SYNTHESIS OF 1-AZABICYCLO[3.2.2]NONAN-4-ONE

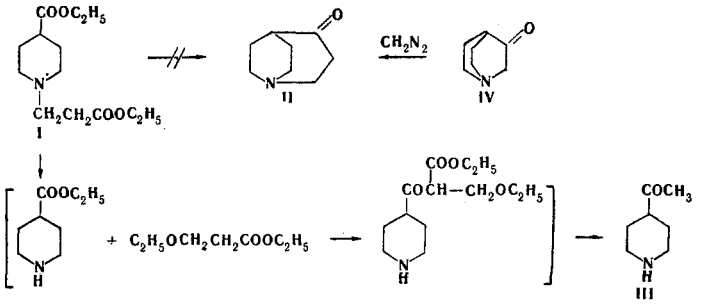
V. Ya. Vorob'eva, E. E. Mikhlina, K. F. Turchin
and L. N. Yakhontov

UDC 547.896:541.67

The synthesis of 1-azabicyclo[3.2.2]nonan-4-one has been effected by the reaction of quinuclidin-3-one with diazomethane.

The synthesis of 1-azabicyloalkanones containing condensed six- and seven-membered rings presents considerable difficulties. This is due to the fact that in the synthesis of these compounds by the intramolecular cyclization of the corresponding piperidine diesters, i.e., by the method used successfully for the production of a large number of other 1-azabicyclic ketones, the thermodynamically more favorable processes of intermolecular polycondensation acquire a predominating nature. Apparently, the low yield (0.7%) of 1-azabicyclo[3.2.2]nonan-3-one from the cyclization of 1,4-di(methoxycarbonyl)piperidine [1] is due to the factor mentioned above.

We have shown that in connection with the difficulty of intramolecular cyclization and the closure of a seven-member ring starting from piperidine derivatives, in the case of compounds of this type not only intermolecular polycondensation but also other processes take place. Thus, for example, the reaction of 4-ethoxycarbonyl-1(β-ethoxycarbonylethyl)piperidine with potassium ethoxide gave 4-acetylpiperidine (III). Its structure was confirmed by its identity with the product described in the literature [2], and also by its conversion into the oxime and its reduction to 4-(α-hydroxyethyl)piperidine. The formation of 4-acetylpiperidine is probably connected with the following reactions: the dealkylation of the initial diester with the splitting out of ethyl acrylate, nucleophilic addition of an ethoxy group to the latter, Claisen condensation of the ethyl β-ethoxypropionate and ethyl isonipecotinate with the subsequent hydrolytic cleavage of the 4-(α-ethoxycarbonyl-β-ethoxypropionyl)piperidine to 4-acetylpiperidine.



In view of this, for the synthesis of 1-azabicyclo[3.2.2]nonan-4-one (II) it appeared to us that it was desirable to start from quinuclidin-3-one (IV), making use of ring expansion by the reaction of IV with diazomethane. The reaction mentioned was performed with equivalent amounts of reactants, and also using 20, 50 and 100% excesses of diazomethane. The composition of the reaction products was monitored by

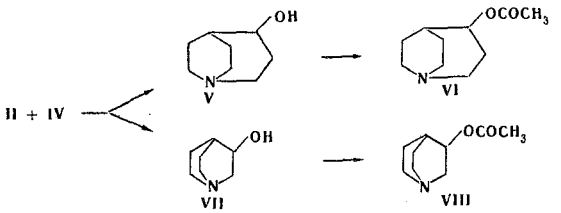
Ordzhonikidze All-Union Scientific-Research Institute of Pharmaceutical Chemistry, Moscow. Translated from Khimiya Geterotsiklicheskikh Soedinenii, Vol. 6, No. 8, pp. 1037-1040, August, 1970. Original article submitted May 5, 1969.

GLC*. In the first case we isolated a mixture of the initial quinuclidin-3-one (IV) and of 1-azabicyclo-[3.2.2]nonan-4-one (II) in a ratio of 1 : 1 (for proof of the position of the oxo group see below). The isomeric 3-oxo derivative was absent from the reaction products.

When the amount of diazomethane was increased (20% excess), the ratio of the ketones II and IV was 1.3 : 1 together with a small amount of a third substance, the amount of which at a 50% excess of diazomethane was found in a ratio to II and IV of 1 : 7 : 3. A twofold excess of diazomethane led mainly to byproducts apparently arising through the further opening of the ring of ketone II. The structure of these substances was not studied further.

Varying the temperature of the reaction from -15 to +20°C and its time from 30 min to 48 hr at a molar ratio of reactants did not change the yield of 1-azabicyclo[3.2.2]nonan-4-one.

It was impossible to separate the ketones II and IV either by GLC or by crystallizing their hydrochlorides or picrates. The alcohols obtained by reducing the ketones were not separated, either. Crystallizing salts of the acetoxy and benzoyloxy derivatives of quinuclidin-3-ol (VII) and 1-azabicyclo[3.2.2]nonan-4-ol (V) also did not give the desired results. The separation was achieved by chromatographing a mixture of the acetoxy derivatives VI and VIII in a preparative gas-liquid chromatograph.



The pure 4-acetoxy-1-azabicyclo[3.2.2]nonane (VI) obtained was converted into 1-azabicyclo[3.2.2]-nonan-4-ol (V) by reaction with lithium aluminum hydride. The oxidation of V with chromic anhydride in dilute acetic acid gave the ketone II.

The oxidation of the azabicycloalkanols to ketones was studied for the case of quinuclidin-3-ol (VII). It was found that only the use of a threefold excess of chromic anhydride made it possible to obtain the pure ketone IV uncontaminated by the initial alcohol VII. These results were confirmed by the oxidation of the alcohol V.

The structure of the substances II, V, and VI obtained was established by means of their PMR spectra. In contrast to quinuclidin-3-one (IV), which has the singlet signal at 3.10 ppm characteristic for the NCH_2-CO grouping [3] in the PMR spectrum of II there is no singlet in this region but there is an unsymmetrical triplet in a stronger field (2.47, 2.55 and 2.62 ppm) corresponding to the A_2 part of a spectrum of the A_2B_2 type, which is characteristic for the NCH_2CH_2CO grouping. The weak-field part of this spectrum (B_2) is superposed on the multiplets formed by the other methylene groups in the α position to the nitrogen with a center at 2.85 ppm.

The PMR spectrum of 4-acetoxy-1-azabicyclo[3.2.2]nonane (VI) is also in harmony with this structure for II. In the spectrum of VI, together with the singlet of the CH_3 group of the acetoxy residue (δ 1.96 ppm) there is a multiplet at δ 4.82 ppm with an intensity of 1 proton unit, which must be assigned to the proton in the α position to the acetoxy group. The signals of the other protons from two groups of multiplets, one of which – in the range from 2.50 to 3.10 ppm with a center at 2.80 ppm (intensity six proton units) – must be assigned to the methylene protons in the α position to the nitrogen, while the other group of multiplets (7 proton units) in the range from 1.35 to 2.05 ppm with a center at 1.70 ppm unites all the β protons and the methine proton at C_5. The considerable differences in the chemical shifts of these two groups of protons enabled the double resonance method to be used to answer the question of what are the groups with which the proton in the α position to the acetoxy group in VI interacts. It was found that when a saturating field with a frequency differing from the resonance frequency of this proton by 308 Hz was superposed, its signal was converted into a broadened singlet. Consequently, the chemical shift of the

*The GLC analysis was carried out on a Carlo Erba Fractovap chromatograph. The column was 2 m long, the stationary phase was 20% of E-301 elastomer on Chromosorb W, the temperature 180°C, and the rate of flow of the carrier gas (helium) 10 liters/hr.

protons with which the proton on the carbon connected with the acetoxy group interacts is approximately 1.74 ppm, which corresponds to strongly polar protons not in the α positions to the nitrogen. The imposition of a saturating field with a frequency differing from the resonance frequency for the proton with δ 4.82 ppm by 150-250 Hz did not lead to any changes whatever in the signal of this proton, which shows the absence of interaction with an appreciable constant of the proton on the carbon connected with the acetoxy group and of any of the protons in the α positions to the nitrogen. These results show that in VI the acetoxy group is located on carbon atom C_4.

EXPERIMENTAL

4-Ethoxycarbonyl-1-(β-ethoxycarbonylethyl)piperidine (I). A mixture of 21.6 g (0.138 mole) of ethyl isonipecotinate, 23.4 g (0.138 mole) of ethyl β-bromopropionate, and 13.5 g of sodium carbonate in 50 ml of ethanol was boiled for 4 hr. The reaction mixture was evaporated in vacuum and the residue was dissolved in water and extracted with ether. The extract was dried, the solvent was driven off, and the product was distilled. This gave 30.45 g (93%) of I in the form of a mobile colorless liquid readily soluble in organic solvents. bp 125-126°C (0.4 mm); n_D^{20} 1.4546. Found, %: C 60.53; H 9.25; N 5.35. Calculated for $C_{13}H_{23}NO_4$, %: C 60.67; H 9.01; N 5.44.

Reaction of 4-Ethoxycarbonyl-1(β-ethoxycarbonylethyl)piperidine with Potassium Ethoxide. At 120°C, a solution of 30.8 g (0.12 mole) of I in 75 ml of toluence was added to the potassium ethoxide prepared from 12 g (0.307 g-at.) of potassium and 18 ml (0.31 mole) of ethanol in 50 ml of toluene. The reaction mixture was boiled for 5 hr, cooled, and treated with 300 ml of concentrated hydrochloric acid. The acid solution was separated off and boiled for 16 hr. The hydrochloric acid was distilled off in vacuum and the residue was treated with 35 ml of 50% potassium carbonate solution and extracted with benzene. After the benzene had been driven off, the substance was distilled in vacuum to give 1.5 g of 4-acetylpiperidine (III) in the form of a colorless mobile liquid. bp 110°C (19 mm); n_D^{20} 1.4748 [2]. Picrate – yellow acicular crystals, mp 163-165°C (from methanol). Found, %: C 43.36; H 4.66; N 15.70. Calculated for $C_7H_{13}NO \cdot C_6H_3N_3O_7$, %: C 43.82; H 4.53; N 15.73.

4-Acetylpiperidine Oxime. A solution of 0.2 g (1.6 mmole) of the ketone III in 5 ml of ethanol was treated with 0.11 g (5.8 mmoles) of hydroxylamine hydrochloride and the reaction mixture was boiled for 4 hr. On dilution with ether, the solution deposited the hydrochloride of 4-acetylpiperidine oxime in the form of colorless crystals readily soluble in water and ethanol. mp 175-176°C (from ethanol). Found, %: Cl 19.97; N 15.96. Calculated for $C_7H_{14}N_2O \cdot HCl$, %: Cl 19.84; N 15.68.

4-(α-Hydroxyethyl)piperidine. A mixture of 2.7 g (0.021 mole) of the ketone III, 80 ml of ethanol, and 0.1 g of platinum oxide was shaken in an atmosphere of hydrogen at room temperature. After the absorption of 1 mole of hydrogen, the platinum black was filtered off, the solution was evaporated, and the residue was distilled in vacuum. Yield 2.2 g (81%), colorless viscous liquid readily soluble in water and organic solvents. bp 121-122°C (16 mm). Found, %: C 65.00; H 11.40; N 10.35. Calculated for $C_7H_{15}NO$, %: C 65.07; H 11.70; N 10.84.

Reaction of Quinuclidin-3-one with Diazomethane. In portions, 30.4 g (0.22 mole) of nitrosomethylurethane and 1.35 g of barium oxide were added to a solution of 27.5 g (0.22 mole) of quinuclidin-3-one in 70 ml of methanol at -5 to -15°C, after which it was evaporated in vacuum. The residue was dissolved in ether and the ethereal solution was saturated with hydrogen chloride, giving a voluminous precipitate. The ether was decanted off and the precipitate was washed with ether and was then treated with 50% caustic potash solution and extracted with benzene. The benzene solution was dried with potassium carbonate and evaporated in vacuum, and the residual oily crystals were sublimed at 55-60°C (1 mm). This gave 18.63 g of a mixture of quinuclidin-3-one (IV) and 1-azabicyclo[3.2.2]nonan-4-one (II) in a ratio of 1 : 1 in the form of colorless hygroscopic crystals.

Five grams of a mixture of the ketones II and IV was hydrogenated in solution in 50 ml of ethanol in the presence of 0.3 g of platinum oxide. After the absorption of 1 mole of hydrogen, the platinum black was filtered off, the ethanolic solution was evaporated in vacuum, and the residue was sublimed in vacuum (0.5 mm) at 90-100°C. This gave 4.5 g of a mixture of quinuclidin-3-ol (VII) and 1-azabicyclo[3.2.2]nonan-4-ol (V).

4.5 g of the mixture of alcohols V and VII and 20 ml of acetic anhydride were heated on the water bath for 2 hr. The solution was evaporated in vacuum and the residue was treated with 50% potassium carbonate

solution and extracted with ether. This gave 4.5 g of a colorless mobile liquid consisting of a mixture of 3-acetoxyquinuclidine (VIII) and 4-acetoxy-1-azabicyclo[3.2.2]nonane (VI) with bp 120-123°C (12 mm), which was separated in a preparative gas-liquid chromatograph of the Varian system [Aerograph Autoprep 705, column length 6 m, diameter 9 mm, Chromosorb W 80-100 mesh], stationary phase 10% of PEG-20,000, temperature 210°C, rate of flow of the carrier gas (nitrogen) 160 ml/min.

3-Acetoxyquinuclidine: bp 112-114°C (14 mm): n_D^{20} 1.4820.

4-Acetoxy-1-azabicyclo[3.2.2]nonane: bp 122-123°C (14 mm); n_D^{20} 1.4881. Found, %: C 65.56; H 9.17; N 8.06. Calculated for $C_{10}H_{17}NO_2$, %: C 65.54; H 9.35; N 7.68.

Hydrochloride: colorless crystals mp 222-224°C. Found, %: C 54.65; H 8.34; Cl 16.34; N 6.47. Calculated for $C_{10}H_{17}NO_2 \cdot HCl$. C 54.67; H 8.20; Cl 16.13; N 6.37.

Picrate: yellow crystals, mp 162-164°C. Found, %: C 46.54; H 4.99; N 13.75. Calculated for $C_{10}H_{17}NO_2 \cdot C_6H_3N_3O_7$, %: C 46.60; H 4.89; N 13.58.

1-Azabicyclo[3.2.2]nonan-4-ol (V). Over 20 min, a solution of 1.3 g (7 mmoles) of compound VI in 30 ml of benzene was added to a suspension of 0.53 g (15 mmoles) of lithium aluminum hydride in 30 ml of ether. The mixture was boiled with stirring for 3 hr, cooled, and treated with 1.2 ml of water and the inorganic precipitate was filtered off with suction and washed with benzene. The ether–benzene solution was evaporated and the residue was sublimed in vacuum (0.7 mm) at 100-110°C (bath temperature) to give 0.75 g (82%) of V. Colorless crystals readily soluble in ether, benzene, ethanol, acetone, and water, and insoluble in petroleum ether. mp 192-194°C. Found, %: C 67.94; H 10.80; N 9.97. Calculated for $C_8H_{15}NO$, %: C 68.04; H 10.77; N 9.92.

Hydrochloride: colorless crystals, mp 322-324°C (decomp.). Found, %: C 53.93; H 8.96; Cl 19.81; N 7.77. Calculated for $C_8H_{15}NO \cdot HCl$, %: C 54.09; H 9.01; Cl 20.20; N 7.89.

Picrate: Yellow crystals, mp 236-238°C. Found, %: C 45.59; H 5.18; N 15.02. Calculated for $C_8H_{15}NO \cdot C_6H_3N_3O_7$, %: C 45.40; H 4.90; N 15.12.

1-Azabicyclo[3.2.2]nonan-4-one (II). With ice-water cooling, 0.97 g (10 mmoles) of chromic anhydride in 9.7 ml of 90% acetic acid was added to a solution of 0.68 g (48 mmoles) of V in 7 ml of 90% acetic acid. The mixture was kept at room temperature for 70 hr and evaporated to 1/4 of its original volume, and the residue was made alkaline with 10 ml of 50% caustic potash solution and extracted with benzene. The benzene was driven off and the residue was sublimed in vacuum (0.9 mm) at 50-60°C (bath temperature). This gave 0.4 g (60%) of II in the form of colorless hygroscopic crystals soluble in water and organic solvents. Mp 115-118°C. Found, %: C 68.84; H 9.40; N 9.90. Calculated for $C_8H_{13}NO$, %: C 68.95; H 9.48; N 10.06. R_f 0.33; no alcohol II was present*. Hydrochloride: colorless crystals, mp 210-211°C (from a mixture of ethanol and acetone). Found, %: Cl 20.27; N 8.03. Calculated for $C_8H_{13}NO \cdot HCl$, %: Cl 20.18; N 7.96. Picrate: yellow crystals, mp 207-208°C (from ethanol). Found, %: C 45.52; H 4.19. Calculated for $C_8H_{13}NO \cdot C_6H_3N_3O_7$, %: C 45.65; N 4.38. Oxime: obtained by boiling 0.1 g of the ketone II and 0.067 g of hydroxylamine hydrochloride for 4 hr. Colorless crystals, mp 222.5-223°C (from ethanol). Found, %: C 50.22; H 7.82; Cl 18.82; N 14.91. Calculated for $C_8H_{14}N_2O \cdot HCl$, %: C 50.39; H 7.87; Cl 18.63; N 14.69.

Oxidation of Quinuclidin-3-ol. A solution of 1 g (8 mmoles) of quinuclidin-3-ol in 10 ml of 90% acetic acid was treated with 1.59 g (16 mmoles) of chromic anhydride in 16 ml of 90% acetic acid. The reaction was carried out as described above, giving 0.98 g (92%) of quinuclidin-3-one. Mp 140-142°C. Chromatography showed the absence of the initial quinuclidin-3-ol from the ketone obtained.

LITERATURE CITED

1. N. J. Leonard, J. M. Carry, and J. J. Sagura, J. Am. Chem. Soc., 75, 6249 (1953).
2. A. T. Nielsen, D. W. Moore, J. H. Mazur, and K. H. Berry, J. Org. Chem., 29, 2898 (1964).
3. E. E. Mikhlina, A. D. Yanina, V. I. Sheichenko, Yu. N. Sheinker, and M. V. Rubtsov, ZhOrKh, 2, 179 (1966).

*Here and below, chromatography was carried out on a fixed layer of silica gel with benzene–ether–diethylamine (20:15:5) as the mobile phase.