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reaction scheme

Figure 1: reaction scheme

Abstract

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SYNTHESIS OF 3-VINYLQUINUCLIDINE

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One of the most difficult problems in the chemistry of quinuclidine derivatives is the introduction of a vinyl group into the β-position of the quinuclidine nucleus. Czech investigators I. Ernest and R. Lukeš [(1)] showed that, with various methods for constructing such a double bond, its migration to the semicyclic position occurs and 3-ethylidenequinuclidine is formed. Despite the large number of methods tested for the synthesis of 3-vinylquinuclidine, only in one case was I. Ernest [(2)] able to introduce a vinyl group into the quinuclidine nucleus in the dehydration of 3-(β-hydroxyethyl)quinuclidine with phthalic anhydride and benzenesulfonic acid. However, in this case as well a mixture of isomeric 3-ethylidene- and 3-vinylquinuclidine was obtained, from which the latter could be isolated only by repeated recrystallization of the stifnate salts.

We have developed a preparative method for introducing a vinyl group into the β-position of the quinuclidine nucleus using the Wittig reaction.

As starting material, quinuclidone-3 (I) [(3)] was used, since β-ketoquinuclidines are accessible compounds of this series [(4)].

The synthesis of 3-vinylquinuclidine (III) is based on the conversion of quinuclidone-3 (I) into 3-formylquinuclidine (II), followed by treatment of the latter with triphenylmethylenephosphorane. The yield of pure 3-vinylquinuclidine (III) by the Wittig reaction is 65.6%. III was characterized as the base, picrate, acidic and neutral stifnates.

For further proof of the structure and characterization of the purity of the obtained 3-vinylquinuclidine, it was necessary to carry out its comparative study with 3-ethylidenequinuclidine (IV). The latter was obtained by us in 71% yield by the Wittig reaction through the interaction of quinuclidone-3 (I) with triphenylethylidenephosphorane and was likewise characterized as the base, picrate, acidic and neutral stifnates.

The IR spectra (UR-10 spectrophotometer) of III and IV coincided with the spectra described by I. Ernest [(2)] and had absorption bands characteristic respec-

Fig. 1

Figure 2: Fig. 1

tively of 3-vinylquinuclidine (910, 995, 1640 cm^{-1}) and 3-ethylidenequinuclidine (1385 cm^{-1}) (Fig. 1). IR spectroscopy proved to be the most sensitive method for analyzing the purity of the compounds obtained, allowing small admixtures of the isomeric compound to be determined by the presence or absence of characteristic bands.

The NMR spectra (INM C-60 spectrometer, solvent CCl_4, internal standard $(CH_3)_4Si$) unambiguously proved the structure of each of the isomers III and IV (Fig. 2). In the spectrum of III, the multiplet at 5.85 ppm corresponds to the signal from the methine proton at C_8, interacting with the protons at C_9 and C_2. The complex signal from the vinyl protons at C_9 at 4.9 ppm is split into the principal doublet under the influence of the proton at C_8. Signals from the β-methylene protons at C_4 and C_7 appear in the region 1.3–

1.75 ppm (4 proton units), whereas the protons located in the α-position to nitrogen (C_1, C_5, C_6), as well as the methine protons at C_2 and C_3, give signals in the region 2.2–2.95 ppm. The ratio of the number of hydrogen atoms at the double bond to the remaining hydrogen atoms of the molecule is 3:12, which also corresponds to the structure of 3-vinylquinuclidine (III).

Fig. 1. IR spectra: 1–3-vinylquinuclidine (III), 2–3-ethylidenequinuclidine (IV)

In the NMR spectrum of IV at 5.09 ppm there appears a quartet from the proton at C_8 with $I_{H8,H_9} = 7$ Hz, additionally split into triplets with $I = 2$ Hz owing to interaction with the protons at C_1. The influence of the magnetic anisotropy of the exocyclic double bond on the chemical shift of the protons at C_4 has led to displacement of their corresponding signal into the region of weaker fields (3.24 ppm); broadening of the signal is caused by interaction of the protons at C_1 and C_8 ($\Delta\nu_{1/2} = 7.5$ Hz). Multiplet signals in the regions 1.3–1.75 ppm and 2.2–2.95 ppm are assigned, respectively, to the protons at the β-carbon atoms of the quinuclidine nucleus (C_4, C_7), together with the protons at C_9, whose signal is shifted into the region of weaker field owing to the allylic character of the methyl group, and to the protons at the α-carbon atoms C_5 and C_6 and of the methine group at C_3. The ratio of the number of hydrogen atoms at the double bond to the remaining hydrogen atoms of the molecule in this case is the value 1:14, characteristic of 3-ethylidenequinuclidine. It is interesting to note that the NMR spectra of III and IV are in good agreement with the NMR spectra, described by us earlier (5), of the hydrochlorides of 3-oxy-3-vinylquinuclidine and 3-(β-chloroethylidene)quinuclidine, respectively.

Fig. 2. NMR spectra: 1–3-vinylquinuclidine (III), 2–3-ethylidenequinuclidine (IV)

Fig. 2

Figure 3: Fig. 2

The Wittig reaction in the preparation of 3-ethylidenequinuclidine (IV) from quinuclidone-3 and triphenylethylidenephosphorane proceeds unambiguously and in high yield. 3-Ethylidenequinuclidine (IV) with a slight admixture of III (according to the IR spectra) was also obtained by dehydrohalogenation of 3-(β-chloroethylidene)quinuclidine (V) with lithium in liquid ammonia. The use of zinc in 80% acetic acid in the presence of potassium iodide (20°, 4.5 h) for the reduction of V was accompanied by partial allylic rearrangement. As a result, a mixture containing 3-vinylquinuclidine (III) and IV in a ratio of 3:6 was obtained in an overall yield of 35.9%.

Preparation of 3-ethylidenequinuclidine by the method described in the literature ([1]), by dehydration of 3-(β-hydroxyethyl)quinuclidine (VI) with phosphorus pentoxide, also did not lead to the formation of an individual compound. In this case the ratio III : IV was 2 : 6.

Conclusions about the quantitative ratios of the isomeric products, as well as additional control of the purity of the 3-vinyl- and 3-ethylidenequinuclidines synthesized by means of the Wittig reaction, were made using partition gas–liquid chromatography on a Fractovap instrument (Carlo Erba). Column length 2 m; stationary phase—E-301 elastomer, applied in an amount of 20% to Chromosorb W; carrier gas—helium; gas flow rate 5.8 l/h; column temperature 140°. The results of the analyses are shown in Fig. 3.

Experimental Part

3-Vinylquinuclidine III. To a solution of sodium amide prepared from 1.12 g of sodium in 180 ml of liquid ammonia was added 17.4 g of triphenylmethylphosphonium bromide. The orange-red reaction mass was diluted with 100 ml of anhydrous ether, the ammonia was evaporated, and, with stirring, 3.34 g of 3-formylquinuclidine* was added. The reaction mixture, which rapidly became decolorized, was stirred at room temperature for another 80 min, monitoring the process by paper chromatography (disappearance of the spot of 3-formylquinuclidine with R_f 0.64)**. The precipitate that separated was filtered off and washed with ether. From the ethereal solution the base was extracted with 10% hydrochloric acid. The hydrochloric-acid solutions were washed with ether and chloroform and made alkaline with 50% potassium hydroxide solution. The product was distilled with steam. The distillate (800 ml) was acidified with 1 N hydrochloric acid to pH 5, washed with ether, and evaporated in vacuo to dryness. The residue was treated with 50% potassium hydroxide solution and extracted with ether. The ethereal extract, dried over potassium hydroxide, was evaporated without vacuum. The residue was distilled. Collected: 2.2 g (65.6%) of 3-vinylquinuclidine, bp 72–73°/15 mm. Colorless mobile liquid with

Fig. 3. Gas-liquid chromatograms: 1—3-vinylquinuclidine (III), 2—3-ethylidenequinuclidine (IV), 3—product of dehalogenation of 3-(β-chloroethylidene)quinuclidine (V) with lithium in liquid ammonia, 4—product of dehalogenation of 3-(β-chloroethylidene)quinuclidine (V) with zinc in acetic acid, 5—product of dehydration of 3-(β-hydroxyethyl)quinuclidine (VI) with phosphorus pentoxide

Figure 4: Fig. 3. Gas-liquid chromatograms: 1—3-vinylquinuclidine (III), 2—3-ethylidenequinuclidine (IV), 3—product of dehalogenation of 3-(β-chloroethylidene)quinuclidine (V) with lithium in liquid ammonia, 4—product of dehalogenation of 3-(β-chloroethylidene)quinuclidine (V) with zinc in acetic acid, 5—product of dehydration of 3-(β-hydroxyethyl)quinuclidine (VI) with phosphorus pentoxide

an amine odor, readily soluble in common organic solvents, poorly soluble in water. n_D^{20} 1.4915 ([2]). R_f 0.72. Gas-liquid chromatogram (Fig. 3)—one peak, retention time 6.8 min. IR spectrum—1640, 995, 910 cm^{-1}, with absence of a band at 1385 cm^{-1} (Fig. 1).

Fig. 3. Gas-liquid chromatograms: *1*—3-vinylquinuclidine (III), *2*—3-ethylidenequinuclidine (IV), *3*—product of dehalogenation of 3-(β-chloroethylidene)quinuclidine (V) with lithium in liquid ammonia, *4*—product of dehalogenation of 3-(β-chloroethylidene)quinuclidine (V) with zinc in acetic acid, *5*—product of dehydration of 3-(β-hydroxyethyl)quinuclidine (VI) with phosphorus pentoxide.

* The methods for converting quinuclidone-3 into 3-formylquinuclidine will be described separately.

** Here and below, descending paper chromatography in the system *n*-butanol—water—acetic acid 5 : 4 : 1, detection with Dragendorff reagent.

Found, %: C 78.41; H 11.18; N 10.50
$C_9H_{15}N$. Calculated, %: C 78.77; H 11.02; N 10.21

Picrate—yellow crystals, m.p. 151.5-152° (from water) [(2)].

Found, %: N 15.45
$C_9H_{15}N \cdot C_6H_3N_3O_7$. Calculated, %: N 15.30

Acid styphnate—yellow crystals, m.p. 154-154.5° (from water) [(2)]. A mixed-melting test with a sample of acid 3-vinylquinuclidine styphnate, kindly provided to us by Dr. I. Ernest, gave no depression.

Found, %: N 14.56
$C_9H_{15}N \cdot C_6H_3N_3O_8$. Calculated, %: N 14.66

Normal styphnate—yellow crystals, m.p. 174.5-175° (from water).

Found, %: C 55.09; H 6.37; N 13.57
$(C_9H_{15}N)_2 \cdot C_6H_3N_3O_8$. Calculated, %: C 55.48; H 6.40; N 13.48

3-Ethylidenequinuclidine IV. To a solution of sodium amide (from 1.84 g of sodium) in 200 ml of liquid ammonia, 29.7 g of triphenylethylphosphonium bromide was added. The orange-red reaction mass was diluted with 150 ml of anhydrous ether, the ammonia was evaporated, and 5 g of quinuclidone-3 in 50 ml of anhydrous ether was added. The reaction mixture was left overnight at room temperature, then boiled for 6 h, monitoring the course of the reaction by paper chromatography (disappearance of the quinuclidone-3 spot with R_f 0.42). Isolation of 3-ethylidenequinuclidine was carried out as in the case of 3-vinylquinuclidine. 3.9 g (71%) of 3-ethylidenequinuclidine was obtained, b.p. 76-77°/15 mm, n_D^{20} 1.4990 (1), R_f 0.76. Gas-liquid chromatogram—1 peak, retention time 7.3 min (Fig. 3). IR spectrum: 1385 cm^{-1}, with absence of bands at 1640, 995, and 910 cm^{-1} (Fig. 1).

Found, %: C 78.44; H 10.96; N 10.57
$C_9H_{15}N$. Calculated, %: C 78.77; H 11.02; N 10.21

Picrate—yellow crystals, m.p. 132.5-133° (from water) [(1)].

Found, %: N 15.10
$C_9H_{15}N \cdot C_6H_3N_3O_7$. Calculated, %: N 15.30

Acid styphnate—yellow crystals, m.p. 162.5-163° decomp. (from water) [(1)].

Found, %: N 14.91
$C_9H_{15}N \cdot C_6H_3N_3O_8$. Calculated, %: N 14.66

Normal styphnate—yellow crystals, m.p. 193-195° (from water).

Found, %: C 55.42; H 6.28; N 13.67
$(C_9H_{15}N)_2 \cdot C_6H_3N_3O_8$. Calculated, %: C 55.48; H 6.40; N 13.48

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Note: Figure translations are in progress. See original paper for figures.