SYNTHESIS OF 1, 2-DIAZABICYCLO [2.2.2] OCTANE, 1, 2-DIAZABICYCLO [3.2.1]-OCTANE, AND THEIR DERIVATIVES

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1, 2-Diazabicyclo [2.2.2] octane, its 6-methyl homolog, and 1, 2-diazabicyclo [3.2.1] octane are synthesized by a general method involving nitrosation of piperidine carboxylic acids, subsequent reduction to 1-aminopiperidine carboxylic acids, cyclization to 3-keto-1, 2-diazabicycloalkanes, reduction of the latter to 1, 2-diazabicycloalkanes. A number of 2-substituted 1, 2-diazabicyclo [2.2.2] octanes are synthesized.

In a previous communication [1] we described a synthesis of 1, 2-diazabicyclo [4.4.0] decane, one of the representatives of the previously unknown 1, 2-diazabicycloalkanes. Continuing research on the series, we have effected a synthesis of 1, 2-diazabicyclo [2.2.2] octane, its isomer 1, 2-diazobicyclo [3.2.1] octane and some of their derivatives. These compounds were prepared by a general method which we previously used to synthesize 1, 2-diazabicyclo [4.4.0] decane [1]. This scheme for synthesis of 1, 2-diazabicyclo [2.2.2] octanes is represented by the following series of conversions:

\[
\begin{array}{c}
\text{COOH} \\
\text{I} \\
\text{R} \\
\text{NH} \\
\hline
\text{NO} \\
\text{II} \\
\text{R} \\
\hline
\text{COOH} \\
\text{III} \\
\text{R} \\
\text{NH_2} \\
\hline
\text{IV} \\
\text{O} \\
\text{V} \\
\end{array}
\]

1-Nitrosoisonipecotinic acid (IIa), prepared from isonipecotinic acid (Ia), is reduced by zinc in acetic acid at 25-35°C to 1-aminonipecotinic acid (IIIA). A higher temperature promotes reductive deamination of the amino acid IIIa. Without being isolated this latter is converted, by heating in a vacuum, to 3-keto-1, 2-diazabicyclo [2.2.2]-octane (IVa). The process of splitting off water starts at 180-200°C, and proceeds more completely at 250-255°C. Formation of IVa is also observed when ethyl 1-aminonipecotinic acid (XI) is heated to 250°C. However, the reaction is accompanied by marked resinification, and the yield of IVa is considerably lower (25-30%) than by cyclizing the appropriate amino acid IIIa (55-57%). Introduction of a methyl group at position 2 in the piperidine ring lowers the temperature of cyclization. Thus, 1-aminono-2-methylisonipecotinic acid (IIIb) prepared by the same method, is converted at 210-220°C to 3-keto-6-methyl-1, 2-diazabicyclo [2.2.2] octane (IVb).

The cyclic hydrazide IVa forms salts with mineral acids, and quaternary salts with alkyl halides, and it is acylated with acetic anhydride, and by benzoyl chloride. Reduction of IVa and IVb by lithium aluminum hydride gives 1, 2-diazabicyclo [2.2.2] octane (Va), and its 6-methyl homolog (Vb).

Similar transformations based on nipecotinic acid (VI) were effected. Nitrosation of VI under the usual conditions gives 1-nitrosonipecotinic acid (VII). VII was reduced with zinc-acetic acid at 20-25°C, raising the temperature to 30-35°C facilitated deamination, to give the 1-aminonipecotinic acid (VIII). Cyclization of VIII to 3-keto-1, 2-diazabicyclo [3.2.1] octane (IX) took place at a higher temperature (260-270°C) than in the previous cases. The total yield of IX was 17%. The indicated yield of cyclic hydrazine IX could not be raised by varying the conditions for reduction of VII or for cyclization of VIII. IX gives 1, 2-diazabicyclo [3.2.1] octane (X), and its N-benzoyl derivative.

2-Nitroso-2, 2-acyl-, and 2-alkyl (aralkyl)-1, 2-diazabicyclo [2.2.2] octane were synthesized from Va. The latter readily undergoes the Mannich reaction with formaldehyde and phthalimide, and with formaldehyde sodium bisulfite and sodium cyanide, and it adds acrylonitrile. Introduction of powerful electron-accepting substituents (nitroso, diphenylacetyl, phthalimidomethyl groups) at position 2 in V, deprives the compounds of their basic properties (hydrochlorides not formed).

2-Cyanomethyl-1, 2-diazabicyclo [2.2.2] octane was converted successively to 2- (β-aminomethyl)- and 2-(β-
guanidoethyl)-1,2-diazabicyclo[2.2.2]octane. The 2-(β-cyanoethyl derivatives gives 2-(β-carboxyethyl)-1,2-diazabicyclo[2.2.2]octane.

Ethyl 1-aminoisonipecotinate (XI), prepared from acid IIa, was converted by reaction with aromatic aldehydes to the benzal derivatives (XII), while the acyl derivatives (XIII) were synthesized by treating it with the acid chlorides.

Experimental

1-Nitroso-2-methylisonipecotinic acid (IIb). A solution of 4.35 g (0.063 mole) NaN₃ in 15 ml water, was added to a solution of 10 g (0.055 mole) 2-methylisonipecotinic acid hydrochloride in 16 ml water at 70°C. An acid reaction to congo red was maintained by periodically adding 2 N HC₁. The reaction mixture was held for 2 hr at 70°C, cooled, and extracted with CH₂Cl₂, to give 7.8 g (81.2%) IIb, colorless crystals, mp 108-110°C (ex benzene). Found: C 48.80; H 6.88; N 16.01%. Calculated for C₁₀H₁₇N₂O₆: C 48.88; H 7.02; N 16.27%.

1-Nitroisonipecotinic acid (VII). Nitrosation of 37 g (0.22 mole) nipecotinic acid hydrochloride as described above, gave 9.3 g (39%) VII. Colorless crystals, mp 104-106°C (ex benzene). Found: C 45.50; H 6.36; N 17.68%. Calculated for C₁₀H₁₅N₂O₃: C 45.56; H 6.87; N 17.71%.

8-Keto-1,2-diazabicyclo[2.2.2]octane (IVa). 80 ml 85% AcOH was added to a suspension of 20 g (0.127 mole) 1-nitrosoisonipecotinic acid and 50.5 g (0.8 g at) Zn dust in 175 ml water, at 25-80°C. The mixture was held at the latter temperature for 2 hr more, filtered, and the solution evaporated under reduced pressure. After removing AcOH and water, the residue was heated at 5-10 mm for 1 hr 30 min at 250-255°C (Wood's metal bath). The reaction products were dissolved in water, made alkaline with K₂CO₃, and extracted with CH₂Cl₂, to give 9.1 g (57%) IVa, as colorless crystals, readily soluble in CH₂Cl₂ and water, sparingly soluble in benzene, AcOEt, Me₂CO. Mp 171-178°F (ex benzene). Found: C 57.14; H 7.94; N 22.20%. Calculated for C₁₀H₁₅N₂O: C 57.12; H 7.98; N 22.20%.

Hydrochloride. Colorless crystals, mp 220-222°F (decomp, ex EtOH). Found: Cl 22.10; N 17.53%. Calculated for C₁₀H₁₅N₂O·HCl: Cl 21.80; N 17.23%.

Methiodide. Colorless crystals, mp 214-215°C (decomp, ex EtOH). Found: I 47.79; N 10.49%. Calculated for C₁₀H₁₅N₂O·HCl: I 47.33; N 10.44%.

3-Keto-1,2-diazabicyclo[2.2.2]octane (IVa). 80 ml 85% AcOH was added to a suspension of 20 g (0.127 mole) 1-nitrosoisonipecotinic acid and 50.5 g (0.8 g at) Zn dust in 175 ml water, at 25-80°C. The mixture was held at the latter temperature for 2 hr more, filtered, and the solution evaporated under reduced pressure. After removing AcOH and water, the residue was heated at 5-10 mm for 1 hr 30 min at 250-255°C (Wood's metal bath). The reaction products were dissolved in water, made alkaline with K₂CO₃, and extracted with CH₂Cl₂, to give 9.1 g (57%) IVa, as colorless crystals, readily soluble in CH₂Cl₂ and water, sparingly soluble in benzene, AcOEt, Me₂CO. Mp 171-173°C (ex benzene). Found: C 57.14; H 7.94; N 22.20%. Calculated for C₁₀H₁₅N₂O: C 57.12; H 7.98; N 22.20%.

Hydrochloride. Colorless crystals, mp 220-222°C (decomp, ex EtOH). Found: Cl 22.10; N 17.53%. Calculated for C₁₀H₁₅N₂O·HCl: Cl 21.80; N 17.23%.

Methiodide. Colorless crystals, mp 214-215°C (decomp, ex EtOH). Found: I 47.79; N 10.49%. Calculated for C₁₀H₁₅N₂O·HCl: I 47.33; N 10.44%.

3-Keto-6-methyl-1,2-diazabicyclo[2.2.2]octane (IVb). 9.5 g (0.055 mole) IIb in 78 ml water was reduced with 22.5 g Zn dust and 36 ml 85% AcOH, at 25-30°C. Cyclization was effected at 210-220°C, to give 4.4 g (57%) IVb, colorless crystals, mp 111-113°C (ex benzene-petrol ether). Found: C 59.85; H 8.53; N 19.97%. Calculated for C₁₀H₁₇N₂O: C 59.97; H 8.63; N 19.98%.

3-Keto-1,2-diazabicyclo[2.2.2]octane (IVa). 10 g (0.065 mole) VII in 80 ml water was reduced with 25 g Zn dust and 40 ml 85% AcOH, at 15-20°C. Cyclization was effected at 260-270°C, to give 1.7 g (17%) IX, colorless crystals, mp 172-173°C (ex AcOEt). Found: C 57.37; H 8.17; N 22.03%. Calculated for C₁₀H₁₅N₂O: C 57.12; H 7.98; N 22.20%.

Hydrochloride: mp 172-174°F.

2-Acetyl-3-keto-1,2-diazabicyclo[2.2.2]octane. Prepared by heating together 2.4 g (0.019 mole) IVa and 15 ml Ac₂O, yield 2.75 g (84%), colorless crystals, readily soluble in ether, benzene, alcohols, sparingly soluble in petrol ether. Mp 124-126°C (ex petrol ether + benzene). Found: C 57.07; H 7.06; N 16.89%. Calculated for C₁₀H₁₅N₂O: C 57.18; H 7.19; N 16.66%.

2-Benzoyl-3-keto-1,2-diazabicyclo[2.2.2]octane. 3 g (0.024 mole) IVa, 3.35 g (0.024 mole) benzoyl