AHC–Hydroquinone Complex (2:1) (XIII). Alcohol solutions of 4.32 g (20 mmole) of AHC and 10 mmole of hydroquinone were mixed, after which the solvent was removed by vacuum distillation at room temperature, and the dry residue was pulverized, washed with ether, dried, and crystallized to give a product with mp 201-206°. Found, %: C 70.5; H 4.8; N 5.1. $C_{32}H_{26}Cl_2N_2O_2$. Calculated, %: C 71.0; H 4.8; N 5.2.

AHC–Pyrogallol Complex (2:1) (XIV). Complex XIV was similarly obtained and had mp 190-194°. Found, %: C 69.1; H 4.9; N 5.1. $C_{32}H_{26}Cl_2N_2O_2$. Calculated, %: C 68.9; H 4.7; N 5.0.

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1,4-DIAZABICYCLO[2.2.2]OCTANES.

I. METHOD FOR THE SYNTHESIS OF 1,4-DIAZABICYCLO[2.2.2]OCTANES WITH FUNCTIONAL SUBSTITUENTS OR CONDENSED WITH BENZENE RINGS

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The reaction of substituted 1,4-dimethylpiperazines and tetrahydroquinoxaline with dibromoethane gives the corresponding 1,4-diazabicyclo[2.2.2]octanes.

In contrast to quinuclidine compounds which have been investigated in detail [1], insufficient study has been devoted to 4-azaquinuclidines (1,4-diazabicyclo[2.2.2]octanes). Only the unsubstituted 1,4-diazabicycle [2] and its C-alkyl [3] and quaternary [4] derivatives have been described. Compounds with functional substituents are unknown. The available information regarding the strange properties of benzo(b)-1,4-diazabicyclo[2.2.2]octane [5] raises doubts that a compound with precisely this structure was obtained.

The difficulties involved in the synthesis of 1,4-diazabicyclo[2.2.2]octanes are determined by the fact that the methods for the construction of the quinuclidine ring are usually unsuitable for the corresponding 4-azaquinuclidines. It has been shown [6] that N-(β-carboxy-β-methyleneethyl)piperazine derivatives are formed in the reaction of piperazines with formaldehyde and malonic acid (or its esters) instead of the products of the Mannich reaction — 4-(β,β-dicarbonylethyl)piperazines — due to intramolecular fragmentation. Reductive fragmentation also occurs in the reaction of piperazinylmethylenemalonic esters with sodium borohydride or hydrogen [7]. 1,1,4,4-Tetramethylpiperazinium dibromide is formed in all cases in the reaction of 1,4-dimethylpiperazine with substituted 1,2-dibromoalkanes [8].

In the present paper we describe a method for the synthesis of 1,4-diazabicyclo[2.2.2]-octanes with functional substituents attached to the carbon atoms of the bicycle or condensed with aromatic rings; the method is based on the reaction of the corresponding sub-

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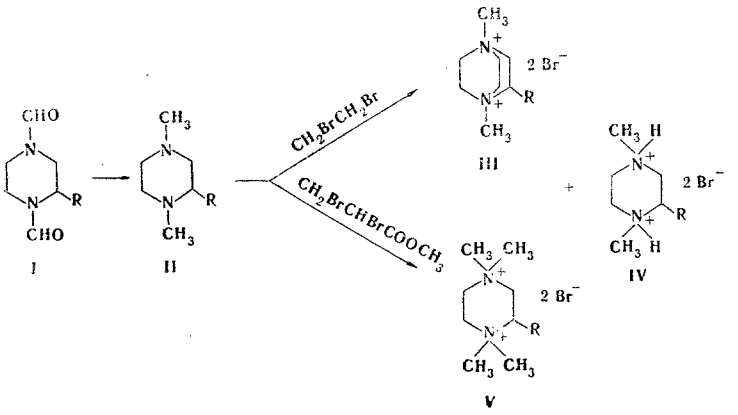
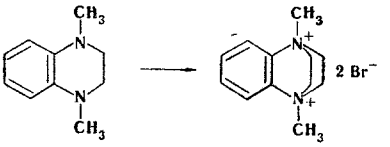


I a R=H; b R=COOH; c R=$COOCH_3$;
II-V a R=H; b R=CH_2OH



VI VII

stituted or condensed 1,4-dimethylpiperazines with 1,2-dibromoethane. This scheme has been used only for the synthesis of 4-azaquinuclidine itself [9].

In the reaction of 1,4-dimethylpiperazine (IIa) with dibromoethane we observed not only closing of 1,4-diazabicycle IIIa but also the formation of 1,4-dimethylpiperazine dihydrobromide IVa.

As should be expected, an increase in the polarity of the solvent in the indicated reaction raises the yield of 1,4-diazabicyclic compound III [the IIIa to IVa ratio in ethanol is 4:1, as compared with 5:1 in dimethylformamide (DMF), and the yield of 1,4-diazabicyclic compound IIIa is 62%].

A similar effect of the solvent polarity is also observed in the reaction of 1,4-dimethylpiperazine IIa with methyl α,β-dibromopropionate, in which the final products are 1,1,4,4-tetramethylpiperazinium dibromide (Va), which arises via nucleophilic substitution and subsequent transalkylation, and 1,4-dimethylpiperazine dihydrobromide (IVa), which is formed as a result of splitting out of hydrogen bromide. Only IVa was obtained in 63% yield in cyclohexane (about 35% of starting IIa was recovered unchanged), and Va was isolated in about 5% yield in ethanol, whereas the yield of Va rose to 46% in DMF, and the yield of dihydrobromide IVa fell to 7%. A shift to favor the formation of 1,4-diazabicyclic derivative IIIa was also observed when equimolar amounts of IIa and dibromoethane were heated without a solvent.

We used this synthetic variant also in the preparation of 1,4-diazabicyclo[2.2.2]octane derivative IIIb from 1,4-diformylpiperazine-2-carboxylic acid (Ib) [10], which was initially converted to the corresponding methyl ester (Ic) under the influence of diazomethane.* The simultaneous reduction of the two amide and ester groups in 1,4-diformyl-2-methoxycarbonylpiperazine (Ic) with lithium aluminum hydride gave 1,4-dimethyl-2-hydroxymethylpiperazine (IIb), which also reacts with dibromoethane to give IIIb. Benzo(b)-1,4-diazabicyclo[2.2.2]-octane (VII) was obtained from 1,4-dimethyl-1,2,3,4-tetrahydroquinoxaline (VI) [11].

Dequaternization of the methylbromides of 4-azaquinuclidine derivatives by vacuum sublimation of the compound was verified in the case of IIIa.

EXPERIMENTAL

The PMR spectra of D_2O solutions of the compounds were recorded with a JNM-4H-100 spectrometer with $(CH_3)_3COH$ (δ_{CH_3} 0.23 ppm) as the internal standard. Thin-layer chromatography

*Esterification with alcohols in the presence of acid catalysts proved to be unsuitable, inasmuch as it was accompanied by splitting out of the formyl residues from the nitrogen atoms.

(TLC) was carried out on Silufol UV-254 plates in a methanol—25% ammonia system (10:1) with development with chloro-o-toluidine (blue coloration; R_f IVa 0.55 and IVb 0.43; quaternary derivatives III, V, and VII remained at the starting point).

1,4-Diazabicyclo[2.2.2]octane Dimethylbromide (IIIa). A) A mixture of 3.42 g (0.03 mole) of IIa and 5.94 g (0.03 mole) of dibromoethane was heated at 140° for 2 h and at 125° for 2 h, after which it was cooled and triturated with 20 ml of ethanol. The solid material was removed by filtration and recrystallized from alcohol to give 6.2 g (69%) of IIIa as colorless crystals with mp 305-306° (dec.). The product was quite soluble in water, less soluble in alcohols and DMF, and insoluble in the ordinary organic solvents. PMR spectrum (δ, ppm): 3.40 s, 6H (CH_3); 4.06 s, 12H (CH_2). Found, %: C 31.4, H 5.9, Br 53.0, N 9.3. $C_8H_{18}Br_2N_2$. Calculated, %: C 31.8, H 5.9, Br 52.9, N 9.3.

B) A solution of 2.28 g (0.02 mole) of IIa and 3.76 g (0.02 mole) of dibromoethane in 25 ml of DMF was refluxed for 4 h, after which the white crystals of IIIa were removed by filtration and washed with DMF and anhydrous ether to give 3.75 g (62%) of a product with mp 305-306° (dec.). The mother liquor was evaporated, the residue was triturated with 10 ml of acetone, and the solid material was removed by filtration to give 0.63 g (11%) of IVa with mp 239-240° (dec.). No melting-point depression was observed for a mixture of this product with an authentic sample of 1,4-dimethylpiperazine dihydrobromide. The ratio of IIIa to IVa in a similar experiment in absolute ethanol was 4:1.

1,1,4,4-Tetramethylpiperazinium Dibromide (Va). A) A solution of 2.28 g (0.02 mole) of IIa and 4.92 g (0.02 mole) of methyl α,β-dibromopropionate in 15 ml of absolute ethanol was refluxed for 8 h, after which the precipitated crystals were removed by filtration and recrystallized from ethanol to give 0.3 g (5%) of Va as colorless crystals with mp 325-326° (dec.). The product was quite soluble in water but only slightly soluble in the ordinary organic solvents. Found, %: C 31.6, H 6.8, Br 52.2, N 9.4. $C_8H_{20}Br_2N_2$. Calculated, %: C 31.6, H 6.6, Br 52.6, N 9.2. The combined ethanol solutions were vacuum evaporated to dryness, the residue was triturated with 10 ml of acetone, and the solid was removed by filtration to give 3.63 g (66%) of IVa with mp 239-240° (dec.).

B) A solution of 2.28 g (0.02 mole) of IIa and 4.92 g (0.02 mole) of methyl α,β-dibromopropionate in 25 ml of DMF was refluxed for 4 h, after which it was vacuum evaporated. The residue was dissolved in 50 ml of water, and the solution was decolorized with charcoal and filtered, during which water-insoluble impurities separated. The aqueous filtrate was vacuum evaporated to dryness, and the residue was recrystallized from ethanol to give 2.81 g (46%) of Va with mp 325-326° (dec.). The alcohol mother liquor was evaporated, and the residue was triturated with 10 ml of acetone to give 0.16 g (7%) of IVa with mp 239-240° (dec.).

Benzo(b)-1,4-diazabicyclo[2.2.2]octane Dimethylbromide (VII). A mixture of 3.24 g (0.02 mole) of 1,4-dimethyl-1,2,3,4-tetrahydroquinoxaline (VI) [11] and 3.76 g (0.02 mole) of dibromoethane was heated at 130° for 2 h, after which the markedly resinified reaction mass was triturated with 5 ml of methanol and filtered to give 0.62 g (9%) of VII as colorless crystals with mp 218-219° (dec., from ethanol). The product was quite soluble in water, less soluble in alcohols and DMF, and only slightly soluble in other ordinary organic solvents. PMR spectrum (δ, ppm): 4.06 s, 6H (CH_3); 4.10 m, 4H (syn-CH_2); 4.62 m, 4H (anti-CH_2); 8.02 m, 4H (C_6H_4). Found, %: C 41.2, H 5.2, Br 45.5, N 8.2. $C_{12}H_{18}Br_2N_2$. Calculated, %: C 41.2, H 5.2, Br 45.7, N 8.0.

1,4-Dimethyl-2-hydroxymethylpiperazine (IIb). A solution of 2.0 g (0.0102 mole) of Ib [10] in 50 ml of methanol was added at 5° to 250 ml of an ether solution of 0.6 g of diazomethane, and the solution was allowed to stand at 5° for 12 h, after which it was evaporated to dryness. The residue (2.06 g) was dissolved in 30 ml of absolute tetrahydrofuran (THF) and added to a suspension of 1.5 g of lithium aluminum hydride in 40 ml of absolute ether. The mixture was refluxed for 6 h, after which it was treated with 4 ml of water. The precipitated hydroxides were washed with THF, and the combined filtrates were vacuum evaporated to give 0.97 g (63%) of IIb as a colorless mobile liquid with bp 81-82° (0.6 mm) and n_D^{20} 1.4862. The product was quite soluble in ordinary organic solvents. Found, %: C 58.2, H 11.5. $C_7H_{16}N_2O$. Calculated, %: C 58.3, H 11.1.

2-Hydroxymethyl-1,4-diazabicyclo[2.2.2]octane Dimethylbromide (IIIb). A mixture of 0.5 g (3.47 mmole) of IIb and 0.67 g (3.47 mmole) of dibromoethane was heated at 130° for 4 h, after which it was triturated with 6 ml of absolute ethanol, and the resulting precipitate

was removed by filtration to give 0.38 g (33%) of IIIb as colorless crystals with mp 244-245° [dec., from ethanol–methanol (10:1)]. The product was quite soluble in water and methanol, less soluble in ethanol and DMF, and only slightly soluble in other ordinary organic solvents. PMR spectrum (δ, ppm): 3.43 s, 6H (CH_3); 3.90-4.60 m, 13 H ($C_6H_{11}N_2CH_2$). Found, %: C 32.4, H 6.1, Br 47.94, N 8.4. $C_9H_{20}Br_2N_2O$. Calculated, %: C 32.5, H 6.0, Br 48.19, N 8.4.

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CHEMISTRY OF ESTERS OF KETO ACIDS OF THE ACETYLENE SERIES.

X.* ADDITION OF AMINES TO 3-PHENYLETHYNYL-1-QUINOXALONE

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The reaction of 3-phenylethynyl-2-quinoxalones with aliphatic and aromatic amines gives alkyl(aryl)imines of 3-phenacylidene-2-quinoxalone, the structures of which were proved by alternative synthesis from 3-phenacylidene-2-quinoxalone and the appropriate amines.

3-Arylethynyl-2-quinoxalones [1] are formed in the reaction of esters of arylethynylglyoxylic acids with o-phenylenediamine in anhydrous solvents. It seemed of interest to study the effect of the quinoxalone ring on the addition of nucleophilic reagents to the acetylenic bond in these compounds; reactions of this sort made it possible to pass to derivatives containing a quinoxaline system with potential pharmacological activity [2, 3].

The electrophilicity of the acetylene bond in ethynylquinoxalones was found to be reduced, but the capacity for reaction with aliphatic and aromatic amines and arylhydrazines is retained (reaction at 80°C for aliphatic nucleophiles and at 100-185° for aromatic nucleophiles). The fact that the addition occurs exclusively at the carbon atom bonded to the aryl grouping constitutes evidence for polarization of the acetylenic bond (see scheme at top of following page).

The structure of products II was proved by alternative synthesis from 3-phenylacylidene-2-quinoxalones (III) and the appropriate amines. Isomerization of the reaction products to an azomethine (IV) or an enamine (V) is possible under the conditions used to carry out the synthesis; the IR and UV spectra were used to prove their structures.

*See [1] for communication IX.

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