REACTION OF 2-ETHOXYCARBONYL-3-OXOQUINUCLIDINE WITH NUCLEOPHILIC REAGENTS

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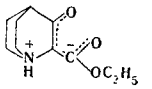
UDC 547.834.4

The quinuclidine ring in the reaction of 2-ethoxycarbonyl-3-oxoquinuclidine with nucleophilic reagents under mild conditions is cleaved at the C_2-C_3 bond to give 1-carboxymethylisonipecotic acid and its derivatives.

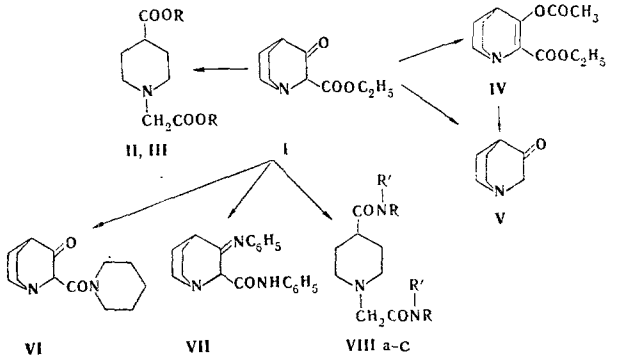
Some peculiarities of the reaction of 2-ethoxycarbonyl-3-oxoquinuclidine (I), which has a high basicity, with nucleophilic reagents have been studied. Thus, we have found that I readily undergoes acid cleavage to give 1-carboxymethylisonipecotic acid (II) on brief heating with water, or diethyl ester III on prolonged heating with alcohol. Cleavage with alcohol is accelerated by the addition of triethylamine. We have previously shown that I exists primarily as the dipolar ion in hydroxyl-containing solvents (alcohol and water) [1]. The decrease in the electron density on the $C_{(3)}$ atom in polarized molecule Ia promotes nucleo-



Ia

philic attack of the hydroxyl or alkoxy group and subsequent cleavage of the quinuclidine ring at the $C_{(2)}-C_{(3)}$ bond. The absence of this effect in aliphatic β-keto esters (for example, in acetoacetic ester) makes them resistant to heating to 100°C with water and to 180° with alcohol [2].

2-Ethoxycarbonyl-3-acetoxyl-Δ^2-dehydroquinclidine (IV), which is similar in structure to Ia but less polarized, was obtained by reaction of I with acetic anhydride at room temperature. Refluxing I with acetic anhydride gives 3-oxoquinuclidine (V), the generation of which can be explained by splitting out of an ethoxycarbonyl group in IV to give a mixed anhydride of acetic and carbonic acids. Compound IV is converted to



II R = H; III R = C_2H_5; VIII a R, R' = $C_5H_{10}N$; b R = C_6H_5, R' = H; c R = $C_6H_4OCH_3$, R' = H

3-oxoquinuclidine (V) on heating with hydrochloric acid and to a mixture of V and keto ester I on refluxing with ethanolic hydrogen chloride. The first step in the reaction of IV with an alcohol solution of hydrogen chloride is apparently conversion of IV to I as a consequence of transesterification, and the subsequent

S. Ordzhonikidze All-Union Scientific-Research Pharmaceutical Chemistry Institute, Moscow. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 8, pp. 1125-1128, August, 1974. Original article submitted August 8, 1973.

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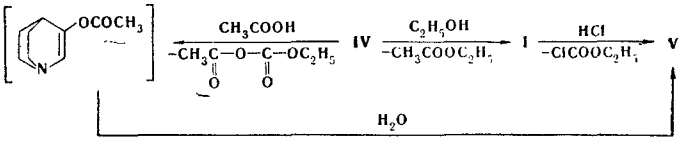
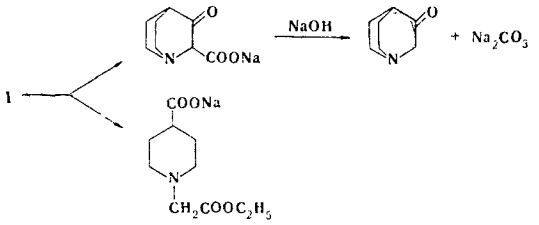
reaction of keto ester I with dry hydrogen chloride leads to splitting out of ethyl chlorocarbonate and ketone V.



A similar process is observed when keto ester I is heated with aqueous sodium hydroxide.



The prevailing reaction in this case is splitting out of a carboxyl group under the influence of sodium hydroxide to give sodium carbonate and ketone V; the quinuclidine ring is simultaneously cleaved at the $C_{(2)}-C_{(3)}$ bond to give a piperidine derivative.

Cleavage of keto ester I at the $C_{(2)}-C_{(3)}$ bond is also observed when I is heated with amines (piperidine, aniline, and p-anisidine). However, when the reaction is carried out in a large excess of amine, it proceeds in another direction to give either 3-oxoquinuclidine-2-carboxamide acid VI (with piperidine) or its 3-imino derivative (VII) (with aniline). However, in this case also, the introduction of catalytic amounts of water promotes opening of the quinuclidine ring to give diamides of 1-carboxymethylisonipecotic acid (VIII).

EXPERIMENTAL

Reaction of 2-Ethoxycarbonyl-3-Oxoquinuclidine (I).

1. With Water. A 1-g (5 mmole) sample of keto ester I was refluxed in 10 ml of water. The positive reaction with ferric chloride vanished after 2 h. At the end of the reaction, the aqueous solution was vacuum evaporated, and the residue was recrystallized from 2 ml of water to give 0.78 g (92%) of 1-carboxymethylisonipecotic acid (II) with mp 270-271° (dec.). Found: C 51.2; H 6.8%. $C_8H_{13}NO_4$. Calculated: C 51.2; H 6.9%.

2. With Ethanol. A solution of 2 g (10 mmole) of keto ester I in 10 ml of absolute ethanol was refluxed for 24 h until it no longer gave a positive reaction with ferric chloride. The alcohol was then removed by vacuum distillation, and the residue was fractionated to give 2.05 g (83.5%) of ethyl 1-ethoxycarbonylmethylisonipecotate (III). The IR spectra of the latter and of a sample obtained by the method in [3] coincided. The product had mp 143-145° (4 mm) and n_D^{20} 1.4592. Found: C 59.5; H 8.7; N 6.0%. $C_{12}H_{21}NO_4$. Calculated: C 59.2; H 8.7; N 5.8%.

The quinuclidine ring opened in 15 h when I was heated in ethanol solution in the presence of triethylamine.

3. With Aqueous Sodium Hydroxide Solution. A solution of 3 g (15 mmole) of I in 32 ml of 1 M sodium hydroxide was refluxed for 6 h until it no longer gave a positive reaction with ferric chloride. The aqueous alkaline solution was vacuum evaporated, and the residue was dried and extracted with hot benzene. The benzene was removed by distillation to give 1.3 g (68.3%) of 3-oxoquinuclidine (V), which was identical to a genuine sample. The solid material remaining after removal of 3-oxoquinuclidine was esterified by heating with 30 ml of ethanol and 3 ml of concentrated sulfuric acid to give 0.4 g (10%) of ethyl ester III, which was identical to a genuine sample according to its IR spectrum.

4. With Piperidine. A) A mixture of 3 g (15 mmole) of I and 25 ml of piperidine was refluxed for 10 h, after which the solution was vacuum evaporated, and the residue was fractionated to give 3 g (84%) of 3-oxoquinuclidine-2-carboxylic acidpiperidide (VI) with bp 167-168° (0.6 mm). Found: C 66.2; H 8.5; N 11.6%. $C_{13}H_{20}N_2O_2$. Calculated: C 66.1; H 8.6; N 11.9%. IR spectrum: 1730 (ketone C=O) and 1630 (amide C=O) cm^{-1}.

B) A solution of 2 g (10 mmole) of I and 3 ml of piperidine in 20 ml of benzene was refluxed for 10 h, after which the mixture was vacuum evaporated, and the residue was fractionated to give 1.1 g (47.6%) of

amide VI with bp 167-168° (0.6 mm). The residue remaining after removal of VI by distillation was triturated with acetone, and the mixture was filtered to give 0.6 g (19%) of 1-carboxymethylisonipecotic acid dipiperidide (VIIIa) with mp 261-262°. IR spectrum: 1630, 1700 cm^{-1} (amide C=O groups). Found: C 67.3; H 9.6; N 13.8%. $C_{18}H_{31}N_3O_2$. Calculated: C 67.2; H 9.7; N 13.7%.

5. With Aniline. A) A solution of 3 g (15 mmole) of I and 4.2 g (45 mmole) of aniline in 30 ml of benzene was refluxed for 6 h, after which it was cooled, and the precipitate was removed by filtration and washed successively with benzene and ether to give 3 g (58.5%) of 1-carboxymethylisonipecotic acid dianilide (VIIIb) with mp 249-250° (dec.). Found: C 71.5; H 6.6; N 12.0%. $C_{20}H_{23}N_3O_2$. Calculated: C 71.2; H 6.8; N 12.4%. According to the results of TLC [Silufol, acetone–benzene (1:1), development with bromthymol blue], the mother liquor remaining after separation of VIIIb contained traces of 3-phenyliminoquinuclidine-2-carboxylic acid anilide.

B) A mixture of 2 g (10 mmole) of I and 17 ml of aniline was heated at 100° for 20 h, after which it was cooled, and the resulting precipitate was removed by filtration and washed with ether to give 1.7 g of 3-phenyliminoquinuclidine-2-carboxylic acid anilide (VIIb). Evaporation of the mother liquor gave another 1 g of the same product. The overall yield of product with mp 189-191° (ethanol) was 2.7 g (84%). Found: C 75.3; H 6.5; N 13.2%. $C_{20}H_{21}N_2O$. Calculated: C 75.2; H 6.6; N 13.2%. The mother liquor contained 0.36 g of VIIIb.

C) A mixture of 1 g (5 mmole) of I and 8 ml of aniline oontaining 0.1% water was heated at 100° for 6 h, after which it was cooled, and the resulting precipitate was removed by filtration and washed successively with benzene and ether to give 1 g of a mixture containing equal amounts of VIIb and VIIIb (according to TLC); 0.3 g of the same mixture was detected in the mother liquor.

6. With p-Anisidine. A solution of 3 g (15 mmole) of I and 6.1 g (50 mmole) of p-anisidine in 30 ml of benzene was refluxed for 10 h, and the resulting precipitate was removed by filtration and washed successively with benzene and ether to give 2.5 g (41.5%) of 1-carboxymethylisonipecotic acid di(p-anisidide) (VIIId) with mp 231-233° (dec.). Found: C 66.6; H 6.6; N 10.2%. $C_{22}H_{27}N_3O_4$. Calculated: C 66.7; H 6.8; N 10.6%.

2-Ethoxycarbonyl-3-acetoxy-Δ^2-dehydroquinuclidine (IV).

A solution of 5 g (25 mmole) of I in 100 ml of acetic anhydride was stirred at room temperature for 7 h, after which the acetic anhydride was removed by vacuum distillation, and the residue was fractionated to give 4.9 g (80%) of 2-ethoxycarbonyl-3-acetoxy-Δ^2-dihydroquinuclidine (IV) with bp 110-112° (0.8 mm). Found: C 60.1; H 7.4; N 6.1%. $C_{12}H_{17}NO_4$. Calculated: C 60.2; H 7.2; N 5.8%.

Reaction of 2-Ethoxycarbonyl-3-oxoquinuclidine (I) with Boiling Acetic Anhydride

A solution of 2.5 g (12.5 mmole) of I in 50 ml of acetic anhydride was refluxed for 5 h, after which the acetic anhydride was removed by vacuum distillation, and the residue was treated with 50% potassium carbonate solution and extracted with chloroform to give 1.6 g (92.5%) of 3-oxoquinuclidine (V). The picrate had mp 210°. No melting-point depression was observed for a mixture of this product with a genuine sample [4].

Reaction of 2-Ethoxycarbonyl-3-acetoxy-Δ^2-dehydroquinuclidine (IV) with Aqueous and Ethanol Solutions of Hydrogen Chloride

A) A solution of 1 g (4.2 mmole) of IV and 10 ml of 10% hydrochloric acid was refluxed for 20 h, after which the mixture was vacuum evaporated, and the residue was triturated with acetone to give 0.62 g (92%) of 3-oxoquinclidine hydrochloride with mp 311-313° (dec., aqueous 2-propanol) [5].

B) A solution of 1 g (4.2 mmole) of IV and 10 ml of 15% ethanolic hydrogen chloride was refluxed for 12 h, after which the mixture was vacuum evaporated, and the residue was made alkaline with 50% potassium carbonate solution and extracted with benzene. The benzene was removed, and the residue was vacuum sublimed (0.6 mm) to give 0.3 g of 3-oxoquinuclidine (V). The picrate had mp 210° [4]. No melting-point depression was observed for a mixture of this product with a genuine sample. The substance remaining after sublimation of V was vacuum fractionated to give 0.4 of 2-ethoxycarbonyl-3-oxoquinuclidine (I) with bp 101-102° (0.6 mm) and mp 101-102°.

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