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REACTION OF 2-METHYLENE-3-OXOQUINUCLIDINE WITH INDOLES

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2-(3-Indolylmethyl)- and 2-(phenyl-3-indolylmethyl)-3-oxoquinuclidines were obtained by the reaction of 2-methylene-3-oxoquinuclidine with indole and 2-phenylindole, respectively. Their reduction by the Kishner method and with sodium borohydride was studied. The structures of the products were confirmed by means of their PMR spectra, and the configurations of two diastereomeric 2-(3-indolylmethyl)-3-hydroxyquinuclidines were established.

The reaction of 2-methylene-3-oxoquinuclidine (I) with various nucleophilic reagents (water, alcohol, phenols and naphthols), which makes it possible to synthesize a number of previously unknown 2-substituted 3-oxoquinuclidines, was described in previous communications [1, 2]. The transformations of the synthesized compounds, particularly the formation of diquinuclidine derivatives and polycyclic quinuclidine compounds, have been studied.

In a continuation of these investigations and in order to synthesize 2-indolylquinuclidines we studied the reaction of I with indoles. A number of compounds of the indoloquinuclidine class have been described in the literature. This is primarily true of the alkaloid cinchonamine and its derivatives, obtained by partial [3] or total synthesis [4, 5], and alkaloids of the aimaline, sarpagine, and quinamine group. Some synthetic representatives of this group of substances are also known [6-8].

We have shown that indole does not react with I without a catalyst. The electrophilic addition of unsaturated ketone I to indole and 2-phenylindole proceeds readily in the presence of both basic (sodium ethoxide) and acidic (acetic acid) catalysts and leads to 2-(3-indolylmethyl)- and 2-(2-phenyl-3-indolylmethyl)-3-oxoquinuclidines (II, III). It should be noted that whereas the use of sodium ethoxide makes it possible to obtain II and III in ~60% yields, II is formed in quantitative yield in the case of an acidic catalyst. In this case, when acetic acid is present, the increase in the electrophilicity of the olefinic bond in unsaturated ketone I due to the acceptor properties of the positively charged nitrogen atom of the quinuclidine ring is of substantial significance. In contrast to the literature data [9], the addition of acetic anhydride leads to a decrease in the yield of II. 1-Methyl-2-phenylindole does not react with unsaturated ketone I either in the presence of alkalis

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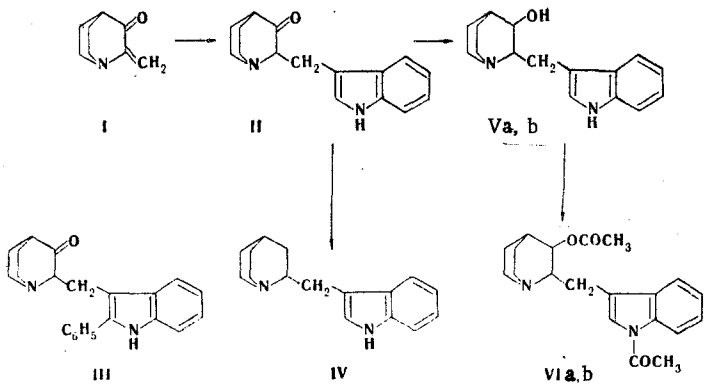

or in the presence of acidic catalysts. The precursor of 2-methylene-3-oxoquinuclidine (I) – 2-dimethylaminomethyl-3-oxoquinuclidine – can be used in place of I in the reaction with indole. This precursor is formed by the reaction of 3-quinuclidine with dimethylamine and formaldehyde [10]. The subsequent use of the above-described catalysts – sodium ethoxide or acetic acid – makes it possible to obtain II in 25.8 and 67% yields, respectively.

2-(3-Indolylmethyl)quinuclidine (IV), which is the cyclic analog of tryptamine, is formed in 63% yield in the Huang–Minlon modification of the Kishner reduction of ketone II. It should be noted that the same compound was previously synthesized [8] from β-(4-pyridyl)propionic acid in six steps in an overall yield of 7.5%.

Indoloquinuclidine II was converted to a mixture of diastereomeric 2-(3-indolylmethyl)-3-oxoquinuclidines (Va, Vb) by reduction with sodium borohydride in methanol. Individual diastereomeric alcohols Va, b were isolated by fractional crystallizatin of the mixture from ethanol. Acetylation of the mixture of diastereomeric alcohols Va,b led to a mixture of two 2-(1-acetyl-3-indolylmethyl)-3-acetoxyquinuclidine diastereomers (VIa,b).

Signals of the protons of the indole ring are observed at weak field in the PMR spectra of II, IV, and V: a multiplet of 4-H, 5-H, 6-H, and 7-H protons, a broad singlet of the proton of the indole NH group, and a doublet (due to spin–spin coupling with the 1-H proton) at 6.8-7.3 ppm, which, on the basis of the chemical shift, was assigned to the 2-H proton of the indole ring. The spectra of III and VIa,b also contain signals of the 4-H, 5-H, 6-H, and 7-H protons of the quinuclidine ring, but the spectrum of III does not contain a signal from the 2-H proton of the indole ring; the spectra of diastereomeric VIa,b do not contain signals of the proton of the indole NH group, and the signals of the 2-H proton of the indole ring are singlets.

These data constitute evidence that II, IV, and Va,b are 3-substituted compounds, VIa and VIb are 1,3-disubstituted compounds, and III is a 2,3-disubstituted compound. The signals of the protons of the quinuclidine rings in II-VI are also presented in Table 1. The character of the multiplicity of the 4-H signal [a multiplet with spin–spin coupling constants (SSCC) ranging from 2 to 4.5 Hz] demonstrates retention of the quinuclidine ring, while a comparison of the integral intensities of the strong-field (quinuclidine) and weak-field (indole) signals of the protons makes it possible to determine the ratios of the quinuclidine and indole rings, which were 1:1 in all of the investigated compounds.

The difference in the chemical shifts and SSCC of the 3-H proton of diastereomeric alcohols Va,b and their acetates (VIa,b) was used to establish the configurations of these compounds. As demonstrated in [11], higher $J_{2,3}$ and $J_{3,4}$ values and higher chemical shifts of the 3-H proton than in the case of the corresponding trans isomers are observed in the spectra of the cis isomers of 2,3-disubstituted quinuclidines. On the basis of this, VIa (which is present in the mixture with VIb) with spectral parameters $\delta_{3\text{-H}} \approx 5.13$ ppm, $J_{2,3} \approx 8.5$ Hz, and $J_{3,4} \approx 4.5$ Hz was assigned to the cis isomer series, and VIb with parameters $\delta_{3\text{-H}} \approx 4.65$ ppm, $J_{2,3} \leq 7$ Hz, and $J_{3,4} \leq 3$ Hz was assigned to the trans isomer series. The signals of the 3-H protons in the spectra of diastereomeric alcohols Va and Vb are broadened; this is due to additional coupling with the proton of the hydroxy group, which experiences slow proton exchange. In conformity with the material presented above, Va, in the spectrum of which the width of the signal of the 3-H proton at half the height of the peak was 15 Hz, and $\delta_{3\text{-H}} = 3.77$ ppm, was assigned to the cis isomer series; Vb, with the corresponding spectral parameters ~11 Hz and 3.35 ppm, was assigned to the trans isomer series.

TABLE 1. Chemical Shifts of the Protons of II-VI (δ, ppm)

Compound	Solvent	Indole ring			CH_2	Quinuclidine ring				
		1-H	2-H	4-H—7-H		2-H	6-H, 7-H	3-H	5-H, 8-H	4-H
II	d_6-DMSO	10,7 br s	7,12 d	6,9—7,55	2,92 q 3,11 q	3,45 q	2,6—3,05	—	1,8—2,0	2,29 m
III	d_6-DMSO	11,1 br s	(7,25—7,75)[a]	7,25—7,75	3,28	3,38	2,5—3,05	—	1,75—1,95	2,28 m
IV	$CDCl_3$	8,94 br s	6,8 d	7,0—7,6	2,6—3,2			1,25—1,65		1,74 m
Va	d_6-DMSO	10,64 br s	7,09	6,9—7,55	2,7—3,3	3,07	2,4—3,2	3,77	1,1—1,9	1,76 m
Vb	d_6-DMSO	10,65 br s	7,14	6,9—7,55	2,5—3,0			3,35	1,1—1,85	1,68 m
VIa[b]	$CDCl_3$	(2,56s)[c]	7,25 s	7,15—8,35	2,75—3,5			4,65 (1,96)[d]	1,5—2,15	1,7 m
VIb[b]	$CDCl_3$	(2,58 s)[c]	7,28 s	7,15—8,35	2,75—3,5			5,13 (1,72)[d]	1,5—2,15	1,7 m

a) Aromatic 2-C_6H_5 protons. b) This is the spectrum of a mixture of diastereomers. c) These are the 1-$COCH_3$ signals. d) These are the 3-$OCOCH_3$ signals.

EXPERIMENTAL

The IR spectra of mineral oil suspensions of the compounds were recorded with a UR-10 spectrometer. The PMR spectra were recorded with a JNM-4H-100 spectrometer with tetramethylsilane as the internal standard.

2-(3-Indolylmethyl)-3-oxoquinuclidine (II). A) A 14.55-g (0.12 mole) sample of indole and a solution of 16.33 g (0.12 mole) of I in 20 ml of ethanol were added successively to a solution of sodium ethoxide [3.36 g (0.12 g-atom) of sodium in 150 ml of ethanol], and the mixture was refluxed for 12 h. It was then allowed to stand at room temperature for 20 h, and the resulting precipitate was removed by filtration to give 15.35 g (60%) of a product with mp 227-229°C (dec., from ethanol). IR spectrum (in mineral oil): 1720 (C=O); 3050, 3100, and 3140 cm^{-1} (NH). Found: C 75.7; H 7.0; N 11.2%. $C_{16}H_{18}N_2O$. Calculated: C 75.7; H 7.1; N 11.0%.

B) A mixture of 2.32 g (20 mmole) of indole, 2.74 g (20 mmole) of unsaturated ketone I, and 16 ml of acetic acid was heated at 90°C for 1 h, after which it was cooled and treated with 100 ml of water and, with cooling, 30% aqueous sodium hydroxide solution. The resulting precipitate was removed by filtration, washed with water, and dried at 90°C for 7 h. The yield of product with mp 227-229°C (dec.) was 5 g (quantitative). The melting point of the product did not change after recrystallization from methanol.

C) A mixture of 2 g (16 mmole) of 3-quinuclidone, 2.7 g of a 40% aqueous solution of dimethylamine, 1.95 g of a 37% aqueous solution of formalin in 2.5 ml of alcohol, and 10 ml of water was heated at 100°C for 1 h and at 70°C for 17 h, after which it was evaporated in vacuo. Benzene was then added to the residue and was removed by distillation; this procedure was repeated. A 1.87-g (16 mmole) sample of indole and an alcohol solution of sodium ethoxide [0.37 g (0.016 g-atom) of sodium and 25 ml of ethanol] were added to the residue, and the mixture was refluxed for 10 h. It was then cooled, and the resulting precipitate was removed by filtration and washed with ethanol and ether to give 1.05 g (26%) of a product with mp 227-229°C (dec.).

D) The Mannich base was obtained as in method C. The reaction mixture was evaporated, the residue was treated with 1.87 g of indole and 24 ml of acetic acid, and the mixture was heated at 90°C for 1 h. It was then dissolved in 80 ml of water, and aqueous sodium hydroxide solution was added with cooling. The resulting precipitate was removed by filtration, washed with water, and dried at 90°C for 10 h. The yield of product with mp 227-229°C (dec.) was 2.7 g (67%).

Hydrochloride. Acetone (15 ml) and an alcohol solution of hydrogen chloride were added to 2 g (7.82 mmole) of base II, and the resulting precipitate was triturated and treated with 25 ml of dry ether. The mixture was allowed to stand at 4°C for 2.5 h, after which it was worked up to give 2.2 g (96.3%) of the hydrochloride of II with mp 264-266°C (dec.). Found: C 65.9; H 6.6; Cl 11.8; N 9.8%. $C_{16}H_{18}N_2O \cdot HCl$. Calculated: C 66.0; H 6.5; Cl 12.2; N 9.6%.

2-(2-Phenyl-3-indolylmethyl)-3-oxoquinuclidine (VI). A solution of 4.62 g (22.5 mmole) of 2-phenylindole and a solution of 3.08 g (22.5 mmole) of the unsaturated ketone in 20 ml of ethanol were added successively to a solution of sodium ethoxide [0.52 g (22.5 mg-atom) of sodium and 40 ml of ethanol], and the mixture was refluxed for 14 h, during which a homogeneous solution formed gradually. The mixture was cooled, and the resulting precipitate was removed by filtration and washed with ethanol and ether to give 4.52 g (58.8%)

of a product with mp 214-216°C (from ethanol). IR spectrum: 1730 (C=O) and 3220 cm^{-1} (NH). Found: C 79.5; H 6.6; N 8.3%. $C_{22}H_{22}N_2O$. Calculated: C 79.7; H 6.7; N 8.5%.

2-(3-Indolylmethyl)quinuclidine (IV). A mixture of 6 g (2.36 mmole) of II, 10 ml of hydrazine hydrate, 14 g of potassium hydroxide, and 60 ml of diethylene glycol was refluxed for 1.5 h, after which the water and excess hydrazine hydrate were removed by distillation as the bath temperature was raised to 200°C in the course of an hour. The resulting precipitate was triturated, removed by filtration, washed with water, air dried, and dissolved by heating in 150 ml of acetone. The insoluble material was removed by filtration, and the acetone solution was evaporated in vacuo. The residue was crystallized from acetone to give 4.3 g (63.3%) of a product with mp 184-185.5°C. IR spectrum: 3040 and 3140 cm^{-1} (NH). Found: C 80.1; H 8.3; N 11.7%. $C_{16}H_{20}N_2$. Calculated: C 80.3; H 8.0; N 11.7%. The hydrochloride had mp 232-233°C (from ethanol). Found: C 69.5; H 7.6; Cl 12.5; N 10.1%. $C_{16}H_{20}N_2 \cdot HCl$. Calculated: C 69.7; H 7.3; Cl 12.9; N 10.1%.

2-(3-Indolylmethyl)-3-hydroxyquinuclidines (Va,b). Sodium borohydride (3 g) was added in the course of 30 min to a suspension of 3.85 g (15.1 mmole) of ketone II in 60 ml of methanol, and the mixture was refluxed for 2 h. A white precipitate began to form during the heating period. The reaction mixture was allowed to stand at room temperature for 16 h, and the resulting precipitate was removed by filtration and washed with ethanol to give 2.75 g of a mixture of diastereomeric alcohols Va,b, which was recrystallized from 60 ml of ethanol to give 1 g of cis isomer Va with mp 231-233°C. IR spectrum: 3200, 3050, and 2640-2710 cm^{-1} (NH and associated OH). Found: C 74.6; H 7.8; N 11.3%. $C_{16}H_{20}N_2O$. Calculated: C 75.0; H 7.8; N 10.9%. The hydrochloride had mp 232-234°C. Found: Cl 12.1; N 9.3%. $C_{16}H_{20}N_2O \cdot HCl$. Calculated: Cl 11.8; N 9.8%.

The mother liquor after separation of alcohol Va was evaporated, and the residue was recrystallized from ethanol to give 0.95 g of trans-isomer Vb containing 3-5% cis-isomer Va with mp 223-225°C.

The alkaline methanol solution remaining after separation of isomers Va and Vb was evaporated, and the residue was dissolved in 20 ml of water. The aqueous solution was extracted with chloroform, and the chloroform solution was dried with magnesium sulfate. The solvent was removed by distillation, and the residue was recrystallized from 20 ml of ethanol to give an additional 0.35 g of trans isomer Vb with mp 223-225°C. IR spectrum: 3200, 3050, and 2600-2720 cm^{-1} (NH and associated OH). Found: C 74.8; H 7.8; N 11.1%. $C_{16}H_{20}N_2O$. Calculated: C 75.0; H 7.8; N 10.9%.

2-(1-Acetoxy-3-indolyl)-3-acetoxyquinuclidines (VIa,b). A solution of 4.9 g (1.9 mmole) of a mixture of alcohols Va,b in 60 ml of acetic anhydride was heated at 140°C for 5 h, after which it was evaporated in vacuo, and the residue was dissolved in 20 ml of water. The aqueous solution was allowed to stand for 15-20 min, after which 30 ml of 15% sodium hydroxide solution was added, and the oil that separated was extracted with ether. The ether extract was dried with magnesium sulfate and evaporated, and the residue was distilled in vacuo to give 3.35 g (51.5%) of a mixture of diastereomers VIa,b in the form of a vitreous mass with bp 242-245°C (0.6 mm, mercury column). IR spectrum: 1720 cm^{-1} (C=O). Found: C 70.4; H 7.0; N 7.9%. $C_{20}H_{24}N_2O_3$. Calculated: C 70.4; H 7.0; N 8.2%.

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