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REACTIONS OF 2-METHYLENE-3-OXOQUINUCLIDINE WITH CARBONYL COMPOUNDS

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The reaction of 2-methylene3-oxoquinuclidine with ketones, β-diketones, keto esters, and cyano esters was studied. Products of mono- and diaddition of the unsaturated ketone are formed in the presence of catalytic or equimolar amounts of sodium ethoxide, as well as without a catalyst (in the case of β-keto esters and β-diketones).

In a continuation of our research on the reactions of 2-methylene-3-oxoquinuclidine (I) with various nucleophilic reagents that make it possible to synthesize a number of previously unknown 2,3-disubstituted quinuclidines, including condensed systems that include a quinuclidine ring [1-3], we studied the reaction of unsaturated ketone I with carbonyl compounds, viz., ketones, β-diketones, keto esters, and cyano esters. Prior to our studies in this direction, only the reactions of ketone I with malonic ester and its C-substituted derivatives, benzyl methyl ketone, and propyl methyl ketone had been described [4].

We accomplished the reaction of 2-methylene-3-oxoquinuclidine (I) with carbonyl compounds (the Michael reaction) in the presence of catalytic or equimolar amounts of sodium ethoxide (in the case of the ketones and cyano esters), as well as without a catalyst (in the case of β-keto esters and β-diketones). In the latter case autocatalysis by the highly basic quinuclidine molecule evidently occurs. Products of mono- and diaddition of unsaturated ketone I were obtained with the indicated carbonyl compounds. Thus 2,2-bis(3-oxo-2-quinuclidinylmethyl)cyclopentanone (II) and ethyl 2,2-bis(3-oxo-2-quinuclidinylmethyl)cyanoacetate (III), respectively, were obtained in the reaction of I with cyclopentanone and cyanoacetic ester in the presence of equimolar and catalytic amounts of sodium ethoxide in ethanol at room temperature and upon heating. Monoaddition products were not isolated.

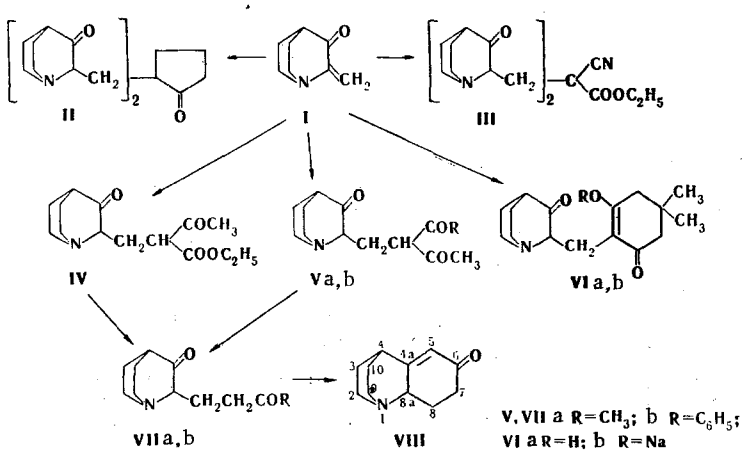

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TABLE 1. ^{13}C Chemical Shifts

Compound	δ, ppm						
	C_2	C_3	C_4	C_5, C_8	C_6, C_7	C_9	R
II	66,7	220,6*	39,6	24,7 27,2	40,2 48,5	35,2	221,6* (1′), 47,7 (2′), 30,2 (3′), 19,6 (4′), 38,1 (5′)
III	67,2	219,5	39,4	24,0 28,3	41,0 48,3	34,4	46,6 (quat. C) 118,3 (CN), 168,1 (COO), 61,9 (OCH_2), 13,7 (CH_3)
IV†	67,0	219,3	39,83	25,7*,‡	40,7; 40,9	24,8†	56,0, 56,3 (CH), 202,2 [CO(Ac)], 29,5, 29,6 [CH_3(Ac)], 169,0, 169,3 (COO),
	67,5	220,2	39,78	26,8*,‡	48,5; 48,6		61,3r (OCH_2), 14,02, 14,06 [CH_3(Et)]
VIIa	68,64	220,8	39,9	25,3 26,2	40,2 48,7	21,9	40,7 (CH_2), 207,7 (CO), 30,0 (CH_3)

*Inverse assignment of the signals labeled by the same let-
†Two sets of signals corresponding to the diastereomers.
‡The signals of the diastereomers coincide.

The structures of II and III were confirmed by the ^1H and ^{13}C NMR and mass spectra.

The location of the methylenequinuclidine residues in II and III at one carbon atom follows from the presence in the ^{13}C NMR spectra of sp^3-hybridized quaternary carbon atoms [47.7 (II) and 46.6 ppm (III)] in the α position relative to the carbonyl group (see Tables 1 and 2).

More reactive β-dicarbonyl compounds that contain keto groups (acetoacetic ester, acetyl- and benzoylacetones, and dimedone) react with 2-methylene-3-oxoquinuclidine (I) in the absence of a catalyst at room temperature to give monoaddition products (IV-VI). The process can be realized without a solvent and also in acetone or isopropyl alcohol. Mixtures of substances that are difficult to separate are formed in methanol and ethanol. It is possible that in these solvents the principal reaction, which takes place in 10-14 days, is accompanied by a side reaction, viz., the addition of alcohols to give 2-alkoxymethyl-3-oxoquinuclidines, which hinders separation of the reaction products. A similar pattern is observed when the components are heated also in the presence of sodium ethoxide. Under these conditions only the sodium salt (VIb) of the enol was isolated in low yield from the products of the reaction of ketone I with dimedone.

The position of the tautomeric equilibrium for the β-dicarbonyl residue attached to C_2 in IV, Va, b, and VIa was established by means of the ^1H NMR spectra. Signals of the CH protons of the dicarbonyl residue at 3.6-3.7 and 4.7-4.8 ppm are observed in the spectra of the mixtures of diastereomers IV and Vb obtained, but signals are absent at weak field (> 8 ppm); this indicates the existence of these compounds in the keto form. Triketone Va, in the spectrum of which signals are observed at both strong field (at 3.89 ppm, relative intensity ∿1 proton unit) and weak field (at 16.9 ppm, relative intensity $\leqslant$0.07 proton unit), evidently exists in the form of a mixture of the keto and enol forms with preponderance of the keto form. Compound VIa, in the spectrum of which signals of the α-methylidine proton of a β-dicarbonyl fragment are absent but in which a broad signal of a proton of an OH group is present at 12.65 ppm, evidently exists primarily in the enol form.

When tricarbonyl derivatives IV-VI are heated briefly (for 2-5 h) with hydrochloric acid, they undergo hydrolytic cleavage to give 2-(2-acylethyl)-3-oxoquinuclidines (VIIa, b). When

TABLE 2. ^1H Chemical Shifts

Compound	δ, ppm			
	4-H	2-, 6- and 7-H	5-, 8- and 9-H	R
II	2,36	2,8—3,1	1,7—2,3	1,7—2,1 (3′, 4′), 3,16 (5′)
III	2,40	2,5—3,1 3,4—3,55	1,8—2,3	1,25 (CH_3), 4,07 (CH_2)
IV	2,39	2,5—3,2	1,8—2,3	1,26 [CH_3(Et)], 4,16, 4,14 (OCH_2)
VII[a]	2,38	2,8—3,2	1,6—2,1	2,26 [CH_3(Ac)], 3,72 (CHCOO) 2,15 ($COCH_3$), 2,64 (CH_2CO)

triketone Va is refluxed for a long time (30 h) with hydrochloric acid, it undergoes intramolecular aldol condensation, as a result of which we obtained 6-oxo-6,7,8,8a-tetrahydrobenzo[b]quinuclidine (VIII). The latter is also formed when triketone Va and diketone VIIa are heated with a 3% aqueous solution of sodium hydroxide. The structure of VIII was confirmed by the presence in its ^{1}H NMR spectrum of a signal of a vinyl proton (5-H) at 5.84 ppm and by the presence in its ^{13}C NMR spectrum of a signal of a conjugated ketone (C_6) at 198.4 ppm.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra of solutions of the compounds in $CDCl_3$ were recorded with an XL-100A spectrometer with operating frequencies of 100 MHz for ^{1}H nuclei and 25.2 MHz for ^{13}C nuclei with tetramethylsilane as the internal standard. The ^{13}C NMR spectra were recorded with complete and incomplete decoupling of the spin-spin coupling with the protons.

2,2-Bis(3-oxo-2-quinuclidinylmethyl)cyclopentanone (II). A solution of 2.74 g (20 mmole) of 2-methylene-3-oxoquinuclidine (I) and 1.68 g (20 mmole) of cyclopentanone in 10 ml of isopropyl alcohol was added in the course of 15 min to a solution of sodium isopropoxide [from 30 mg (1.3 mmole) of sodium and 10 ml of isopropyl alcohol], and the reaction mixture was maintained at 20°C for 20 h and at 4°C for 20 h. The precipitate was removed by filtration and washed with isopropyl alcohol to give 1.34 g (38%) of a product with mp 189-191°C (from ethanol). IR spectrum: 1710-1740 cm^{-1} (C=O). Found: C 70.3; H 8.4; N 7.8%. $C_{21}H_{30}N_2O_3$. Calculated: C 70.4; H 8.6; N 7.8%.

Ethyl 2,2-Bis(3-oxo-2-quinuclidinylmethyl)cyanoacetate (III). An alcohol solution of sodium ethoxide [from 40 mg (1.75 mmole) of sodium and 10 ml of ethanol] was added to a solution of 17 g (124 mmole) of ketone I and 14 g (107 mmole) of cyanoacetic ester in 80 ml of ethanol, and the reaction mixture was allowed to stand at room temperature for 7 days. The precipitate was removed by filtration and washed with ethanol to give 11.8 g (47%) of a product with mp 178-180°C (from ethanol). IR spectrum: 1720-1735 (C=O) and 2260 cm^{-1} (C≡N). Found: C 64.6; H 7.2; N 10.6%. $C_{21}H_{29}N_3O_4$. Calculated: C 65.0; H 7.5; N 10.8%.

Ethyl 2-(3-Oxo-2-quinuclidinylmethyl)acetoacetate (IV). A solution of 7.3 g (53.1 mmole) of ketone I and 6.93 g (53.2 mmole) of acetoacetic ester in 10 ml of ethanol was maintained at 20°C for 5 days, after which it was evaporated *in vacuo*, and the residue was distilled to give 9.7 g (62%) of a product with bp 165-167°C (0.6 mm). IR spectrum: 1710-1730 cm^{-1}(C=O). Found: C 62.7; H 8.3; N 5.0%. $C_{14}H_{21}NO_4$. Calculated: C 62.8; H 7.9; N 5.2%.

2-(2-Acetyl-3-oxobutyl)-3-oxoquinuclidine (Va). A mixture of 2.74 g (20 mmole) of ketone I and 2 g (20 mmole) of acetylacetone was maintained at room temperature for 10 days, after which it was diluted with a fourfold volume of acetone and treated with a 15% alcohol solution of hydrogen chloride. The precipitated hydrochloride of triketone Va was removed by filtration and washed with acetone to give 3.15 g (58%) of a product with mp 211-213°C (from ethanol). IR spectrum: 1732, 1750 (C=O); 2480-2550 cm^{-1} ($\overset{+}{N}$H). Found: C 57.2; H 7.4; Cl 13.3; N 5.1%. $C_{13}H_{19}NO_3 \cdot HCl$. Calculated: C 57.0; H 7.4; Cl 13.0; N 5.1%. Base Va, with bp 163-165°C (0.9 mm), was isolated in the usual way from the hydrochloride. Found: C 66.1; H 8.1; N 6.2%. $C_{13}H_{19}NO_3$. Calculated: C 65.8; H 8.0; N 5.9%.

Diastereomeric 2-(2-Benzoyl-3-oxobutyl)-3-oxoquinuclidine (Vb). A solution of 1.6 g (11.7 mmole) of ketone I and 1.9 g (11.7 mmole) of benzoylacetone in 25 ml of acetone was maintained at 20°C for 7 days, after which it was treated with an alcohol solution of hydrogen chloride. The precipitated mixture of diastereomeric hydrochlorides of Vb was removed by filtration and washed with acetone to give 3.35 g (85%) of a product with mp 213-215°C (from ethanol). IR spectrum: 1690, 1725, 1745 (C=O); 2470, 2540 cm^{-1} ($\overset{+}{N}$H). Found: C 64.4; H 6.4; Cl 10.5; N 4.3%. $C_{10}H_{21}NO_3 \cdot HCl$. Calculated: C 64.3; H 6.6; Cl 10.5; N 4.1%.

2-(2-Hyxroxy-4,4-dimethyl-6-oxo-1-cyclohexenylmethyl)-3-oxoquinuclidine (VIa). A mixture of 4.1 g (29.9 mmole) of ketone I and 4.18 g (29.9 mmole) of dimedone in 35 ml of isopropyl alcohol was shaken until the solids dissolved, during which the reaction mixture warmed up. As the mixture cooled, it yielded a precipitate, which, after 20 h, was removed by filtration and washed with ether to give 7.2 g (87%) with mp 181-182°C (dec.). IR spectrum: 1740 (C=O), 1635 (C=C–C=O), and 2320-2550 cm^{-1} (associated OH). Found: C 69.3; H 8.3; N 5.3%. $C_{16}H_{23}NO_3$. Calculated: C 69.2; H 8.4; N 5.1%. Hydrochloride. A 20% alcohol solu-

tion of hydrogen chloride was added to a suspension of 1 g (3.6 mmole) of VIa in 15 ml of acetone until the mixture was acidic, after which it was evaporated, and the residue was triturated with ether. Workup gave 0.9 g (88%) of a product with mp 263-264°C (dec.). Found: C 61.2; H 7.6; Cl 11.4%. $C_{16}H_{23}NO_3 \cdot HCl$. Calculated: C 61.2; H 7.3; Cl 11.3%.

2-(2-Hydroxy-4,4-dimethyl-6-oxo-1-cyclohexenylmethyl)-3-oxoquinuclidine Sodium Salt (VIb). A solution of 2.87 g (20 mmole) of dimedone and 2.74 g (20 mmole) of ketone I in 10 ml of ethanol was added to a solution of sodium ethoxide [from 0.5 g (22 mmole) of sodium and 15 ml of ethanol], and the mixture was stirred at 20°C for 3 h and at 4°C for 1 h. The precipitate was removed by filtration and washed with ethanol to give 1.12 g (19%) of a product with mp 284-286°C (dec.). Found: C 63.7; H 7.4; N 4.7%. $C_{16}H_{23}NaNO_3$. Calculated: C 64.0; H 7.3; N 4.7%.

2-(3-Oxobutyl)-3-oxoquinuclidine (VIIa). A) A solution of 2 g (7 mmole)of the hydrochloride of Va in 20 ml of concentrated hydrochloric acid was refluxed for 2 h, after which it was evaporated *in vacuo*. The residue was made alkaline with 25% potassium carbonate solution and extracted with benzene. Workup of the extract gave 1.3 g (91%) of a product with bp 127-129°C (1.2 mm). Found: C 67.7; H 8.8; N 7.3%. $C_{11}H_{17}NO_2$. Calculated: C 67.7; H 8.8; N 7.2%. The hydrochloride had mp 183-185°C (from ethanol). Found: C 57.1; H 8.0; Cl 15.2; N 6.0%. $C_{11}H_{17}NO_2 \cdot C_{11}H_{17}NO_2 \cdot HCl$. Calculated: C 57.0; H 7.8; Cl 15.3; N 6.0%.

B) A solution of 2 g (7.3 mmole) of the hydrochloride of Va in 20 ml of a 20% alcohol solution of hydrogen chloride was refluxed for 10 h, after which it was evaporated *in vacuo*. The residue was triturated with acetone and recrystallized from ethanol to give 1.5 g (88%) of the hydrochloride of VIIa with mp 183-185°C.

C) A solution of 4 g (15 mmole) of IV in 40 ml of concentrated hydrochloric acid was refluxed for 2 h, after which it was worked up to give 2.3 g (78%) of a product with bp 173-176°C (15 mm).

2-(2-Benzoylethyl)-3-oxoquinuclidine (VIIb). A solution of 2 g (6 mmole) of the hydrochloride of Vb in 20 ml of concentrated hydrochloric acid was refluxed for 5 h, after which it was cooled, and the resulting precipitate was removed by filtration and washed with acetone to give 1.25 g (71%) of the hydrochloride with mp 245-246°C (from 90% ethanol). Found: C 65.4; H 6.8; Cl 12.1; N 4.8%. $C_{16}H_{19}NO_2 \cdot HCl$. Calculated: C 65.3; H 6.9; Cl 12.1; N 4.8%.

6-Oxo-6,7,8,8a-tetrahydrobenzo[b]quinuclidine (VIII). A) A solution of 9 g (33 mmole) of the hydrochloride of Va in 90 ml of concentrated hydrochloric acid was refluxed for 30 h, after which it was evaporated *in vacuo*, and the residue was triturated with acetone to give 2.45 g (35%) of the hydrochloride of VIII with mp 283-285°C (dec., from methanol). Found: C 61.6; H 7.7; Cl 16.4; N 6.4%. $C_{11}H_{15}NO_2 \cdot HCl$. Calculated: C 61.8; H 7.8; Cl 16.6; N 6.5%.

B) A mixture of 6 g (22 mmole) of the hydrochloride of Va and 96 ml of a 4% aqueous solution of sodium hydroxide was refluxed for 5 h, after which it was cooled and treated with 4 g of sodium hydroxide. The resulting mixture was extracted with benzene, the extract was evaporated, and the residue was sublimed *in vacuo* (0.4 mm) at a bath temperature of 95-100°C to give 3.3 g (77%) of a product with mp 87-89°C. Found: C 74.7; H 8.7; N 7.7%. $C_{11}H_{15}NO$. Calculated: C 74.5; H 8.5; N 7.9%. ^1H NMR spectrum: 2.8-3.2 (m, 5H, 2-, 9-, and 8a-H), 1.8-2.1 (m, 6H, 3-, 8-, and 10-H), 2.38 (m, 1H, 4-H), 5.84 (d, J_{57} = = 2.5 Hz, 1H, 5-H), and 3.51 ppm (t, 2H, 7-H). ^{13}C NMR spectrum: 37.9, 42.5, 48.9 (C_2, C_7, C_9); 23.4, 28.0, 31.4 (C_3, C_8, C_{10}); 32.4 (C_4); 175.9 (C_{4a}); 121.4 (C_5); 198.4 ppm (C_6).

C) A mixture of 1.3 g (6.7 mmole) of diketone VIIa and 20 ml of a 3% aqueous solution of sodium hydroxide was refluxed for 5 h, after which it was worked up as in method B to give 0.92 g (78%) of a product with mp 87-89°C.

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CYCLIZATION OF N-ALKYLAZINIUM CATIONS WITH BISNUCLEOPHILES.

3.* endo ADDUCTS IN THE REACTION OF QUINOXALIUM SALTS WITH β-DIKETONES AND THEIR X-RAY DIFFRACTION ANALYSIS

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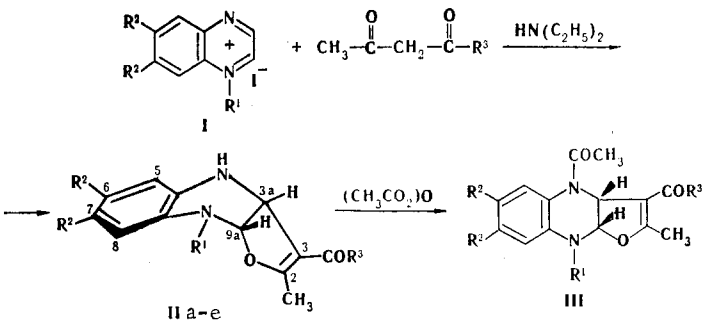
The cyclization of N-alkylquinoxalinium salts with the anions of β-dicarbonyl compounds proceeds regioselectively and stereoselectively and leads to endo-3a, 4,9,9a-tetrahydrofuro[2,3-b]quinoxalines. The structure of the cycloadducts was established on the basis of the ^{1}H and ^{13}C NMR spectra and the results of x-ray diffraction analysis.

The meta bonding of polynitroaromatic compounds and their heterocyclic analogs by bisnuclophiles has recently become one of the effective methods for the one-step synthesis of complex and practically useful two-ring compounds [2-8]. Two-ring intermediates formed due to meta bonding have also been postulated or recorded in the course of transformations of heterocyclic systems [9, 10]. A new cyclization reaction of quinoxalinium salts with enamines of cyclic ketones that has a number of principles in common with meta-bonding reactions but differs with respect to ortho bonding of a heteroaromatic system has been reported [11, 12]. A new ortho-cyclization reaction of N-alkylquinoxalinium salts with β-diketones is described in the present paper, and its stereochemical aspects are examined.

The reaction of quinoxalinium salts I with acetylacetone and acetoacetic ester in the presence of bases (diethyl- and triethylamines) proceeds with an appreciable exothermic effect, and the reaction was therefore carried out at -50 to +20°C in ethanol. Under these conditions the reaction was complete after a few minutes and gave endo-3a,4,9,9a-tetrahydrofuro[2,3-b]quinoxalines (IIa-e) in high yields (Table 1).



The structure of IIa-e was established on the basis of spectral data (Tables 1 and 2). The chemical shift of the protons of the N-methyl group at δ 3.04 ppm and the narrow multiplet of aromatic protons (δ 6.4-6.9) correspond to a tetrahydroquinoxaline structure [13]. The 9a-H proton appears in the PMR spectrum of IIa as a doublet with $^{3}J_{9a,3a}$ = 9 Hz. The 3a-H proton, in addition to coupling with 9a-H, has a long-range spin-spin coupling constant (SSCC) with the protons of the methyl group in the 2 position of the furan ring ($^{5}J_{3a}$ = 0.9 Hz) and gives a doublet of quartets with 5.04 ppm (Fig. 1).

*See [1] for Communication 2.

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