AZACYCLOALKANES.

XIV. SYNTHESIS AND SOME REACTIONS OF 1,4-DIAZABICYCLO[4,m,0]ALKANES*

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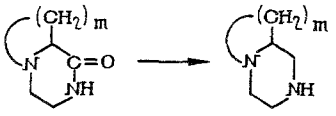
In [2] we proposed a new comprehensive method for preparing 1,4-diazabicyclo[4, m, 0]-alkanones (Ia-c). In the present article, we will describe the reduction of the amide group in lactams (Ia-c) to form condensed piperazine systems (IIa-c).



I where a) m = 3
b) m = 4
c) m = 5

II

The reduction was carried out with lithium aluminum hydride in absolute ether with a yield of 70-80% or, to avoid the use of ether when the process is carried out on a large scale, in triethylamine with a yield of 65%.

The compounds (IIa-c) obtained by the reduction, which contain a NH group in their structure, were then used for carrying out various reactions characteristic of secondary aliphatic amines. In the case of 1,4-diazabicyclo[4, 3, 0]nonane (IIa), we investigated reactions such as alkylation and acylation, and also the reaction with α,β-unsaturated carbonyl compounds (see reaction scheme).

Since it is known that many piperazine derivatives have physiological activity and that some are used as drugs [3], the specific synthesis examples were selected so as to provide substances for which one form of pharmacological activity or other could be expected owing to the presence of certain functional groups in them. (See scheme on following page.)

Compound (IIa) readily undergoes alkylation and acylation reactions. Thus, when it was treated with a mixture of formaldehyde and 85% formic acid, we obtained from (IIa) its N-methyl derivative of (III), and when the amine (IIa) is heated with ethyl γ-bromobutyrate, we obtain ethyl γ-(1,4-diazabicyclo[4, 3, 0]nonan-4-yl)butyrate (VI). Under mild conditions (in methanol at room temperature), the amine (IIa) can be alkylated with ethylene oxide to form the hydroxyethyl derivative (V). Acylation of amine (IIa) with benzoyl chloride or trimethoxybenzoic acid under Schotten–Baumann conditions or in the presence of excess base to bind the hydrogen chloride leads to the formation of the corresponding amides (VIa) and (VIb).

By reaction of amine (IIa) with acrylic acid derivatives, the corresponding addition products are obtained in high yield. Thus, heating amine (IIa) with methyl acrylate leads to the formation of N-(β-methoxycarbonylethyl)-1,4-diazabicyclo[4, 3, 0]nonane (VII), which

*See [1] for communication XIII.

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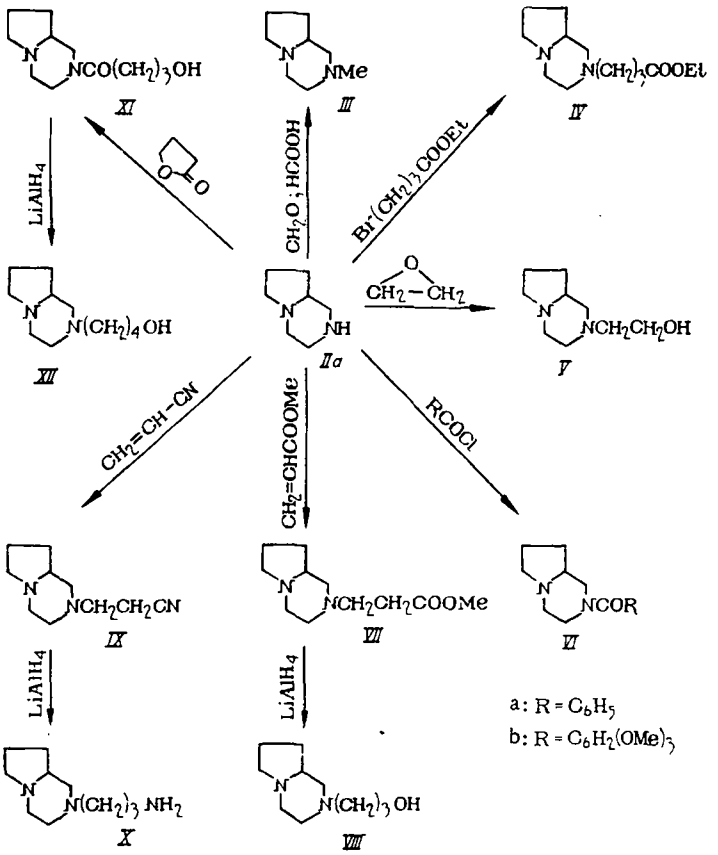

was reduced with lithium aluminum hydride to the corresponding hydroxypropyl derivative (VIII). Cyanoethylation of amine (IIa), which takes place at room temperature, gives the nitrile (IX), which can be reduced with lithium aluminum hydride to form the aminopropyl derivative (X).

Reaction of amine (IIa) with γ-butyrolactone at 100° followed by reduction of the N-(γ-hydroxybutyryl)-1,4-diazabicyclo[4, 3, 0]nonane (IX) formed with lithium aluminum hydride gives the hydroxybutyl derivative (XII).

The amides (VIa) and (VIb) synthesized in the course of the work, the series of homologous amine alcohols (V), (VII) and (XII), and also amine (X) were examined for neurotropic activity using a pharmacological screening program. The tests were performed on white mice. We investigated the effect of the compounds on spontaneous motor activity, on the duration of narcosis induced by intravenous injection of sodium thiopental in a dose of 30 mg/kg, and on spasms and tremors induced by the subcutaneous administration of corazol (120 mg/kg) or arecoline (15 mg/kg). We also evaluated the overall behavior of the animals, viz., their posture, exploratory activity, signs of changes in muscle tone, and cataleptic effects. The analgetic effect was studied by Haffner's method.

The compounds tested showed no significant neurotropic activity at doses of 20-160 mg/kg. Only an insignificant increase in the duration of sodium thiopental narcosis was noted in the case of certain mice, but this effect was not regular and appeared only when high doses of the compounds were used.

EXPERIMENTAL METHOD

1,4-Diazabicyclo[4, 3, 0]nonane (IIa). A suspension of 5 g of lithium aluminum hydride in 250 ml of absolute ether was treated with 14 g of lactam (Ia), and the mixture boiled while stirring for 12 h. When the heating was stopped, the reaction mixture was decomposed by successive dropwise addition of the following reagents while stirring: 6.7 ml of water, 3.7 ml of 20% sodium hydroxide solution, 18.9 ml of water, and 21.8 ml of 40% sodium hydroxide solution. The ether phase was decanted off, dried with sodium hydroxide, and the ether distilled off to give 10.3 g of (IIa) (82%) in the form of a colorless oil, bp 65-65.5°/10 mm, n_D^{20} = 1.4922. Found, %: C 66.50; H 11.24; N 21.96. $C_7H_{14}N_2$. Calculated %: C 66.58; H 11.17; N 22.19. The dipicrate was obtained by mixing alcoholic solutions of

the base and picric acid, mp 246-247.5° (decomp., from water). Found, %: N 19.22. $C_{19}H_{20}N_8O_{14}$. Calculated, %: N 19.18.

1,4-Diazabicyclo[4, 4, 0]decane (IIb). A suspension of 1 g of lithium aluminum hydride in 50 ml of absolute ether was treated with 2.5 g of lactam (Ib). The mixture was stirred at room temperature for 2 h, boiled for 10 h, and then decomposed by successive dropwise addition of the following reagents while stirring: 1.3 ml of water, 0.7 ml of 20% sodium hydroxide solution, 3.7 ml of water, and 4.2 ml of 40% sodium hydroxide solution. The ether phase was decanted off and the residue heated with 20 ml of ether. The combined ether extracts were dried with sodium hydroxide and the ether evaporated off to give 1.01 g of (IIb) (45%), bp 68-69°/10 mm, n_D^{20} = 1.4989. Found, %: N 19.86. $C_8H_{16}N_2$. Calculated, %: N 19.99.

1,4-Diazabicyclo[4, 5, 0]undecane (IIc). A suspension of 2.9 g of lithium aluminum hydride in 100 ml of absolute ether was treated with 8.4 g of lactam (Ic), stirred at room temperature for 2 h, and boiled for 3 h. The reaction mixture was decomposed by successively adding 4.2 ml of water, 3.9 ml of 20% sodium hydroxide solution, 7.8 ml of water, and 7.8 ml of 40% sodium hydroxide solution. The ether phase was decanted off, the residue extracted with 50 ml of ether, and the combined ether extracts dried over sodium hydroxide. The ether was evaporated off to give 6.64 g of (IIc) (87%), bp 67-68°/3 mm, n_D^{20} = 1.5062. Found, %: C 69.82; H 11.60; N 18.05. $C_9H_{18}N_2$. Calculated, %: C 70.06; H 11.76; N 18.16.

N-Methyl-1,4-Diazabicyclo[4, 3, 0]nonane (III). A mixture of 3.15 g of amine (IIa), 3.81 g of 85% formic acid and 1.2 g of 32% aqueous formaldehyde solution was boiled for 12 h. The reaction mixture was acidified to pH 1.0 with concentrated hydrochloric acid and evaporated to dryness. The residue was treated with 60% potassium hydroxide solution to pH 9.0-10.0 and extracted with chloroform. The chloroform was distilled off, and the residue was evaporated with dry benzene and distilled *in vacuo*, to give 2.56 g of (III) (73%), bp 72-73°/20 mm, d_D^{20} = 0.9221, n_D^{20} = 1.4776. Found, %: C 68.43; H 11.65; N 20.10. $C_8H_{16}N_2$. Calculated, %: C 68.55; H 11.50; N 19.99.

Ethyl γ-(1,4-diazabicyclo[4, 3, 0]nonanyl)butyrate (IV). A mixture of 5.04 g of amine (IIa) and 3.9 g of ethyl γ-bromobutyrate was heated at 80° for 15 min, extracted with ether, the ether evaporated off, and the residue distilled *in vacuo* to give 3.2 g of IV (66%), bp 114-116°/2 mm, n_D^{20} = 1.4752. Found, %: C 64.82; H 10.16; N 11.75. $C_{13}H_{24}N_2O_2$. Calculated, %: C 64.97; H 10.07; N 11.66.

N-(β-Hydroxyethyl)-1,4-Diazabicyclo[4, 3, 0]nonane (V). A mixture of methanolic solutions of 6.3 g of (IIa) and 4.4 g of ethylene oxide was kept at room temperature for 1 day, the methanol evaporated off, and the residue distilled *in vacuo* to give 4.22 g of (V) (49.6%), bp 95-96°/1 mm, n_D^{20} = 1.5034. Found, %: C 63.48; H 10.58; N 16.40. $C_9H_{18}N_2O$. Calculated, %: C 63.49; H 10.65; N 16.46.

N-Benzoyl-1,4-Diazabicyclo[4, 3, 0]nonane (VIa). A mixture of 2 g of amine (IIa) and 7.6 ml of 10% sodium hydroxide solution was treated dropwise with 3.37 g of benzoyl chloride while stirring vigorously and cooling. After treating the reaction mixture with 40% sodium hydroxide solution, the reaction product was extracted with benzene and the extract washed with 10% sodium hydroxide solution and water. The benzene was distilled off and the residue distilled *in vacuo*, the fraction with a bp of 140°/1 mm being collected. The product crystallized on standing, giving 2.34 g of (VIa) (64%), mp 84-87°. Found %: C 73.03; H 8.06; N 12.29. $C_{14}H_{18}N_2O$. Calculated, %: C 73.03; H 7.88; N 12.17.

N-(3,4,5-Trimethoxybenzoyl)-1,4-Diazabicyclo[4, 3, 0]nonane (VIb). A solution of 2.31 g of 3,4,5-trimethoxybenzoyl chloride in 13 ml of absolute benzene was added dropwise to a stirred boiling solution of 2.52 g of amine (IIa) in 12 ml of absolute benzene. The reaction mixture was boiled for 3 h, filtered on cooling, the filtrate evaporated, and the residue distilled in vacuo to give 1.59 g of (VIb) (49%), bp 203-205°/0.5 mm. The product was crystallized from absolute ether, mp 99-101°. Found, %: C 63.74; H 7.50; N 8.72. $C_{17}H_{24}N_2O_4$. Calculated, %: C 63.73; H 7.55; N 8.74.

N-(β-Methoxycarbonylethyl)-1,4-Diazabicyclo[4, 3, 0]nonane (VII). A mixture of 7.56 g of amine (IIa) and 15.48 g of methyl acrylate containing a catalytic amount of hydroquinone was boiled for 24 h, the excess methyl acrylate distilled off, and the residue evaporated with dry benzene and distilled *in vacuo* to give 10.9 g of (VII) (85.8%), bp 92-93°/2 mm, n_D^{20} = 1.4802. Found, %: C 62.20; H 9.59; N 13.39. $C_{11}H_{20}N_2O_2$. Calculated, %: C 62.24; H 9.50; N 13.20.

N-(γ-Hydroxypropyl)-1,4-Diazabicyclo[4, 3, 0]nonane (VIII). A solution of 4.24 g of amino ester (VII) in 20 ml of absolute ether was added dropwise to a stirred suspension of 1.52 g of lithium aluminum hydride in 40 ml of absolute ether. When heat evolution ceased, the reaction mixture was boiled for 0.5 h, kept at room temperature for a day, and then decomposed by successive dropwise addition of 1.5 ml of water, 1.2 ml of 20% sodium hydroxide solution and 5.3 ml of water. The mixture was heated for 0.5 h, filtered, and the filtrate dried with magnesium sulfate, evaporated, and distilled *in vacuo* to give 1.88 g of (VII) (51%), bp 99-101°/1 mm, n_D^{20} = 1.5030. Found, %: C 64.92; H 11.04; N 15.21. $C_{10}H_{20}N_2O$. Calculated, %: C 65.16; H 10.94; N 15.21.

N-(β-Cyanoethyl)-1,4-Diazabicyclo[4, 3, 0]nonane (IX). A mixture of 2.52 g of amine (IIa), 3.18 g of acrylonitrile and a catalytic amount of hydroquinone was kept at room temperature for a day, and then the excess acrylonitrile distilled off and the residue distilled *in vacuo* to give 3.05 g of (IX) (85%), bp 106-109°/1 mm, n_D^{20} = 1.4965. Found, %: N 23.50. $C_{10}H_{17}N_3$. Calculated, %: N 23.43.

N-(γ-Aminopropyl)-1,4-Diazabicyclo[4, 3, 0]nonane (X). A solution of 3.86 g of nitrile (IX) in 20 ml of absolute ether was added to a stirred suspension of 2.5 g of lithium aluminum hydride in 40 ml of absolute ether. The mixture was boiled for 0.5 h, kept at room temperature for a day, and decomposed by the successive dropwise addition of the following reagents while stirring: 2.5 ml of water, 1.9 ml of 20% sodium hydroxide solution, and 8.75 ml of water. The ether solution was decanted off, the residue extracted with ether while heating, and the ether extracts dried with magnesium sulfate, evaporated, and the residue distilled *in vacuo* to give 1.21 g of (X) (33%), bp 90-91°/1 mm, n_D^{20} = 1.4988. Found, %: C 65.21; H 11.71; N 22.96. $C_{10}H_{21}N_3$. Calculated, %: C 65.51; H 11.53; N 22.93.

N-(γ-Hydroxybutyryl)-1,4-Diazabicyclo[4, 3, 0]nonane (XI). A mixture of 2.52 g of amine (IIa) and 1.72 g of γ-butyrolactone was kept at 100° for 5 h, and then distilled *in vacuo* to give 2.96 g of (XI) (70.5%), bp 155-156°/1 mm, n_D^{20} = 1.5153. Found, %: C 62.01; H 9.47; N 13.25. $C_{11}H_{20}N_2O_2$. Calculated, %: C 62.32; H 9.50; N 13.20.

N-(δ-Hydroxybutyl)-1,4-Diazabicyclo[4,3,0]nonane (XII). A solution of 3 g of hydroxy amide (XI) in 20 ml of absolute ether was added to a stirred suspension of 1.6 g of lithium aluminum hydride in 30 ml of absolute ether. The mixture was kept at room temperature for a day, boiled for 10 h, and decomposed by successive dropwise addition of 1.6 ml of water, 1.2 ml of 20% sodium hydroxide solution, and 5.6 ml of water. The mixture was boiled for 1 h, the ether phase decanted off, and the residue extracted with ether. The combined extracts were dried with magnesium sulfate, evaporated, and the residue distilled to give 2.26 g of (XII) (81.6%), bp 120-121°/1 mm, n_D^{20} = 1.4998. Found, %: C 66.40; H 11.19; N 14.32. $C_{11}H_{22}N_2O$. Calculated, %: C 66.61; H 11.18; N 14.13.

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