Synthesis of 4,5-decamethyleneimidazole, 4,5-decamethyleneoxazole, 4,5-decamethyleneisoxazole, 4,5-decamethyleneimidazolone-2, and 4,5-decamethylenepyrazole from cyclododecanone derivatives

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4,5-Decamethyleneimidazole, 4,5-decamethyleneoxazole, and 4,5-decamethyleneimidazolone-2 were synthesized by reactions of 2-bromocyclododecanone and 2-hydroxycyclododecanone with formamide, ammonium formate, and urea, respectively. Condensation of 2-formylcyclododecanone with hydroxylamine and hydrazine hydrate resulted in 4,5-decamethyleneisoxazole, and 4,5-decamethylenepyrazole, respectively.

Key words: 2-bromocyclododecanone, 2-hydroxycyclododecanone; 4,5-decamethyleneimidazole, 4,5-decamethyleneoxazole, 4,5-decamethyleneimidazolone-2, 4,5-decamethyleneisoxazole, 4,5-decamethylenepyrazole.

A number of bicyclic systems, including six- and five-membered heterocycles fused with a dodecamethylene ring, have been synthesized based on cyclododecanone.^{1,2} Among these, compounds possessing biological activity and natural compounds, *e.g.*, muscopyridines, have been found.³

In the present work, a number of 4,5-decamethyleneazoles have been synthesized from cyclododecanone derivatives. In a study of the reaction of 2-bromocyclododecanone (1) with HCONH₂ in the presence of H_2SO_4 it was found that, depending on the reaction temperature, either only 4,5-decamethyleneimidazole (2), compound 2 with an admixture of 4,5-decamethyleneoxazole (3), or compound 3 with an admixture of compound 2 are formed.



It has been shown previously^{4,5} that reactions of aliphatic α -haloketones with formamide in the presence of H₂SO₄ also result in mixtures of the corresponding imidazoles and oxazoles.

In the series of five-membered heterocycles containing two heteroatoms and fused with the dodecamethylene ring at positions 4 and 5, only 4,5-decamethyleneoxazole⁶ is known, which has been synthesized from 2-hydroxycyclododecanone, formamide, and H_2SO_4 (the experimental procedure has not been described). We found that the reaction of the above reagents at 100-150 °C results in a mixture of imidazole 2 and oxazole 3.

$$(CH_{2})_{10} \xrightarrow{C=0}_{CHOH} + HCONH_{2} \xrightarrow{H_{2}SO_{4}}_{140-150 \circ C} 2 + 3$$

However, the reaction of 2-hydroxycyclohexanone with $HCONH_2$ and H_2SO_4 under the same conditions did not give 4,5-tetramethyleneimidazole.⁷

We showed that heating compound **3** with HCONH₂ and H₂SO₄ to 140-150 °C results in replacement of the O atom by an NH group to give compound **2**.

$$3 \xrightarrow[140-150 \circ C]{\text{HCONH}_2 + H_2SO_4} 2$$

This result explains why heterocycle 2 is formed from bromoketone 1 and $HCONH_2$ in the presence of H_2SO_4 at elevated temperatures.

If the reaction of compound 1 with HCONH₂ is carried out in the presence of silica gel at 190 °C, imidazole 2 is formed in a good yield, while oxazole 3 is not formed under these conditions. However, compound **3** was obtained in a good yield (the admixture of compound **2** did not exceed 2 %) by treatment of ketone **1** with HCOONH₄ in 100 % HCOOH at 100 °C according to the procedure reported previously.⁷

Boiling bromoketone 1 with urea in AcOH in the presence of aqueous ammonia gives 4,5-decamethylene-imidazolone-2 (4).



4,5-Decamethyleneizoxazole ($\mathbf{6}$) is smoothly formed when 2-formylcyclododecanone ($\mathbf{5}$) is heated with hydroxylamine hydrochloride in AcOH.



Treatment of isoxazole 6 with sodium methoxide at 20 °C affords 2-cyanocyclododecanone (7). The latter is cleaved when heated with KOH to give brassilic acid (8).



Compound 5 is readily formed⁸ by condensation of cyclododecanone with ethyl formate in the presence of MeONa. Treatment of formyl derivative 5 with hydrazine hydrate in ethanol affords 4,5-decamethylenepyrazole (9).



Experimental

4,5-Decamethyleneimidazole (2). *A*. A mixture of $HCONH_2$ (20 g, 0.44 mol) and conc. H_2SO_4 (5 g) was added at 140–150 °C to a solution of ketone **1** (10 g, 38.3 mmol) in

HCONH₂ (20 mL) over a period of 2 h. The reaction mixture was cooled, treated with 8 % NaOH to a weakly alkaline pH, and extracted with chloroform. The extract was evaporated to dryness, and the solid residue was recrystallized from a methanol-water mixture (1 : 0.1) to give 5.1 g (64 %) of compound **2**, m.p. 185–186 °C. Found (%): C, 75.90; H, 10.84; N, 13.55. C₁₃H₂₂N₂. Calculated (%): C, 75.72; H, 10.67; N, 13.59. Compound **2** was transformed to the picrate, m.p. 161–162 °C (toluene). Found (%): C, 54.52; H, 5.88; N, 16.18. C₁₉H₂₃N₅O₆. Calculated (%): C, 54.67; H, 5.51; N, 16.78.

B. A mixture of 2-hydroxycyclododecanone (4 g, 20 mmol), HNCONH₂ (20 mL, 0.5 mol), and conc. H₂SO₄ (2 g) was heated for 3.5 h with stirring at 100 °C and for 1 h at 150 °C. Then the reaction mixture was diluted with water (50 mL), extracted with ether, and the extract was dried with Na₂SO₄. The ether was distilled off. Distillation of the residue gave 1 g of 4,5-decamethyleneoxazole (3), b.p. 112-114 °C (1 Torr). Lit. data:⁶ b.p. 84-85 °C (0.155 Torr). The aqueous solution was treated with 5 % KOH to a weakly alkaline pH. The white precipitate that formed was filtered off, repeatedly washed with water, dried, and crystallized from a methanol-water mixture (1 : 0.1) to give 1.5 g of compound 2, m.p. 185-186 °C. The sample does not cause depression of m.p. when mixed with an authentic sample of imidazole 2. Found (%): C, 75.76; H, 10.61; N, 13.60. C₁₃H₂₂N₂. Calculated (%): C, 75.72; H, 10.67; N, 13.59.

C. Ketone 1 (10 g, 38.3 mmol) in HCONH₂ (30 mL, 0.75 mol) was heated for 6 h at 190–195 °C in the presence of silica gel. The reaction mixture was cooled and filtered. The mother liquor was poured into ice water. The precipitate that formed was filtered off, washed with water (3×10 mL), and dried to give 4.5 g (57 %) of imidazole 2, m.p. 185–186 °C (methanol–water).

4,5-Decamethyleneoxazole (3). *A.* HCONH₂ (10 g, 0.22 mol) and H₂SO₄ (5 g) were slowly added to a solution of ketone **1** (8 g, 30.6 mmol) in HCONH₂ (25 mL, 0.63 mol). The mixture was heated for 5 h at 105–110 °C, cooled, poured into water, and extracted with ether (2×20 mL). The combined ethereal extracts were washed with water and dried with Na₂SO₄. The ether was removed, and the residue was distilled to give 4.4 g (70 %) of oxazole **3**, b.p. 120–121 °C (3 Torr). Found (%): C, 75.89; H, 10.04; N, 6.28. $C_{13}H_{21}NO$. Calculated (%): C, 75.36; H, 10.14; N, 6.76. The aqueous solution was alkalized, and the precipitate that formed was separated to give 0.2 g of compound **2**, m.p. 183–184 °C; there was no depression of m.p. when it was mixed with an authentic sample.

B. 100 % HCOOH (25 g, 0.543 mol) and HCOONH₄ (10 g, 0.212 mol) were added to ketone **1** (5 g, 19.2 mmol). The mixture was stirred for 6 h at 105–110 °C, cooled, poured into water, extracted with ether, and dried with Na₂SO₄. Distillation gave 2.77 g (71 %) of oxazole **3**, b.p. 120–121 °C (3 Torr).

Transformation of oxazole 3 into imidazole 2. A solution of oxazole 3 (1.42 g, 6.8 mmol) in HCONH₂ (5 mL, 0.126 mol) and H₂SO₄ (0.5 mL) was heated for 6 h at 150 °C. The solution was cooled, diluted with water, and extracted with ether. The aqueous layer was alkalized, and the precipitate that formed was isolated to give 0.65 g of compound 2, m.p. 183–184 °C, and the picrate, m.p. 159–160 °C. No depression of m.p. was observed when it was mixed with an authentic sample.

4,5-Decamethyleneimidazolone-2 (4). Aqueous ammonia (30 %, 10 mL) was slowly added with stirring to a mixture of ketone 1 (6 g, 23 mmol), AcOH (60 mL, 1.05 mol), and urea

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(6 g, 0.1 mol). The mixture was boiled for 2.5 h, cooled, poured into water (200 mL), and left overnight. The white precipitate that formed was filtered off and washed with water and ether to give 1.92 g (40 %) of imidazolone **4**, m.p. 305-306 °C (ethanol). Found (%): C, 69.11; H, 9.93; N, 12.70. C₁₃H₂₂N₂O. Calculated (%): C, 70.00; H, 9.90; N, 12.56. IR, v/cm⁻¹: 1669 (C=O).

4,5-Decamethyleneisoxazole (6). A solution of 2-formylcyclododecanone (5) (3.1 g, 150 mmol) in dry AcOH (20 mL) and NH₂OH \cdot HCl (1.38 g, 20 mmol) were boiled for 6 h under argon. The reaction mixture was cooled, poured into 5 % NaOH, and extracted with CH₂Cl₂. The solvent was removed, and the residue was distilled to give 2 g (65 %) of compound **6**, b.p. 118–120 °C (1 Torr), m.p. 47–48 °C (pentane). Found (%): C, 74.67; H, 10.47; N, 6.81. C₁₃H₂₁NO. Calculated (%): C, 75.36; H, 10.14; N, 6.76.

2-Cyanocyclododecanone (7). Compound **6** (1.2 g, 6 mmol) in dry benzene (12 mL) was added to a solution of MeONa obtained from Na (0.17 g, 7.4 mmol) in methanol (6 mL). The mixture was stirred for 20 h and poured onto ice. The benzene layer was separated and extracted with 3 % NaOH (6×7 mL). The combined alkaline extracts were acidified with conc. HCl. The solid precipitate that formed was extracted with ether. The ether was removed, and the precipitate was recrystallized from pentane to give 1.02 g (84 %) of compound 7, m.p. 96–97 °C. Lit. data:⁹ m.p. 97–98 °C.

Brassilic acid (8). A mixture of compound 7 (0.5 g, 2.4 mmol) and a solution of KOH (1 g, 18 mmol) in water (1 mL) and ethanol (5 mL) was boiled for 8 h, diluted with water, and extracted with ether. The aqueous layer was acidified with HCl. The precipitate that formed was filtered off, repeatedly washed with water, dried *in vacuo* at 80 °C, and recrystallized from toluene to give 0.5 g (90 %) of acid 8, m.p. 111-112 °C. Lit. data:⁸ m.p. 112.5-113 °C.

4,5-Decamethylenepyrazole (9). A solution of $NH_2NH_2 \cdot HCl (0.5 g, 10 mmol)$ in ethanol (5 mL) was gradually added to compound **5** (2 g, 9.5 mmol) in ethanol (10 mL). The mixture was heated for 2 h at 70–75 °C. The ethanol was removed *in vacuo*. The residue crystallized on storage. 1.1 g (56 %) of pyrazole **9** was obtained, m.p. 81–82 °C (pentane). Found (%): C, 75.73; H, 10.60; N, 13.55. $C_{13}H_{22}N_2$. Calculated (%): C, 75.72; H, 10.68; N, 13.60. The picrate was also isolated, m.p. 174–175 °C (ethanol). Found (%): C, 54.25; H, 5.71; N, 16.88. $C_{19}H_{23}N_5O_6$. Calculated (%): C, 54.67; H, 5.51; N, 16.78.

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