THE SYNTHESIS OF 1, 2-DIAZABICYCLO[3, 3, 1]NONANE AND 1, 9-DIAZABICYCLO-[4, 3, 0]NONANE. IV*

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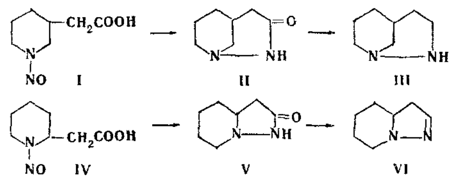
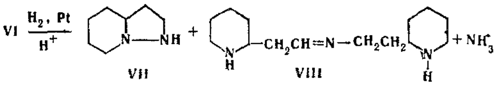
The new bicyclic systems 1, 2-diazabicyclo[3, 3, 1]nonane and 1, 9-diazabicyclo[4, 3, 0]nonane have been synthesized from 2- (and 3-) piperidineacetic acid via their nitroso-derivatives, and 3-oxo-1, 2-diazabicyclo[3, 3, 1]nonane and 8-oxo-1, 9-diazabicyclo[4, 3, 0]nonane.

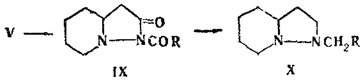
We have previously synthesized some 1, 2-diazabicycloalkanes, and examined their properties [1–3]. In continuation of this investigation, we have synthesized the new representatives of this class of compounds, 1, 2-diazabicyclo[3, 3, 1]nonane and 1, 9-diazabicyclo [4, 3, 0]nonane.

These compounds were obtained by the method used previously with success for the preparation of the other 1, 2-diazabicycloalkanes. Piperidine-3-(-2-)acetic acids were used as starting materials. These were nitrosated to give the 1-nitrosopiperidine-3-(-2-)acetic acids (I and IV), which were reduced with zinc in acetic acid to the corresponding amino compounds. On heating in vacuo, these gave 3-oxo-1, 2-diazabicyclo-[3, 3, 1]nonane (II) and 8-oxo-1, 9-diazabicyclo-[4, 3, 0] nonane (V). It is noteworthy that cyclization of 1-aminopiperidine-2-acetic acid proceeds in higher yield (66%) and at a lower temperature (220–225° C) than that of 1-aminopiperidine-3-acetic acid (yield 10.5%, 260–270° C). Reduction of the bicyclic hydrazide II with lithium aluminohydride gives 1, 2-diazabicyclo[3, 3, 1]nonane (III); under similar conditions, V was converted into 1, 9-diazabicyclo-[4, 3, 0]non-8-ene (VI). The structure of VI was confirmed by its elemental analysis and its IR spectrum. The absorption at 1568 cm^{-1} is characteristic for the C=N bond, and the NH stretching frequency band is absent. Compound VI is not reduced in neutral solution in presence of a platinum catalyst, but in acid media (glacial acetic acid, or alcoholic hydrogen chloride), hydrogen is taken up. Under these conditions the reaction is not well-defined, ammonia being evolved and two substances being formed; 1, 9-diazabicyclo[4, 3, 0] nonane (VII), and a second compound, apparently 2, 2'-piperidylethylideneaminoethylpiperidine (VIII). The structure of VIII follows from its elemental analysis, molecular weight, and the formation of a dihydrochloride and a dibenzoyl derivative.



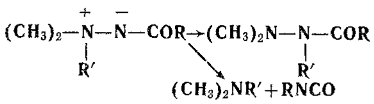


In view of the poor yield of VII obtained by the method described, its 9-derivatives were obtained by the lithium aluminohydride reduction of the 9-acyl derivatives of 8-oxo-1, 9-diazabicyclo[4, 3, 0]nonane (IX).



IX, X a R=CH_3; b R=C_6H_5

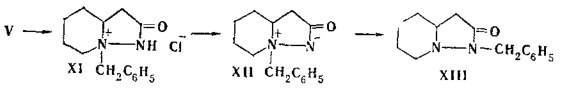
In addition to the conversion of V described above, we have studied the Wawsonek rearrangement in this series, and also in the 3-oxo-1, 2-diazabicyclo[2, 2, 2]-octane series. It is known that, on heating aliphatic aminoimides, the benzoyl group undergoes N → N migration [4]. A similar rearrangement is observed in the pyrrolizidine derivatives (R' = $CH_2C_6H_5$) [5]. When R' = CH_3, fission of the N—N bond



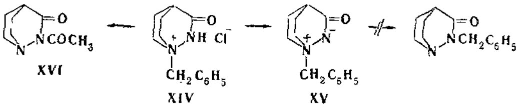
$$(CH_3)_2\text{—}\overset{+}{N}(R')\text{—}\overset{-}{N}\text{—}COR \rightarrow (CH_3)_2N\text{—}N(R')\text{—}COR \qquad \searrow (CH_3)_2NR' + RNCO$$

occurs with the formation of tertiary amines and isocyanides [6].

Compound V readily forms a quaternary salt (XI) with benzyl chloride, and this on treatment with an equimolar amount of caustic alkali is converted into the internal salt (XII). Brief heating of the tricyclic aminoimide XII above its melting point affords 8-oxo-9-benzyl-1, 9-diazabicyclo[4, 3, 0]nonane (XIII). Consequently, as in the case of the aliphatic and monocyclic aminoimides, the Wawsonek rearrangement proceeds with ease.



With the bicyclic aminoimide (XV), a similar N → N migration of the benzoyl group does not occur, apparently owing to steric factors. The internal salt XV, obtained from 1-benzyl-3-oxo-1, 2-diazabicyclo-[2, 2, 2]octanium chloride (XIV), was converted on heating into an oil, from which no pure compounds were obtained.



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*For Part III, see [3].

On heating the quaternary salts XI and XIV with acetic anhydride, dealkylation occurs readily with loss of benzyl chloride; in both cases the acyl derivatives of the corresponding hydrazides are formed. The rate of reaction of XIV was appreciably greater than that of XI, which probably indicates that here also spatial factors are involved, the attacking group in XIV being more readily able to reach the reacting center.

EXPERIMENTAL

1-Nitrosopiperidine-3-acetic acid (I). To a solution of 30 g (0.167 mole) of piperidine-3-acetic acid hydrochloride in 36 ml of water was added at 40° C a solution of 11.5 (0.167 mole) of sodium nitrite in 36 ml of water. The solution was kept acid to Congo red by addition of 2N HCl. The reaction mixture was stirred for 1 hr at 40° C, cooled, and extracted with chloroform. The chloroform extract was dried over magnesium sulfate, evaporated, and the residue recrystallized from a mixture of benzene and light petroleum to give 23.85 g (83.3%) of **I** as colorless crystals, readily soluble in water, alcohol, and benzene, but sparingly soluble in ether; mp 72–73°. Found, %: C 49.00; H 6.73; N 16.08. Calculated for $C_7H_{12}N_2O_3$ %: C 48.83; H 7.02; N 16.26.

1-Nitrosopiperidine-2-acetic acid (IV). Obtained in a similar way to **I**, from piperidine-2-acetic acid hydrochloride. Yield 88%, mp 103–106° C (from light petroleum-benzene). Found, %: C 49.03; H 7.00; N 16.51%. Calculated for $C_7H_{12}N_2O_3$, %: C 48.83; H 7.02; N 16.26.

3-Oxo-1, 2-diazabicyclo[3, 3, 1]nonane (II). To a suspension of 10 g (0.058 mole) of **I** and 25.25 g (0.386 mole) of zinc dust in 88 ml of water was added 40 ml of 85% acetic acid (0.566 mole) during 1.5 hr at 25–30° C. The reaction mixture was stirred at 35–40° C for a further 2 hr, cooled, unreacted zinc dust filtered off, and the acid solution evaporated in vacuo. The residue was heated in vacuo at 260–270° C (10 mm) for 1 hr. The cooled reaction mixture was dissolved in 30 ml of water, basified with a 50% solution of potassium carbonate and extracted with chloroform. After removal of the chloroform, the residue was recrystallized from ethyl acetate, giving 0.85 g (10.5%) of **II** as colorless crystals, readily soluble in alcohol, acetone, chloroform and water, but insoluble in ether; mp 134–136° C. IR spectrum; 3190 cm^{-1} (NH); 1656 cm^{-1} (CO—N). (Infrared absorption spectra were taken on a UR-10 recording infrared spectometer. Crystalline solids were examined as pastes in vaseline oil (7.4–13μ), and liquids as thin layers (0.01–0.02 mm).) Found, %: C 60.01; H 8.23; N 19.98. Calculated for $C_7H_{12}N_2O$, %; C 59.97; H 8.62; N 19.98. **Methiodide,** mp 243–245° (decomp., from a mixture of methanol). Found, %: I 44.96; N 10.08. Calculated for $C_8H_{15}IN_2O$, % I 44.98; N 9.93.

8-Oxo-1, 9-diazabicyclo[4, 3, 0]nonane (V). 10.5 g (0.061 mole) of **IV** in 90 ml of water was reduced with 26.4 g (0.405 mole) of zinc dust and 42 ml of 85% acetic acid (0.6 mole), as described above. The resulting 1-aminopiperidine-2-acetic acid was heated in vacuo at 220–225° C (12 mm) for 1 hr., to give 5.65 g (66%) of **V** as colorless crystals, mp 100–103° C (from ethyl acetate). IR spectrum: 3180 cm^{-1} (NH); 1705 cm^{-1} (CO–N). Found, %: C 59.88; H 8.45; N 20.12. Calculated for: $C_7H_{12}N_2O$, % C 59.97; II 8.62; N 19.98.

1-Benzyl-8-oxo-1, 9-diazabicyclo[4, 3, 0]nonanium chloride (XI). A solution of 1 g (0.0071 mole) of **V** and 0.9 g (0.0071 mole) of benzyl chloride in 10 ml of acetone was boiled for 8 hr. The resulting precipitate was filtered off, and washed with acetone to give **XI** in quantitative yield as colorless crystals, readily soluble in water, sparingly in alcohol, and insoluble in acetone and ether. The melting point (167–170°) was lowered on recrystallization from alcohol, as a result of loss of hydrogen chloride, with partial formation of the internal salt. Found, %: C 62.75; H 7.46; Cl 13.32. Calculated for: $C_{14}H_{19}ClN_2O$, %: C 63.03; H 7.17; Cl 13.28.

1, 2-Diazabicyclo[3, 3, 1]nonane (III). To a suspension of 1.65 g (0.043 mole) of lithium aluminohydride in 40 ml of ether and 40 ml of dioxane was added during 20 min 2 g (0.0143 mole) of **II**. The reaction mixture was stirred at the boil for 18 hr, cooled, and treated with 4 ml of water. The inorganic salts were filtered off and washed with ether. The combined solutions were evaporated, and the residue sublimed in vacuo at 70–80° C (2 mm). The hygroscopic crystals thus obtained were dissolved in ether, and the picrate precipitated, mp 179–180° C (from alcohol). Found, %: C 43.46; H 4.84; N 19.92. Calculated for $C_7H_{19}N_2 \cdot C_6H_3N_3O_7$, %: C 43.94; H 4.82; 19.71.

1, 9-Diazabicyclo[4, 3, 0]non-8-ene (VI). To a suspension of 3.8 g (0.1 mole) of lithium aluminohydride in 150 ml of ether was added a solution of 7 g (0.05 mole) of **V** in 150 ml of benzene. The reaction was carried out as described above, giving 3.6 g (58.5%) of **VI** as a colorless, mobile liquid with a strong ammoniacal odor, readily soluble in water and organic solvents; bp 78–79° C (22 mm), n_D^{20} 1.4935. IR spectrum: 1568 cm^{-1} (C=N). Found %: C 67.50; H 9.73; N 22.40. Calculated for $C_7H_{12}N_2$, %: C 67.74; H 9.72; N 22.58.

Reduction of 1, 9-diazabicyclo[4, 3, 0]non-8-ene. To a solution of 3.3 g (0.0266 mole) of **VI** in 45 ml of ethanol was added 20% alcoholic hydrogen chloride until acid to Congo red, followed by 0.2 g of platinum oxide. The mixture was shaken until no more hydrogen was taken up, the platinum black filtered off, the alcohol removed in vacuo and the residue treated with 50% potassium carbonate solution and extracted with ether. Evolution of ammonia was noted. The residue after removal of the ether was twice fractionated in vacuo. The first fraction was a colorless, mobile liquid, bp 93–95° C (20 mm), which proved to be 1, 9-diazabicyclo[4, 3, 0]nonane (**VII**). IR spectrum: 3300 cm^{-1} (NH). Found, %: C 66.20; H 10.96; N 21.78. Calculated for $C_7H_{14}N_2$, %: C 66.66; H 11.11; N 22.22. The second fraction was a greenish, viscous liquid boiling at 142–144° C (2 mm), and was apparently 2-(piperidyl-2') acetal-aminoethylpiperidine (**VIII**), IR spectrum: 3310 cm^{-1} (NH); 1665 cm^{-1} (C =N). Found %: C 71.10; H 11.45; N 17.72; M 242.1. Calculated for $C_{14}H_{27}N_3$, %: C 70.83; H 11.46; N 17.70; M 237.39 (molecular weights were determined by the thermoelectric method in benzene). Dihydrochloride, mp 230-232°C (from acetone-alcohol). Found, %: C 53.99; H 9.49; Cl 22.95. Calculated for $C_{14}H_{27}N_3 \cdot 2HCl$, %: C 54.17; H 9.42; Cl 22.87.

8-Oxo-9-acetyl-1, 9-diazabicyclo[4, 3, 0]nonane (IXa). A) One gram (0.0071 mole) of **V** and 10 ml of acetic anhydride were boiled for 5 hr. The reaction mixture was evaporated in vacuo, the residue dissolved in 10 ml of water, 15 ml of 50% potassium carbonate added, and extracted with chloroform. The residue after removal of the chloroform was triturated with ether, giving 0.9 g (69%) of **IXa** as colorless crystals, readily soluble in organic solvents and in water, mp 119–121° C (from ethyl acetate). IR spectrum: 1715 cm^{-1}, 1745 cm^{-1} (NCO; $NCOCH_3$). Found, %: C 59.71; H 7.66; H 15.43. Calculated for $C_9H_{14}N_2O_2$, %: C 59.31; H 7.73; N 15.37.

B) One gram (0.0037 mole) of **XI** and 1.15 g (0.01 mole) of acetic anhydride were boiled for 2.5 hr. The reaction mixture was evaporated in vacuo, the residue triturated with ether and the solid filtered off and washed with ether, to give 0.45 g of recovered **XI**. The ethereal solutions were evaporated in vacuo, and the residue triturated with light petroleum and filtered to give 0.18 g of **IXa**, mp 119–121° C (from ethyl acetate). The compound gave no depression of melting point on admixture with a sample of material obtained by method (A). Found, %: C 59.50; H 7.50; N 15.26. Calculated for $C_9H_{14}N_2O_2$, %: C 59.31; H 7.73; N 15.37.

8-Oxo-9-benzoyl-1, 9-diazabicyclo[4, 3, 0]nonane (IXb). To a solution of 3 g (0.021 mole) of **V** and 2.16 g (0.021 mole) of triethylamine in 30 ml of benzene was added with stirring and cooling a solution of 3 g (0.021 mole) of benzoyl chloride in 15 ml of benzene. The reaction mixture was stirred at room temperature for 4 hr, and at the boil for 4 hr. The triethylamine hydrochloride was filtered off, and the benzene solution was evaporated in vacuo to give 2.7 g (51.6%) of **IXb**, mp 108–111° C (from benzene-light petroleum). Found, %: C 68.87; H 6.33; N 11.46. Calculated for $C_{14}H_{16}N_2O_2$, %: C 68.83; H 6.60; N 11.47.

9-Ethyl-1, 9-diazabicyclo[4, 3, 0]nonane (Xa). To a suspension of 1.18 g (0.031 mole) of lithium aluminohydride in 30 ml of ether was added with stirring a solution of 1.25 g (0.0069 mole) of **IXa** in 30 ml of benzene. The reaction was carried out as above, to give 0.85 g (80.5%) of **Xa** as a colorless, mobile liquid, readily soluble in water and organic solvents, bp 91–93° C (25 mm). Found, %: C 69.40; H 11.42; N 18.33. Calculated for: $C_9H_{18}N_2$, %: C 70.07; H 11.76; N 18.16%.

9-Benzyl-1, 9-diazabicyclo[4, 3, 0]nonane (Xb). 1.71 g (0.007 mole) of **IXb** was reduced with 1.2 g (0.032 mole) of lithium aluminohydride in a mixture of 30 ml of benzene and 30 ml of ether. There was obtained 0.8 g (53.2 %) of **Xb** as a colorless, viscous liquid, bp 118–120° C (1 mm). Found, %: C 77.80; H 9.38; N 12.97. Calculated for $C_{14}H_{20}N_2$, %: C 77.73; H 9.32; N 12.95.

1-Benzyl-8-oxo-1,9-diazabicyclo[4,3,0]nonanium hydroxide, internal salt. To a solution of 1.5 g (0.0056 mole) of **XI** in 20 ml of methanol was added a solution of 0.22 g (0.0055 mole) of sodium hydroxide in 5 ml of methanol. The sodium chloride which separated was filtered off, the methanol removed in vacuo, the residue dissolved in 10 ml of anhydrous acetone, filtered, and diluted with 10 ml of ether. After 24 hr, 1.15 g (88.8 %) of the internal salt **XII** separated as colorless crystals, readily soluble in water and alcohol, but insoluble in ethyl acetate and acetonitrile. Mp 151–154° C (from acetone). Found, %: C 67.70; H 8.03; N 11.63. Calculated for $C_{14}H_{18}N_2O$, %: C 67.71; H 8.12; N 11.28.

8-Oxo-1,9-diazabicyclo[4,3,0]nonane (XIII). 2.1 g of **XII** was heated for 1 hr at 160–170° C. The cooled reaction mixture was extracted with ether, the ethereal solution dried over potassium carbonate, and the residue distilled in vacuo to yield 1.1 g (52.5 %) of a colorless, viscous liquid, readily soluble in organic solvents, but sparingly so in water. Bp 150–152° C (0.4 mm). IR spectrum: 1695 cm^{-1} (CO—N). Found, %: C 72.73; H 7.80; N 12.17. Calculated for: $C_{18}H_{18}N_2O$, %: C 73.01; H 7.88; N 12.16.

1-Benzyl-3-oxo-1,2-diazabicyclo[2,2,2]octanium chloride (XIV). A solution of 3 g (0.024 mole) of 3-oxo-1,2-diazabicyclo[2,2,2]octane and 3 g (0.024 mole) of benzyl chloride in 15 ml of acetone was boiled for 14 hr. The precipitate (1.73 g) which separated was filtered off, the acetone solution evaporated in vacuo, and the residue triturated with ether, giving a further 3.75 g of the quaternary salt. Yield 5.48 g (90.5%) of **XIV**, colorless crystals, soluble readily in water and alcohol, but sparingly in acetone, and insoluble in ether. Mp 189–191° C. Found, %: C 61.60; H 6.80; Cl 14.34; N 11.43. Calculated for: $C_{13}H_{17}ClN_2O$, %: C 61.78; H 6.78; Cl 14.02; N 11.08.

1-Benzyl-3-oxo-1,2-diazabicyclo[2,2,2]octanium hydroxide, internal salt (XV). To a solution of 1.6 g (0.0063 mole) of **XIV** in 10 ml of methanol was added a solution of 0.25 g (0.0062 mole) of sodium hydroxide in 5 ml of methanol. The sodium chloride was filtered off, the methanolic solution evaporated in vacuo, and the residue dissolved with heating in a mixture of acetone and ethanol. The solution obtained was filtered to remove the turbidity, evaporated, and the residue triturated with ether. Yield 1.35 g (98%), mp 233–235° C (decomp.). Found, %: C 71.78; H 7.30. Calculated for $C_{13}H_{16}N_2O$, %: C 72.19; H 7.45.

3-Oxo-2-acetyl-1,2-diazabicyclo[2,2,2]octane (XVI). Two grams (0.008 mole) of **XIV** and 2.4 g (0.236 mole) of acetic anhydride were boiled for 4 hr. The solution was evaporated in vacuo, and the residue triturated with ether, affording 1.2 g (90%) of **XVI**, mp 121–124° C (from benzene-light petroleum). Found, %: C 57.51; H 7.00; N 16.39. Calculated for: $C_8H_{12}N_2O_2$, %: C 57.13; H 7.19; N 16.65.

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