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SYNTHESIS OF 1, 2-DIAZABICYCLO [4.4.0] DECANE AND ITS DERIVATIVES

E. E. Mikhlina, N. A. Komarova, and M. V. Rubtsov

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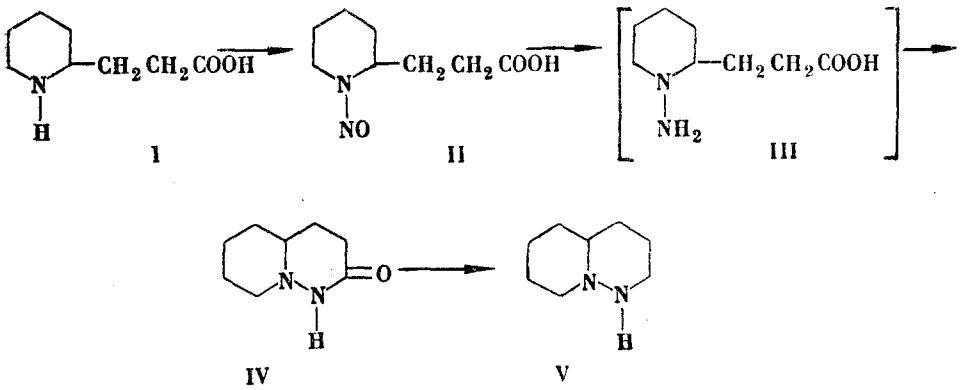
A new heterocyclic system, 1, 2-diazabicyclo [4.4.0] decane is synthesized, starting from β-(piperidyl-2) propionic acid. The latter is converted to β-(1-nitrosopiperidyl-2)-propionic acid, and thence, via β-(1-aminopiperidyl-2) propionic acid, to 3-keto-1, 2-diazabicyclo [4.4.0] decane. Derivatives of 1, 2-diazabicyclo [4.4.0] decane with a substituent at position 2 are prepared.

Up to the present results regarding the synthesis of 1, 2-diazabicycloalkanes* have been lacking in the literature There are, at one and the same time, cyclic derivatives of hydrazine, and representatives of azabicyclic systems, among which are found compounds of marked biological activity.

We worked out a method of synthesizing 1, 2-diazabicyclo [4.4.0]-decane (V) according to the following equations:



The starting compound for the synthesis of V was β-(piperidyl-2)-propionic acid (I), which, in the form of its hydrochloride, was nitrosated with sodium nitrite. The resultant β-(1-nitrosopiperidyl-2)-propionic acid (II) was reduced with zinc dust and dilute acetic acid at 30-60°, to give β-(1-aminopiperidyl-2) propionic acid (III), and under such conditions, no appreciable reductive deamination of the acid III was observed. Without isolating the latter it was heated under reduced pressure. Splitting-out of water from III to give 3-keto-1, 2-diazabicyclo [4.4.0] decane (IV), begins even at 60°, and when the technical mixture is heated at 100°, it is complete in a short time. The structure of the bicyclic hydrazide IV is confirmed by analysis and IR spectrum data (presence of absorption bands characteristic of the NH link and lactam group). Reduction of the hydrazide IV gives 1, 2-diazabicyclo [4.4.0] decane (V). The IR spectrum of the latter exhibits one band characteristic of the NH group. Compounds IV and V are readily acetylated by acetic anhydride or acetyl chloride. 2-Acyl derivatives of 1, 2-diazabicyclo [4.4.0] decane are reduced by lithium aluminum hydride to 2-alkyl derivatives. Heating V with formaldehyde and formic acid to prepare 2-methyl-1, 2-diazabicyclo [4.4.0] decane, led to complete resinification of the reaction products. Compound V readily reacts with sodium formaldehyde bisulfite and sodium cyanide. The resultant 2-cyanomethyl-1, 2-diazabicyclo [4.4.0]-decane (VI) is reduced by lithium aluminum hydride to 2-(β-aminoethyl)-1, 2-diazabicyclo [4.4.0] decane (VII), from which is obtained 2-(β-guanidinoethyl[-1, 2-diazabicyclo [4.4.0] decane (VIII).

When V is hydrogenated at 100°/30 atm using Raney nickel, N-N bond scission and formation of 2-(γ-aminopropyl) piperidine are observed, and utilizing the reaction with formaldehyde and formic acid, the latter is converted into 1-methyl-2-(γ-dimethylaminopropyl)-piperidine. We have applied the plan described here, for synthesizing 1, 2-diazabicyclo [4.4.0] decane (V), to the preparation of other 1, 2-diazabicyclic systems, and this will form the subject of subsequent papers.

Experimental

β-(1-Nitrosopiperidyl-2) propionic acid (II). 4.3 g (0.062 mole) $NaNO_2$ in 16 ml water was added over an hour

*When our work was complete, a paper appeared describing the synthesis of 1, 2-diazabicyclo 2.2.2 octane, and some of its substitution products [1].

to a solution of 10 g (0.052 mole) β-(piperidyl-2) propionic acid hydrochloride in 18 ml water held at 70°. The reaction mixture was kept acid to congo red by periodically adding 2H HCl. It was kept for a further 2 hr at 70°, cooled, and extracted with $CHCl_3$. The $CHCl_3$ solution gave 6.9 g (71.8%) II, colorless crystals, readily soluble in alcohols, $CHCl_3$, sparingly soluble in ether and water, mp 79-81°. Found: C 51.56; H 7.60; N 15.15%. Calculated for $C_8H_{14}N_2O_3$: C 51.60; H 7.58; N 15.04%.

3-Keto-1, 2-diazabicyclo [4.4.0] decane (IV). 24 ml 85% AcOH was added in 2 hr to a stirred suspension of 8.82 g (0.047 mole) II and 18.3 (0.28 g at) Zn dust in 76 ml water, the temperature being held at 25-30°, after which the mixture was held at 60° for 2 hr, cooled, the unreacted Zn filtered off, and washed with water. The bulked filtrates were evaporated under reduced pressure (15-20 mm). At the end of the distillation the temperature was raised to 100°, and the mixture held there for 2 hr. The solid reaction product was dissolved in water, made alkaline, and extracted with $CHCl_3$, to give 6 g (82.2%) IV as colorless crystals, readily soluble in water, ethanol, $CHCl_3$, sparingly soluble in benzene, insoluble in ether. MP 149-151°. IR spectrum: 1670 cm^{-1} (NH). Found: C 62.30; H 9.11; N 18.24%. Calculated for $C_8H_{14}N_2O$: C 62.30; H 9.15; N 18.17%.

1, 2-Diazabicyclo [4.4.0] decane (V). 7g (0.045 mole) IV was added to a suspension of 3.45 g (0.091 mole) $LiAlH_4$ in 100 ml dry benzene and 60 ml dry ether. The mixture was stirred and refluxed for 20 hr, cooled, and treated with 7 ml water. The hydroxides were filtered off and washed with benzene. 5.4 g (84.7%) V was obtained as a mobile colorless liquid, rapidly darkening in air. Bp 104-106° (33 mm). IR spectrum: 3300 cm^{-1} (NH). Found: N 19.76%. Calculated for $C_8H_{16}N_2$: N 19.98%.

Hydrochloride, colorless crystals, mp 149-151° (ex Me_2CO). Found: Cl 20.45; N 15.70%. Calculated for $C_8H_{16}N_2 \cdot HCl$: Cl 20.06; N 15.85%.

2-Acetyl-3-keto-1, 2-diazabicyclo [4.4.0] decane. 1 g (0.0065 mole) IV and 10 ml Ac_2O were refluxed together for 6 hr, then the soltuion was evaporated under reduced pressure, treated with 50% K_2CO_3 solution, and extracted with $CHCl_3$. The $CHCl_3$ solution was dried over K_2CO_3, evaporated under reduced pressure, and the solid residue recrystallized from petrol ether, to give 0.9 g (70.8%) colorless needles, mp 61-63°. Found: C 60.93; H 8.09; N 14.36%. Calculated for $C_{10}H_{16}N_2O_2$: C 61.20; H 8.22; N 14.28%.

2-Acetyl-1, 2-diazabicyclo [4.4.0] decane. 3.5 g (0.025 mole) V and 25 ml Ac_2O were heated together for 2 hr on a water bath. The solution was evaporated, made alkaline, and extracted with ether, to give 4 g (87.9%) compound forming a colorless mobile liquid, rapidly darkening on standing. Bp 145-147° (11 mm). Found: C 65.97; H 9.49; N 15.39%. Calculated for $C_{10}H_{18}N_2O$: C 65.90; H 9.95; N 15.37%.

2-Propionyl-1, 2-diazabicyclo [4.4.0] decane. 1.5 g (0.016 mole) propionyl chloride was added to a solution of 1.5 g (0.0107 mole) V in 15 ml dry benzene. The mixture was allowed to stand at room temperature for 36 hr, refluxed for 3 hr, cooled, 10 ml water added, and the unreacted propionyl chloride extracted with ether. The aqueous solution was made alkaline with K_2CO_3, and extracted with ether, to give 0.6 g (28.6%) compound as a colorless mobile liquid, readily soluble in organic solvents, sparingly soluble in water, bp 122-123° (1 mm). Found: C 67.56; H 10.09; N 14.44%. Calculated for $C_{11}H_{20}N_2O$: C67.31; H 10.26; N 14.29%.

2-Benzoyl-1, 2-diazabicyclo [4.4.0] decane. 2 g (0.014 mole) benzoyl chloride was added to a solution of 2 g (0.014 mole) V in 20 ml dry pyridine. The reaction mixture was stirred for 5 hr at 20°, then the pyridine distilled off under reduced pressure, and the residue treated with 50% K_2CO_3 solution, and extracted with ether, to give 2.5 g (71.8%) of a viscous liquid, which crystallized on standing, bp 162°(0.7 mm). Found: c 73.62; H 8.00; N 11.73%. Calculated for $C_{15}H_{20}N_2O$: C 73.73; H 8.25; N 11.46%.

2-Phenylcarbamoyl-1, 2-diazabicyclo [4.4.0] decane. 0.85 g (0.0071 mole) phenyl isocyanate was added to a cooled solution of 1 g (0.0071 mole) V in 5 ml dry benzene, and the mixture left at room temperature for 4 days. The diphenylurea which was precipitated (0.25 g) was filtered off with suction, and washed with benzene. The total benzene solution was evaporated, and the residue recrystallized from ether–petrol ether mixture, to give 0.4 g (21.1%) colorless crystals, readily soluble in organic solvents, insoluble in water. Mp 112-114°. Found: C 69.20; H 7.87; N 16.26%. Calculated for $C_{15}H_{21}N_3O$: C 69.47; H 8.16; N 16.21%.

2-Ethyl-1, 2-diazabicyclo [4.4.0] decane. 4 g (0.022 mole) 2-acetyl-1, 2-diazabicyclo [4.4.0] decane was reduced with 1.68 g (0.044 mole) $LiAlH_4$ in 60 ml benzene and 60 ml ether. The reaction mixture was refluxed for 18 hr. Worked up in the usual way it gave 3.3 g (89.5%) of a colorless mobile liquid having a sharp ammoniacal odor, which rapidly darkened on standing, bp 117-119° (30 mm). Found: C 70.99; H 11.68; N 16.88%. Calculated for $C_{10}H_{20}N_2$: C 71.37; H 11.97; N 16.64%.

2-Benzyl-1, 2-diazabicyclo [4.4.0] decane. $LiAlH_4$ reduction of 1.75 g (0.071 mole) 2-benzoyl-1, 2-diazabicyclo [4.4.0] decane gave 1.2 g (72.7%) compound as a viscous liquid soluble in the usual organic solvents, insoluble in water, bp 162-163°(7 mm). Found: C 78.32; H 9.56; N 11.87%. Calulated for $C_{15}H_{22}N_2$: C 78.21; H 9.62; N 12.16%

2-Cyanomethyl-1, 2-diazabicyclo [4.4.0] decane (VI). 5 g (0.035 mole) V, followed by a solution of 1.92 g (0.039 mole) NaCN in 7 ml water, was added to 19 ml 27.8% solution of Na fomaldehyde bisulfite warmed to 45°. The mixture was stirred at 50-55° for 3 hr, cooled, and extracted with $CHCl_3$, the extract dried over Na_2SO_4, evaporated, and the residue distilled, to give 2.47 g (38.6%) colorless mobile liquid, readily soluble in organic solvents, sparingly soluble in water, bp 112-114° (8 mm). Found: C 67.26; H 9.75; N 23.44%. Calculated for $C_{10}H_{17}N_3$: C 67.00; H 9.56; N 23.43%.

Hydrochloride, colorless crystals, mp 154-156° (ex Me_2CO). Found: Cl 16.57; N 19.54%. Calculated for $C_{10}H_{17}N_3 \cdot HCl$: Cl 16.43; N 19.50%.

Picrate, colorless crystals, mp 151-152° (decomp, ex EtOH). Found: C 47.27; H 4.97; N 20.56%. Calculated for $C_{10}H_{17}N_3 \cdot C_6H_3N_3O_7$: C 47.05; H 4.94; N 20.58%.

2-(β-Guanidinoethyl)-1, 2-diazabicyclo [4.4.0] decane (VIII). 2.2 g (0.012 mole) VI was reduced with 1.5 g (0.039 mole) $LiAlH_4$ in a mixture of 40 ml ether and 50 ml benzene, to give 1.67 g (74.2%) VII, a colorless mobile liquid, readily soluble in water and organic solvents, bp 143-145° (12 mm). Found: C 64.85; H 11.59; N 22.74%. Calculated for $C_{10}H_{21}N_3$: C 65.52; H 11.54; N 22.92%.

2-(β-Guanidinoethyl)-1,2-diazabicyclo [4.4.0] decane (VIII). A solution of 1.4 g (0.0076 mole) VII and 1.06 g (0.012 mole) S-methylisothiourea in 8 ml 50% EtOH was stirred and refluxed for 6 hr, the reaction products evaporated, and triturated with Me_2CO, to give 1.7 g (81%) VIII, as colorless crystals, readily soluble in water, less soluble in EtOH, insoluble in Me_2CO and benzene. Mp 205-207° (decomp). Found: S 6.05, 6.26%. Calculated for $C_{11}H_{23}N_5 \cdot 1/2\,H_2SO_4$: S 5.94%.

2-(γ-Aminopropyl) piperidine. 2.2 g (0.0157 mole) V, 1 g Raney nickel, and 50 ml EtOH were heated together under an initial H_2 pressure of 30 atm, for 5 hr, the mixture cooled, the catalyst filtered off, and the residue distilled under reduced pressure, to give 1.1 g (49.4%) of a colorless mobile liquid, bp 106-108° (14 mm), n_D^{20} 1.4888. Found: N 19.82%. Calculated for $C_8H_{18}N_2$: N 19.69%.

1-Methyl-2-(γ-dimethylaminopropyl) piperidine. 0.7 g (0.005 mole) 2-(γ-aminopropyl) piperidine, 1.4 g 35% formaldehyde solution (0.016 mole), and 2.07 g (0.045 mole) formic acid were heated together on a water bath for 18 hr, formation of a considerable quantity of resin being observed. The solution was then evaporated under reduced pressure, made alkaline with K_2CO_3, and extracted with ether, to give 0.3 g (31.6%) of a colorless mobile liquid, bp 120-123° (2 mm), n_D^{20} 1.4735. Found: C 71.60; H 12.90; N 15.52%. Calculated for $C_{11}H_{24}N_2$: C 71.67; H 13.12; N 15.20%.

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Ordzhonikidze All-Union Pharmaceutical Chemistry Scientific Research Institute, Moscow