SYNTHESIS AND PROPERTIES OF 2-ETHOXYCARBONYL-3-AMINO-2,3-DEHYDROQUINUCLIDINE

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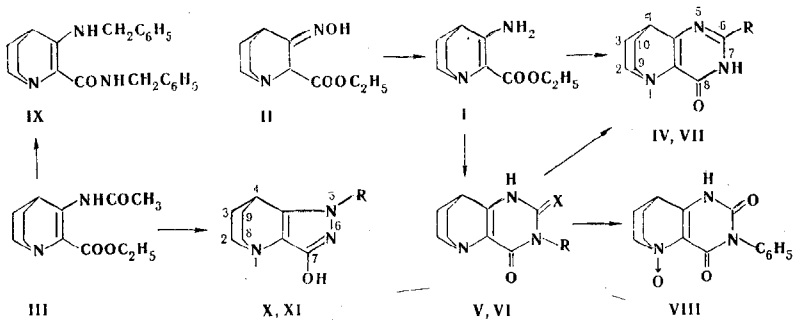
The reduction of 2-ethoxycarbonyl-3-oxoquinuclidine oxime hydrochloride leads to 2-ethoxycarbonyl-3-amino-2,3-dehydroquinuclidine, from which pyrimido[5,4-b]quinuclidine derivatives were obtained by reaction with formamide, methyl isocyanate, and phenyl isothiocyanate. It is shown that 7-hydroxypyrazolo[4,3-b]quinuclidine is formed in the reaction of 2-ethoxycarbonyl-3-acetamido-2,3-dehydroquinuclidine with hydrazine hydrate.

Heterocyclic β-enamino esters of tetrahydropyridine, dihydrothiophene, dihydropyrrole, and other heterocycles have been investigated rather extensively [1-6]. It has been established that these compounds react with mono- and bifunctional reagents to give derivatives involving the amino group or condensed systems. The previously unknown 2-ethoxycarbonyl-3-amino-2,3-dehydroquinuclidine (I) is also a heterocyclic β-enamino ester that differs from the compounds cited above in that the β-enamino ester grouping of atoms in it is included in a rigidly fixed bicyclic quinuclidine system that is virtually incapable of undergoing conformational changes, owing to which the mesomeric effect of a tertiary nitrogen atom is excluded in the molecule. It seemed of interest to synthesize amino ester I and study its properties.

We obtained I by reduction of 2-ethoxycarbonyl-3-oxoquinuclidine oxime hydrochloride (II) [7] in the presence of a platinum catalyst (Adams) at 20°C in glacial acetic acid or ethanol. In the case of hydrogenation of oxime II in 1 N hydrochloric acid we obtained 3-oxoquinuclidine hydrochloride; this was a consequence of hydrolysis of the ester and oxime groups and decarboxylation of the resulting β-keto acid.

Amine I does not react with acetyl chloride, and 2-ethoxycarbonyl-3-acetamido-2,3-dehydroquinuclidine (III) is formed when it is refluxed in acetic anhydride. We were unable to realize the N-benzoylation of amine I by heating it with benzoyl chloride in pyridine.



IV, X R=H; V X=O, R=CH_3; ~~VI~~ X=S, R=C_6H_5; VII R=OCH_3; XI R=$COCH_3$

The structures of I and III were confirmed by the PMR spectra. The character of the multiplicity of the protons of the methylene groups in the 6 and 7 positions of the quinuclidine ring — two (rather than four) octets with nonoverlapped components — indicates the paired equivalence of the protons in these groups, evidently as a consequence of the presence of a plane of symmetry in the molecule. This is possible only in the case of a double bond between the $C_{(2)}$ and $C_{(3)}$ atoms of the quinuclidine ring, which is confirmed by the absence in the spectra of I and III of any signals that could be assigned to the protons attached to

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the $C_{(2)}$ or $C_{(3)}$ atom. A peculiarity of the PMR spectrum of III is the significant weak-field shift of the 4-H signal as compared with this signal in the spectrum of I; this is evidently due to the effect of the spatial closeness of the 4-H proton and the acetyl group in acetamido ester III.

A study of the reactions of I and III with several amines and bifunctional reagents gave the following results. When amine I is heated with formamide at 180-190°C, it is converted to 8-oxo-7,8-dihydropyrimido[5,4-b]quinuclidine (IV); upon prolonged reaction with methyl isocyanate in pyridine in the presence of catalytic amounts of tin octoate, it is converted to 6,8-dioxo-7-methyl-5,6,7,8-tetrahydropyrimido[5,4-b]quinuclidine (V), whereas it is converted to 6-thioxo-7-phenyl-8-oxo-5,6,7,8-tetrahydropyrimido[5,4-b]quinuclidine (VI) upon reaction with phenyl isothiocyanate. As a result of the treatment of VI with equal quantities of methyl iodide and sodium hydroxide in methyl alcohol, followed by treatment with the 6-methylthio derivative, we obtained 6-methoxy-7-phenyl-8-oxo-7,8-dihydropyrimido[5,4-b]quinuclidine VII. The thioxo group in VI is readily removed by reaction with hydrogen peroxide, but in this case one also observes oxidation of the nitrogen atom of the quinuclidine ring and the formation of 6,8-dioxo-7-phenyl-5,6,7,8-tetrahydropyrimido[5,4-b]quinuclidine 1-oxide (VIII).

It should be noted that, as compared with the analogous reactions of other heterocyclic β-enamino esters, the described reactions of I, evidently as a consequence of the inductive effect of the nodal nitrogen atom of the quinuclidine ring, required more severe conditions, viz., prolonged (10-35 h) heating at 100-190°C and, in a number of cases, the use of a catalyst, viz., tin octoate.

N-Acetyl derivative III is also characterized by low reactivity. At temperatures up to 150°C III does not react with thiourea, aniline, or phenylhydrazine, and only destruction of the starting substance and resinification are observed when the temperature is raised. The reaction of III with benzylamine, which is realized by prolonged (30 h) refluxing of the reagents, is accompanied not only by conversion of the ester group to a benzylamido group but also by transamination with replacement of the acetamido grouping by a benzylamino grouping and the formation of 3-benzylamino-2,3-dehydroquinuclidine-2-carboxylic acid benzylamide (IX). 7-Hydroxypyrazolo[4,3-b]quinuclidine (X) was obtained in high yield in the reaction of III with hydrazine hydrate, which also requires rather severe conditions. This compound was formed evidently either as a result of hydrolytic splitting out of the acetamido group and subsequent reaction of 2-ethoxycarbonyl-3-oxoquinuclidine with hydrazine hydrate [8] or via transamination of III to give 2-ethoxycarbonyl-3-oxoquinuclidine hydrazone with cyclization of the latter.

The structures of IV-XI are in good agreement with data from the IR and PMR spectra and the results of elemental analysis. In particular, the PMR spectrum of IV contains a singlet of a proton at 8.44 ppm, which is characteristic for the CH group in the pyrimidine ring; the signals of the protons of the substituents of the pyrimidine and pyrazole rings of V-VII and IX-XI, as well as the signals of the protons of the quinuclidine ring of these compounds, confirm the proposed structures. Just as for III, a significant shift of the proton attached to the $C_{(4)}$ atom to weak field as compared with other quinuclidine derivatives (4.2 instead of 3.1 ppm) is characteristic for XI: this is evidently a consequence of the effect of the spatially close acetyl group [8]. As a consequence of the presence of a plane of symmetry in the molecules, the α and β protons of the quinuclidine ring are equivalent in pairs in all of the compounds.

EXPERIMENTAL

The IR spectra of mineral oil suspensions of the compounds were recorded with a Perkin-Elmer 457 spectrometer. The PMR spectra were recorded with a Varian-100A spectrometer with tetramethylsilane as the internal standard.

2-Ethoxycarbonyl-3-amino-2,3-dehydroquinuclidine (I). A solution of 25 g (0.1 mmole) of 2-ethoxycarbonyl-3-oxoquinuclidine oxime hydrochloride (II) in 750 ml of glacial acetic acid was shaken with hydrogen in the presence of 1 g of platinum oxide, during which one equivalent of hydrogen was absorbed. The platinum black was removed by filtration, the acetic acid was removed by vacuum distillation, and the residue was dissolved in 50 ml of water. The aqueous solution was made alkaline with 50% potassium carbonate solution and extracted with chloroform. The extract was evaporated in vacuo, and the residue was triturated with acetone to give 14.7 g (75%) of a product with mp 175-177°C (from acetone). IR spectrum: 1630, 1685 ($C{=}C{-}COOC_2H_5$); 3400 cm^{-1} (NH). PMR spectrum (d_6-DMSO): 2.23, 2.78 (4H, m, 6- and 7-H); 1.45-1.65 (4H, 5- and 8-H); 2.61 (1H, quintet, 4-H); 1.18 (3H, t, CH_3); 3.99 (2H, q,

CH_2O): 6.25 ppm (2H, broad s, NH_2). Found: C 61.2; H 8.1; N 14.2%. $C_{10}H_{16}N_2O_2$. Calculated: C 61.2; H 8.2; N 14.3%. The hydrochloride had mp 225-226°C (dec.). Found: C 51.4; H 7.2; Cl 14.9; N 12.2%. $C_{10}H_{16}N_2O_2 \cdot HCl$. Calculated: C 51.6; H 7.4; Cl 15.2; N 12.0%.

2-Ethoxycarbonyl-3-acetamido-2,3-dehydroquinuclidine (III). A mixture of 2 g (10 mmole) of I and 20 ml of acetic anhydride was refluxed for 6 h, after which the excess acetic anhydride was removed by vacuum distillation, and the residue was treated with 25% potassium carbonate solution and extracted with chloroform. The solvent was removed, and the residue was triturated with ether to give 1.6 g (66%) of a product with mp 107-109°C (from heptane). IR spectrum: 1660 (C=C), 1690 (CON—), and 3300 cm^{-1} (NH). PMR spectrum ($CDCl_3$): 2.64, 3.02 (4H, m, 6- and 7-H); 1.65-1.75 (4H, 5- and 8-H); 4.37 (1H, quintet, 4-H); 1.34 (3H, t, CH_3); 4.30 (2H, q, CH_2O); 2.16 (3H, s, CH_3N); 10.5 ppm (1H, broad s, NH). Found: C 60.6; H 7.7; N 11.8%. $C_{12}H_{18}N_2O_3$. Calculated: C 60.5; H 7.6; N 11.8%. The hydrochloride had mp 181-182°C (dec., from acetone). Found: Cl 12.8; N 10.2%. $C_{12}H_{18}N_2O_3 \cdot HCl$. Calculated: Cl 12.9; N 10.2%.

8-Oxo-7,8-dihydropyrimido[5,4-b]quinuclidine (IV). A mixture of 1 g (5.1 mmole) of I and 10 ml of formamide was heated at 180-190°C (bath temperature) for 10 h, after which the mixture was evaporated in vacuo, and the residue was triturated with anhydrous ethanol to give 0.47 g (52%) of a product with mp 288-290°C (from 90% ethanol). PMR spectrum (C_5D_5N): 2.63, 3.02 (4H, m, 2- and 9-H); 1.50-1.75 (4H, 3- and 10-H); 3.12 (1H, quintet, 4-H); 8.44 ppm (1H, s, 6-H). Found: C 60.7; H 6.2; N 23.8%. $C_9H_{11}N_3O$. Calculated: C 61.0; H 6.3; N 23.7%. The hydrochloride had mp 213-215°C. Found: Cl 16.5%. $C_9H_{11}N_3O \cdot HCl$. Calculated: Cl 16.6%.

6,8-Dioxo-7-methyl-5,6,7,8-tetrahydropyrimido[5,4-b]quinuclidine (V). A 3-ml sample of methyl isocyanate and two drops of tin octoate were added to a solution of 2 g (10 mmole) of I in 20 ml of dry pyridine, and the mixture was heated at 100°C for 35 h. It was then evaporated in vacuo, and the residue was treated with 20% potassium carbonate solution and extracted with chloroform. The solvent was removed by distillation, and the residue was triturated with heptane to give 0.4 g (18.8%) of a product with mp 275-277°C (from ethyl acetate—ethanol). IR spectrum: 1630, 1650, 1712 (C=C—CONCO); 3100 cm^{-1} (NH). PMR spectrum (CD_3OD): 2.60, 3.07 (4H, m, 2- and 9-H); 1.66, 1.94 (4H, m, 3- and 10-H); 2.96 (1H, quintet, 4-H); 3.26 ppm (3H, s, CH_3N). Found: C 57.7; H 6.3; N 20.3%. $C_{10}H_{13}N_3O_2$. Calculated: C 58.0; H 6.3; N 20.3%.

6-Thioxo-7-phenyl-8-oxo-5,6,7,8-tetrahydropyrimido[5,4-b]quinuclidine (VI). A solution of 6 g (30.6 mmole) of I and 8.32 g (61.7 mmole) of phenyl isothiocyanate in 60 ml of pyridine was refluxed for 24 h, after which it was cooled, and the precipitate was removed by filtration and washed with ether to give 2.7 g of VI. The filtrate was evaporated, and the residue was triturated with xylene. The precipitate was removed by filtration and washed with ether to give an additional 2.3 g of VI for an overall yield of 5 g (69%) of a product with mp 282-284°C [from DMF—ethanol (2:1)]. PMR spectrum (d_6-DMSO): 2.50, 2.97 (4H, m, 2- and 9-H); 1.63, 1.86 (4H, m, 3- and 10-H); 3.12 (1H, quintet, 4-H); 7.1-7.5 ppm (5H, C_6H_5). Found: C 63.2; H 5.4; N 14.4; S 10.9%. $C_{15}H_{15}N_3OS$. Calculated: C 63.1; H 5.3; N 14.7; S 11.2%. The hydrochloride had mp 248-250°C. Found: Cl 11.1; N 13.1; S 9.6%. $C_{15}H_{15}N_3OS \cdot HCl$. Calculated: Cl 11.0; N 13.1; S 10.0%.

6-Methoxy-7-phenyl-8-oxo-7,8-dihydropyrimido[5,4-b]quinuclidine (VII). A mixture of 3 g (10.4 mmole) of VI, 1.5 g (10.4 mmole) of methyl iodide, 0.42 g (10.4 mmole) of sodium hydroxide, and 60 ml of methanol was refluxed for 10 h, after which the methanol was removed by vacuum distillation. The residue was treated with 50% potassium carbonate solution and extracted with chloroform. The solvent was removed, and the residue was triturated with isopropyl alcohol to give 2.4 g (83.3%) of VII with mp 245-247°C (dec., from acetone—ethanol). PMR spectrum (CD_3OD): 2.64, 3.13 (4H, m, 2- and 9-H); 1.74, 2.03 (4H, m, 3- and 10-H); 3.08 (1H, quintet, 4-H); 3.95 (3H, s, CH_3O); 7.2-7.6 ppm (5H, C_6H_5). Found: C 67.5; H 5.7; N 14.6%. $C_{16}H_{17}N_3O_2$. Calculated: C 67.8; H 6.0; N 14.8%.

6,8-Dioxo-7-phenyl-5,6,7,8-tetrahydropyrimido[5,4-b]quinuclidine 1-Oxide (VIII). A 1.5-ml (12.5 mmole) sample of 30% hydrogen peroxide was added in the course of 5 min to a refluxing solution of 0.63 g (2.2 mmole) of VI in 50 ml of 0.5 N aqueous sodium hydroxide solution, and the mixture was refluxed for 1 h. It was then cooled, and the precipitated sodium sulfate was removed by filtration, and the solution was evaporated in vacuo. The residue was treated with 50% potassium carbonate solution and extracted with chloroform to give 0.2 g of VIII with mp 164-165°C (dec.). Found: C 63.5; H 5.4; N 14.7%. $C_{15}H_{15}N_3O_3$. Calculated: C 63.1; H 5.3; N 14.7%.

3-Benzylamino-2,3-dihydroquinuclidine-2-carboxylic Acid Benzylamide (IX). A mixture of 3 g (12.6 mmole) of III and 30 ml of benzylamine was refluxed for 30 h, after which the benzylamine was removed by vacuum distillation, and the residue was distilled. The fraction with bp 225-235°C (0.6 mm) was collected, triturated with petroleum ether, and recrystallized from petroleum ether—ethyl acetate to give 3.5 g (80%) of a product with mp 92-94°C. IR spectrum: 1600, 1623 (C=C—CO); 3310, 3340 cm^{-1} (NH). PMR spectrum ($CDCl_3$): 2.56, 2.83 (4H, m, 2- and 9-H); 1.40-1.60 (4H, 3- and 10-H); 2.87 (1H, quintet, 4-H); 7.3-7.4 (10H, C_6H_5); 8.45 (1H, broad t, NHCO); 7.25 (1H, broad t, NH); 4.47 (2H, d, CH_2NHCO); 4.43 ppm (2H, d, CH_2). Found: C 76.2; H 7.3; N 11.9%. $C_{22}H_{25}N_3O$. Calculated: C 76.0; H 7.3; N 12.1%.

7-Hydroxy-6H-pyrazolo[4,3-b]quinuclidine (X). A solution of 5 g (21 mmole) of III in 150 ml of hydrazine hydrate was refluxed for 20 h, after which water was added, and the excess hydrazine hydrate was removed by vacuum distillation. The resulting precipitate was removed by filtration and washed with ethanol to give 3.4 g (100%) of a product with mp 289-290°C (dec.) [8]. The dihydrochloride had mp 201-202°C (dec., from methanol—ethanol). PMR spectrum (D_2O): 3.11, 3.52 (4H, m, 2- and 8-H); 1.76, 2.17 (4H, m, 3- and 9-H); 3.32 ppm (1H, quintet, 4-H). Found: C 40.2; H 5.4; Cl 29.6; N 17.5%. $C_8H_{11}N_3O \cdot 2HCl$. Calculated: C 40.3; H 5.5; Cl 29.8; N 17.7%.

5-Acetyl-7-hydroxypyrazolo[4,3-b]quinuclidine (XI). A solution of 1.15 g (7 mmole) of X in 12 ml of acetic anhydride was refluxed for 2 h, after which it was evaporated in vacuo, and the residue was treated successively with ice water and 50% potassium carbonate solution and extracted with chloroform. The chloroform solution was evaporated in vacuo, and the residue was recrystallized from 90 ml of ethanol to give 0.9 g (62%) of a product with mp 212-214°C. PMR spectrum ($CDCl_3$): 2.66, 3.21 (4H, m, 2- and 8-H); 1.55-2.05 (4H, 3- and 9-H); 4.23 (1H, quintet, 4-H); 2.60 ppm (3H, s, CH_3). Found: C 57.9; H 6.3; N 20.5%. $C_{10}H_{13}N_3O_2$. Calculated: C 58.0; H 6.3; N 20.3%.

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