28. Novel Syntheses of Gabapentin *via* Addition of Hydrocyanic Acid to Cyclohexylidenemalonate or Cyano(cyclohexylidene)acetate

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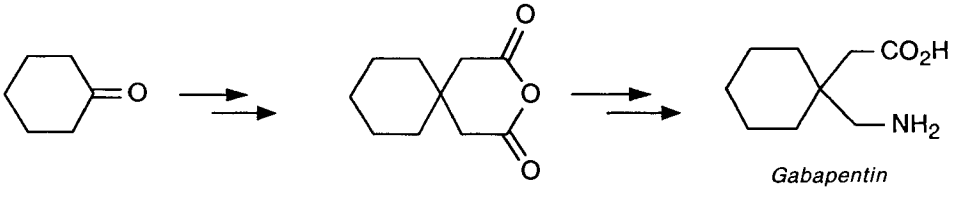
Several synthetic pathways to the anticonvulsivum *gabapentin* (1-(aminomethyl)cyclohexaneacetic acid) have been investigated. Advantages and drawbacks of the different routes are discussed, and the most economical and technically most feasible synthesis is pointed out.

Introduction. – γ-Aminobutyric acid (GABA) occurs in the mammalian central nervous system where it is thought to function as an important inhibitory neurotransmitter. 1-(Aminomethyl)cyclohexaneacetic acid (*gabapentin*) is an amino acid structurally related to GABA, but unlike GABA, it penetrates the blood-brain barrier. Pharmacologically, it is characterized by anticonvulsant properties, especially against seizures elicited by impairment of GABAergic neurotransmission [1]. All reported syntheses of gabapentin involve as an intermediate a glutaric-anhydride derivative which is prepared in several steps from cyclohexanone (*Scheme 1*). After opening of the anhydride, one of the two carboxy groups is transformed into an NH_2 group by a *Hofmann*, *Curtius*, or *Lossen* rearrangement [2] [3]. These syntheses would be costly on a technical scale, since they would require expensive safety precautions for the handling of thermally unstable azides and isocyanates. The purpose of this investigation was to develop a more economical and technically more feasible route to gabapentin.

Scheme 1



Gabapentin

Results. – Our first synthesis of gabapentin (*Scheme 2*) started from cyclohexanone and diethyl malonate which underwent *Knoevenagel* condensation to form diethyl (cyclohexylidene)malonate (**1**; 56% yield). *Michael* addition of HCN led to diethyl (1-cyanocyclohexyl)malonate (**2**; 88% yield). Catalytic hydrogenation using a Ni catalyst led to reduction of the CN group and subsequent cyclisation to ethyl 3-oxo-2-azaspiro-

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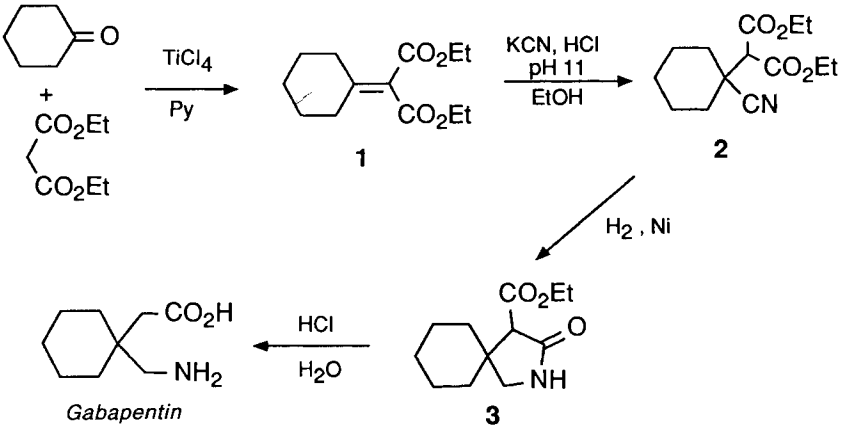
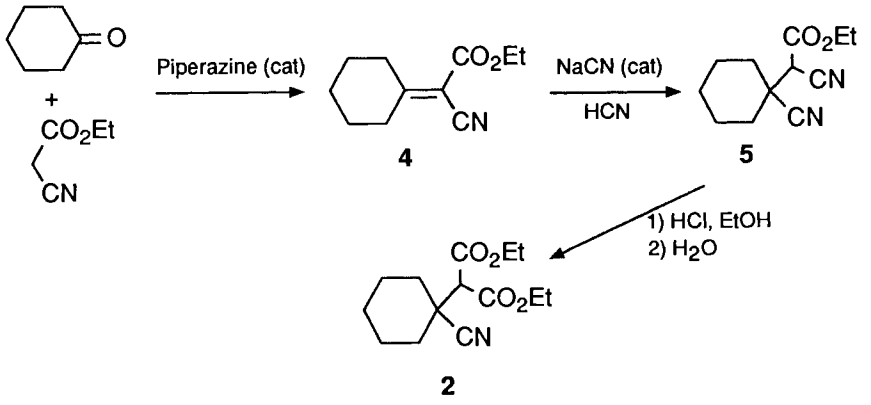
Scheme 2



[4.5]decane-4-carboxylate (**3**; 88% yield). Hydrolysis of **3** furnished gabapentin (75% yield). This route is very straightforward and probably the best way for the synthesis of gabapentin in the laboratory, but it has several drawbacks. *Knoevenagel* condensations of malonates with ketones are usually difficult [4]. The reaction of diethyl malonate with cyclohexanone gives a reasonable yield of condensation product **1** only in the presence of 2 equiv. of $TiCl_4$ and 4 equiv. of pyridine [5]. The large amount of TiO_2-pyridine complex produced needs a special treatment, before it can be disposed of. The disposal of solid, non-burnable residues is a problem in the chemical industry, and so the TiO_2 would have to be purified before use in, for instance, the pigment industry. Moreover, the procedure needs a large amount of solvent, since a voluminous precipitate is formed during the reaction. Only a few literature examples are known for the addition of HCN to α,β-unsaturated-β,β-disubstituted malonates. *Srinivasan* and coworkers [6] added KCN to a solution of diethyl isopropylidenemalonate in $EtOH/H_2O$ and isolated diethyl 1-cyano-1-(methylethyl)malonate in 26% yield. Treatment of **1** with KCN in boiling EtOH gave **2** in 25% yield together with several side products indicating that **2** is not stable under basic conditions. The addition of HCN under acidic conditions in the presence of a catalytic amount of KCN can only be achieved at high temperatures in an autoclave with a large excess of HCN. We found that the reaction runs at 70–78° with an excellent yield, if the pH of the mixture is maintained at 10.5–12. Under these conditions most of the HCN present is deprotonated and, therefore, reactive, whereas the enolate of **2** is immediately protonated and stabilized. In spite of the good yield, the procedure is inconvenient on a technical scale. The handling of solid KCN (at least 1.5 equiv. have to be used) is very difficult and expensive because of the safety precautions needed. Acidic workup of the reaction mixture would give large amounts of HCN which would have to be recovered and stoichiometric amounts of KCl which would have to be disposed of.

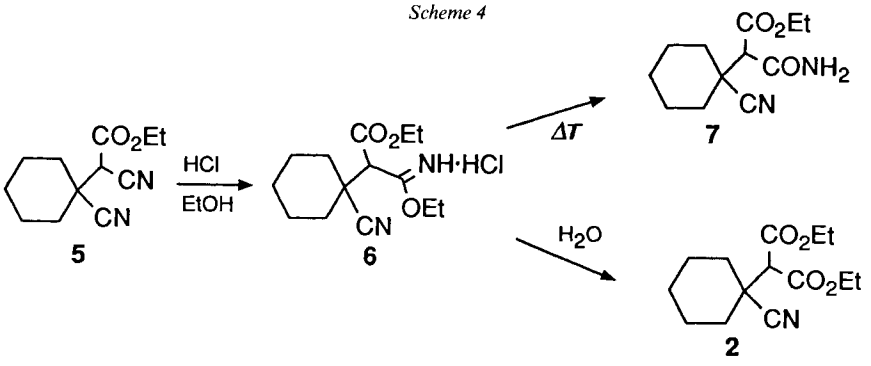
Because of these drawbacks we developed an alternative synthesis of malonate **2** (see *Scheme 3*). Ketones can be condensed with cyanoacetates much easier than with malonates [4]. Ethyl cyano(cyclohexylidene)acetate (**4**) can be prepared in good yields from cyclohexanone and ethyl cyanoacetate under *Knoevenagel* condensation conditions [7–10]. *Smith* and *Horowitz* [9] used KCN in boiling EtOH for the *Michael* addition to **4** and

Scheme 3



obtained ethyl cyano(1-cyanocyclohexyl)acetate (**5**) in a yield of 75% (based on ethyl cyanoacetate). We found that the addition of HCN gave a good yield (90%) in the presence of a catalytic amount of base at 20–30° in EtOH. In addition to the improved yield, this variation has the advantage of not creating a stoichiometric amount of salt in the acidic workup. For the transformation of a CN into an ethyl-ester group, one can react the nitrile with an alcohol in the presence of HCl (*Pinner* reaction) to form an imidate hydrochloride, which gives the ester on hydrolysis [11]. Treatment of **5** with HCl in the presence of EtOH in dimethoxyethane, dioxane, or toluene gave no reaction. Obviously, neither of the two CN groups in **5** is reactive under standard *Pinner*-reaction conditions. However, use of HCl under pressure with EtOH as the solvent led to highly regioselective formation of diethyl (1-cyanocyclohexyl)malonimidate (**6**). Imidate **6** can be isolated as the hydrochloride but decomposes readily to the amide **7** or, in the presence

Scheme 4



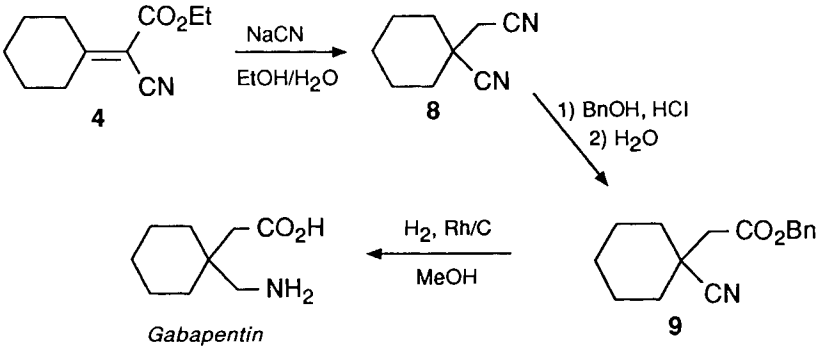
of moisture, undergoes facile hydrolysis to the ester **2** (see *Scheme 4*). Preferable, therefore, is conversion of unisolated **6** to ester **2** by addition of H_2O to the reaction mixture, which gave the product in good yield (79% based on **5**) and high purity.

The synthesis of gabapentin *via* **4**, **5**, **2**, and **3** (*Schemes 2* and *3*) uses cheap reagents and solvents, gives good chemical yields in each step, and, in addition, allows high

productivity, since reaction times are short and concentrations high. It is, therefore, both an economical and a technically feasible new pathway.

Because the last step of this procedure is an acidic hydrolysis, gabapentin is formed as its hydrochloride and must be treated with an ion-exchange resin to release the free amino acid. This is expensive; we, therefore, developed a synthetic route in which gabapentin is formed under neutral conditions (see *Scheme 5*). Treatment of ethyl cyano(cyclohexylidene)acetate (**4**) with NaCN in refluxing EtOH in the presence of 4–5 equiv. of H_2O gave directly (1-cyanocyclohexyl)acetonitrile (**8**; 85% yield). *New* and *Yevich* used KCN together with a larger excess of H_2O and reported a yield of 64% [12]. The

Scheme 5



Pinner reaction of nitrile **8** with $PhCH_2OH$ and HCl followed by hydrolysis gave benzyl (1-cyanocyclohexyl)acetate (**9**; 60% yield). Catalytic hydrogenation of **9** over Rh/C reduced the CN and the benzyl-ester groups to the amine and carboxylic acid, respectively. Free gabapentin could then be isolated directly from the reaction mixture (27% yield). This route is again very straightforward but unsatisfactory in view of the moderate yields for the conversion of **8** to **9** and the reduction of **9** to gabapentin. In addition, the *Pinner* reaction required an excess of the relatively expensive $PhCH_2OH$ and a long reaction time.

In conclusion, we have developed several alternative pathways to gabapentin, from which the five step synthesis *via* **4**, **5**, **2**, and **3** proved to be the most promising for production on a technical scale.

The realization of this work was made possible thanks to the collaboration of our coworkers in the R&D and analytical departments of *Lonza*, Visp. We thank particularly Dr. *M. Hauck* for the NMR spectra, Dr. *A. Gerhard* for the GC/MS spectra and Mrs. *S. Heinzmann*, Miss *C. Zurbriggen*, Mr. *K. Michlig*, and Mr. *R. Zeiter* for the laboratory work.

Experimental Part

General. M.p.: *Büchi SMP 20* apparatus. IR spectra (KBr): *Nicolet FTIR 20 SXB* spectrometer; in cm^{-1}. GLC: *HP 5890* with a fused silica capillary column (5% Ph-Me-silicone gum); in area %. ^1H-NMR spectra: *Nicolet NMC-1280* (300 MHz) spectrometer; δ in ppm relative to TMS as internal reference. GC/MS: *Finnigan 40021*, ionization: EI (70 eV), fused-silica capillary column (5% Ph-Me-silicone gum).

Diethyl (Cyclohexylidene)malonate (**1**). To a mixture of 900 ml of THF and 2800 ml of CH_2Cl_2 were added 455 g (2.40 mol) of $TiCl_4$ (at −5° to 2°, 48 min), 192.2 g (1.20 mol) of diethyl malonate (at −6° to −10°, 3 min), 129.5 g (1.32 mol) of cyclohexanone (at −10°, 5 min), and 379.7 g (4.80 mol) of pyridine (at −10° to −1°, 70 min). The brown suspension was allowed to warm to r.t., stirred overnight, and diluted with H_2O (1500 ml). The phases were separated, and the org. phase was washed with H_2O, dried ($MgSO_4$), and evaporated. The resulting suspension was filtered to give 274.8 g of a yellow liquid which contained 59.1% **1** (GLC, 56.3% yield based on diethyl malonate). A pure sample of **1** was obtained by distillation. B.p. 98°/0.1 mbar. ^{1}H-NMR ($CDCl_3$): 1.30 (*t*, 6 H); 1.58–1.78 (*m*, 6 H); 2.50–2.58 (*m*, 4 H); 4.22 (*q*, 4 H).

Diethyl (1-Cyanocyclohexyl)malonate (**2**). *1*) KCN (45.2 g, 680 mmol) was suspended in 360 ml of EtOH and heated to 72°. Compound **1** (113.6 g, 464 mmol) was added during 15 min. The pH of the mixture was held constant at 11.0–11.2 (measured with a combined pH glass electrode with 3M KCl as bridge electrolyte) by the simultaneous addition of a 17.6% HCl/EtOH soln. During the addition of **1** and over the next 8.5 h at 72–76° and pH 11.0–11.2, a total of 93.5 g (450 mmol) of HCl/EtOH soln. were added. The mixture was then diluted with 200 ml of EtOH and filtered at 65°. The filtrate was evaporated, the residue dissolved in 200 ml of CH_2Cl_2, and filtered again (to remove traces of KCN). The evaporated filtrate was recrystallized from EtOH to give 111.2 g of **2** (purity 98.8%, GLC, 88.6% yield). M.p. 89–90°. ^{1}H-NMR ($CDCl_3$): 1.09–1.38 (*m*, 1 H); 1.31 (*t*, 6 H); 1.39–1.53 (*m*, 2 H); 1.63–1.82 (*m*, 5 H); 2.11–2.22 (*m*, 2 H); 3.40 (*s*, 1 H); 4.21–4.34 (*m*, 4 H). GC/MS: 268 (1, $[M + 1]^+$), 222 (10), 161 (8), 160 (100), 133 (51), 123 (23), 88 (28), 86 (21). Anal. calc. for $C_{14}H_{21}NO_4$ (267.3): C 62.90, H 7.86, N 5.24; found: C 62.9, H 7.9, N 5.5.

2) A soln. of 44.1 g (200 mmol) of **5** in 150 ml of EtOH was stirred for 17 h under a HCl pressure of 2–3 bar at 0° in an autoclave. The reactor was evacuated (0°/15 mbar) for 1 h to remove part of the excess HCl. After dilution with 400 ml of H_2O and stirring for 3.5 h, the suspension was slightly concentrated. The formed crystals were separated by filtration, washed with H_2O and dried to give 47.9 g of **2** (purity 99.1% GLC, 88.7% yield).

3) A soln. of 400 mg (1.3 mmol) of **6** in 10 ml of EtOH was treated with 29 mg (1.6 mmol) of H_2O. GLC of the mixture showed that the conversion of the imidate **6** to the ester **2** was 60% after 4 h and 90% after 24 h at r.t.

Ethyl 3-Oxo-2-azaspiro[4.5]decane-4-carboxylate (**3**). A soln. of 13.5 g (50 mmol) of **2** in 200 ml of EtOH was hydrogenated over 8 g Ni catalyst (*SUEDCHEMIE*, type *G96*) at 8–10 bar and 90° for 22 h. The filtered mixture was evaporated to a weight of 14 g, diluted with 100 ml of petroleum ether (b.p. 80–110°), cooled to 3°, and filtered. The filter cake was washed with petroleum ether and dried to give 10.1 g of **3** (purity 98.1%, GLC, 87.8% yield). M.p. 74–75°. ^{1}H-NMR ($CDCl_3$): 1.29 (*t*, 3 H); 1.25–1.68 (*m*, 10 H); 3.06 (*s*, 1 H); 3.18 (*dd*, 1 H); 3.34 (*d*, 1 H); 4.21 (*q*, 2 H); 6.92 (*s*, 1 H). MS: 225 (21, M^+), 179 (100), 152 (23), 122 (30), 110 (61), 95 (32), 67 (38), 55 (40), 41 (47). Anal. calc. for $C_{12}H_{19}NO_3$ (225.3): C 63.98, H 8.50, N 6.22; found: C 63.6, H 8.6, N 6.4.

[1-(Aminomethyl)cyclohexyl]acetic acid (= *Gabapentin*). *1*) Compound **3** (5.00 g, 21.3 mmol) was dissolved in 100 ml of 20% HCl. After 72 h at reflux, the mixture was evaporated, the residue dissolved in 100 ml of H_2O, and evaporated again. The dried residue was suspended in 40 ml of acetone, filtered, and washed several times with acetone. The isolated raw gabapentin·HCl·½ H_2O weighed 2.50 g (54.2% yield). The filtrate was partially evaporated to give another 0.13 g gabapentin·HCl·½ H_2O (2.8% yield). By recrystallization from acetone/H_2O (10:1), 1.96 g of pure gabapentin·HCl·½ H_2O was obtained (purity 99.9%, titration, 42.4% yield). M.p. 122–123°. ^{1}H-NMR (CD_3OD): 1.35–1.64 (*m*, 10 H); 2.52 (*s*, 2 H); 3.06 (*s*, 2 H). Anal. calc. for $C_9H_{19}NO_{2.5}Cl$ (216.7): C 49.88, H 8.84, N 6.46; found: C 50.1, H 8.9, N 7.0.

2) A soln. of 1.53 g (7.2 mmol) of methyl 3-oxo-2-azaspiro[4.5]decane-4-carboxylate (prepared analogously to **3** in 3 steps from dimethyl malonate and cyclohexanone, see *Scheme 2*) in 30 ml of 20% HCl was refluxed for 24 h. The mixture was evaporated, dissolved in 30 ml H_2O, evaporated again, and dried. The residue was suspended in 20 ml of acetone and filtered. The washed and dried filter cake weighed 894 mg (m.p. 114°). The filtrate was evaporated, the residue dissolved in 10 ml of 20% HCl, and refluxed for 48 h. Workup as above gave another 326 mg of gabapentin·HCl·½ H_2O (m.p. 117°). Total yield of crude product: 75.2% (purity: 96.8%, titration).

3) Compound **9** (1.00 g, 3.85 mmol) was dissolved in 20 ml of MeOH and hydrogenated over 0.2 g of Rh/C 5% at 10 bar and r.t. After 23 h, the mixture was filtered, the filtrate evaporated, and the residue recrystallized from EtOH to give 0.18 g of gabapentin (27% yield). M.p. 148–151°. ^{1}H-NMR (CD_3OD): 1.30–1.62 (*m*, 10 H); 2.47 (*s*, 2 H); 2.89 (*s*, 2 H).

Ethyl Cyano(cyclohexylidene)acetate (**4**) was prepared according to the procedure in [7] with a yield of 92%.

Ethyl Cyano(1-cyanocyclohexyl)acetate (**5**). To 50 ml of EtOH were added successively at 18–30° 0.18 g (8 mmol) of Na, 1.8 g of H_2O (100 mmol), 38.9 g (200 mmol) of **4**, and 5.8 g (210 mmol) of HCN (exothermic reaction). After 1 h at r.t., the reactor was evacuated (15 mbar) for 15 min to remove part of the excess HCN. The mixture was acidified with gaseous HCl and filtered. The filter cake was washed with cold EtOH and dried to give 27.3 g of **5** (purity 100%, GLC, 62.0% yield). From the partly evaporated filtrate, a further 12.5 g of **5** could be

isolated (purity 99.5%, GLC, 28.2% yield). M.p. 50–51°. ^{1}H-NMR ($CDCl_3$): 1.13–1.34 (*m*, 4 H); 1.39 (*t*, 3 H); 1.50–1.93 (*m*, 7 H); 2.04–2.30 (*m*, 2 H); 3.68 (*s*, 1 H); 4.36 (*q*, 2 H). Anal. calc. for $C_{12}H_{16}N_2O_2$ (220.2): C 65.43, H 7.32, N 12.72; found: C 65.5, H 7.8, N 12.6.

Diethyl (1-Cyanocyclohexyl)malonimidate (**6**). A soln. of 44.1 g (200 mmol) of **5** in 150 ml of EtOH was stirred for 17 h under a HCl pressure of 2–3 bar at 0°. After evaporation of one third of the mixture, the residue was dissolved in 50 ml of toluene and treated with 20 ml of hexane. The precipitated crystals were filtered off, washed with cold toluene, and dried to give 11.9 g of **6** (59% yield). IR 3495*w*, 3428*m*, 3415*m*, 2985*s*, 2931*s*, 2858*s*, 2730*s*, 2647*m*, 2240*w*, 1760*s*, 1718*m*, 1662*s*, 1580*m*, 1464*m*, 1442*m*, 1388*m*, 1367*m*, 1339*m*, 1320*m*, 1285*s*, 1259*m*, 1202*s*, 1190*s*, 1164*m*, 1098*m*, 1026*m*, 931*m*, 852*m*, 700*m*. ^{1}H-NMR ($CDCl_3$): 1.19–1.92 (*m*, 15 H, including 1.31 (*t*, 3 H), 1.59 (*t*, 3 H)); 2.56–2.67 (*m*, 1 H); 4.20–4.43 (*m*, 3 H, including 4.39 (*s*, 1 H)); 4.78 (*q*, 2 H); 12.20 (br. *s*, 1 H); 12.95 (br. *s*, 1 H).

Ethyl (1-Cyanocyclohexyl)malonamide (**7**). *1*) A soln. of 22.0 g (100 mmol) of **5** in 100 ml of EtOH was stirred for 8 h under a HCl pressure of 2–3 bar at r.t. The soln. was left to stand overnight at −30°. After evaporation of the solvent, the residue was dissolved in 80 ml of cold H_2O and stirred for 1 h at 0–5°. The precipitated product was filtered off, washed with cold EtOH/H_2O, and dried to give 15.5 g of a product mixture containing 74.4% **2** and 23.5% **7** (GLC). The pure amide **7** was isolated by flash chromatography (CH_2Cl_2/EtOH 25:1). IR: 3441*s*, 3340*s*, 3295*w*, 2940*m*, 2242*w*, 1734*s*, 1694*s*, 1618*m*, 1451*m*, 1382*m*, 1370*m*, 1330*m*, 1298*s*, 1240*m*, 1204*s*, 1182*s*, 1028*m*, 602*m*, 588*m*. ^{1}H-NMR ($CDCl_3$): 1.10–1.89 (*m*, 11 H, including 1.32 (*s*, 3 H)); 1.93–2.20 (*m*, 2 H); 3.28 (*s*, 1 H); 4.29 (*q*, 2 H); 5.93 (br. *s*, 1 H); 6.88 (br. *s*, 1 H). MS: 239 (< 1, $[M + 1]^+$), 221 (< 1), 193 (2), 165 (2), 131 (100), 123 (14), 103 (20), 85 (23), 59 (72), 41 (30). Anal. calc. for $C_{12}H_{18}N_2O_3$ (238.3): C 60.49, H 7.61, N 11.76; found: C 59.6, H 7.8, N 11.1

2) Compound **6** (0.40 g, 1.3 mmol) was dissolved in 10 ml of EtOH and stirred at r.t. After 2 days, GLC showed that 13% of **6** had decomposed to **7**.

(1-Cyanocyclohexyl)acetonitrile (**8**). To a soln. of 10.1 g (200 mmol) of NaCN in 16 ml of H_2O were added 380 ml of EtOH and 38.9 g (200 mmol) of **4**. After 22 h at reflux, the mixture was filtered, the filtrate acidified with gaseous HCl, and filtered again. The filtrate was evaporated to a weight of 156 g and cooled to 5°. The precipitated crystals were filtered off, washed with cold EtOH, and dried to give 18.0 g of **8** (purity 99.8%, GLC, 60.5% yield). A further 7.3 g **8** could be isolated from the partially evaporated mother liquor (purity 98.7%, GLC, 24.0% yield). M.p. 82–83°. ^{1}H-NMR ($CDCl_3$): 1.14–1.90 (*m*, 8 H); 2.02–2.18 (*m*, 2 H); 2.69 (*s*, 2 H). Anal. calc. for $C_9H_{12}N_2$ (148.2): C 72.94, H 8.16, N 18.90; found: C 74.3, H 8.3, N 18.6.

Benzyl (1-Cyanocyclohexyl)acetate (**9**). A soln. of 1.51 g (10 mmol) of **8** in 10.92 g (100 mmol) of $PhCH_2OH$ was saturated with gaseous HCl at 0°. After 21 h, the reactor was evacuated (0°/15 mbar) for 1 h to remove part of the excess HCl. The mixture was then added to 50 ml of cold H_2O, stirred for 5 h at 0–3°, and diluted with 40 ml of AcOEt. The phases were separated, and the org. phase was washed with H_2O, dried (Na_2SO_4), and evaporated. The dried residue was distilled (bulb-to-bulb, 2–5 mbar, 150–200°) to give 1.83 g of an oil, containing 84.5% of **9** (GLC, 60.3% yield). The product can be purified by distillation using high vacuum. B.p. 164–170°/0.2 mbar. ^{1}H-NMR ($CDCl_3$): 1.13–1.41 (*m*, 3 H); 1.59–1.80 (*m*, 5 H); 2.03–2.15 (*m*, 2 H); 2.59 (*s*, 2 H); 5.16 (*s*, 2 H); 7.30–7.43 (*m*, 5 H). GC/MS: 257 (18, M^+), 215 (2), 108 (100), 91 (82), 79 (11), 65 (10). Anal. calc. for $C_{16}H_{19}NO_2$ (257.3): C 74.68, H 7.44, N 5.44; found: C 74.9, H 7.4, N 5.5.

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