C 67.71, H 9.57, N 8.15.

REFERENCES

[1] V. I. Ognyanov, M. Hesse, *Helv. Chim. Acta* **1989**, *72*, 1522.
[2] S. Ozaki, *Chem. Rev.* **1972**, *72*, 457, p. 469.
[3] B. Föhlisch, R. Herter, E. Wolf, J. J. Stezowski, E. Eckle, *Chem. Ber.* **1982**, *115*, 355.
[4] N. S. Zefirov, T. S. Kuznetsova, S. I. Kozhushkov, L. S. Surmina, Z. A. Rashchupkina, *J. Org. Chem. USSR* **1983**, *19*, 474.
[5] A. C. Knipe, C. J. M. Stirling, *J. Chem. Soc. (B)* **1968**, 67.
[6] A. K. Bose, M. S. Manhas, B. G. Chatterjee, R. F. Abdulla, *Synth. Commun.* **1971**, *1*, 51.
[7] H. R. Kricheldorf, *Angew. Chem.* **1979**, *91*, 749.
[8] R. D. Little, J. R. Dawson, *Tetrahedron Lett.* **1980**, *21*, 2609; R. D. Little, R. Verhé, W. T. Monte, S. Nugent, J. R. Dawson, *J. Org. Chem.* **1982**, *47*, 362.
[9] H. Stach, M. Hesse, *Tetrahedron* **1988**, *44*, 1573.
[10] V. Gailius, H. Stamm, *Arch. Pharm.* **1988**, *321*, 337.