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DIAZABICYCLOALKANES WITH NITROGEN ATOMS IN THE NODAL POSITIONS.

5.* SYNTHESIS AND SOME REACTIONS OF 2-HYDROXYMETHYL-1,4-DIAZABICYCLO[2.2.2]OCTANE

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2-Hydroxymethyl-1,4-diazabicyclo[2.2.2]octane was synthesized by reduction of 1,4-diazabicyclo[2.2.2]octane-2-carboxylic acid or its methyl ester with lithium aluminum hydride in tetrahydrofuran and by hydrolysis or hydrogenation of 2-benzyloxymethyl-1,4-diazabicyclo[2.2.2]octane. Depending on the conditions, 2-hydroxymethyl-1,4-diazabicyclo[2.2.2]octane reacts with methyl iodide to give primarily either a bisquaternary or a monoquaternary derivative. The latter is the only product in its alkylation with methyl esters of benzoic and caproic acids.

We have previously described [2, 3] 1,4-diazabicyclo[2.2.2]octane-2-carboxylic acid (I) and 2-benzyloxymethyl-1,4-diazabicyclo[2.2.2]octane (II). Continuing our search for methods for the synthesis of functional derivatives of 1,4-diazabicyclo[2.2.2]octane and our study of the properties of I and II, we used them for the preparation of 2-hydroxymethyl-1,4-diazabicyclo[2.2.2]octane (III) and investigated some of its reactions. 2-Hydroxymethyl-1,4-diazabicyclo[2.2.2]octane bis(methobromide) (IV) has been reported [4]; however, information regarding the synthesis and reactions of base III was not revealed.

The same compound, viz., III, which was characterized in the form of the dihydrobromide (VI), was obtained in the reduction of both acid I and its methyl ester (V) with lithium

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* See [1] for Communication 4.

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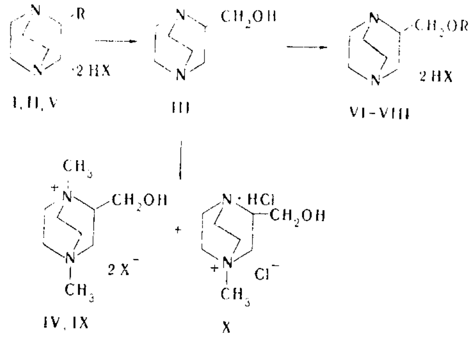
aluminum hydride in tetrahydrofuran (THF). This salt was also isolated after refluxing benzyl derivative II in 48% hydrobromic acid. 2-Hydroxymethyl-1,4-diazabicyclo[2.2.2]octane dihydrochloride (VII) is formed in the hydrogenation of the dihydrochloride (II) of the benzyl derivative in methanol over palladium on charcoal. An analytical sample of base III was obtained from dihydrochloride VII and was purified by sublimation. In all of the subsequent reactions III was used without additional purification. Base III reacts with acetic anhydride under mild conditions to give an acetyl derivative, which was isolated in the form of dihydrochloride VIII.



I $R=COOH$, $HX=HBr$; II $R=CH_2OCH_2C_6H_5$, $HX=HCl$; IV $X=Br$; V $R=COOCH_3$; VI $R=H$, $HX=HBr$; VII $R=H$, $HX=HCl$; VIII $R=COCH_3$, $HX=HCl$; IX $X=I$

Primarily bis(methiodide) IX and a small amount of monoquaternary derivative X, which was isolated in the form of the hydrochloride of the mono(methochloride), are formed by the action of excess methyl iodide in methanol on base III. A small amount of bisquaternary derivative IX is formed along with the monoquaternary salt in the reaction with an equimolar amount of methyl iodide in dioxane. The position of the methyl group in the monoquaternary derivative was not determined; however, it may be assumed that alkylation of base III takes place primarily at the nitrogen atom in the 4 position because of the formation of an intramolecular hydroben bond between the hydroxy group and the nitrogen atom in the 1 position.

One should have expected that the alkylation of base III with weaker alkylating reagents such as carboxylic acid esters, which are known [5, 6] to be capable of alkylating tertiary amines, would proceed more unambiguously to give the monoquaternary salt. However, previous attempts [7, 8] to isolate products of alkylation of 1,4-diazabicyclo[2.2.2]octane with esters of a number of aliphatic and alicyclic acids were unsuccessful.

We used the methyl esters of benzoic acid and the weaker caproic acid in the reaction. In the case of methyl benzoate starting alcohol III is not detected in the reaction mixture after heating for 3 h, and the formation of a compound, the chromatographic behavior of which corresponds to monoquaternary salt X, is observed. The reaction proceeds much more slowly with methyl caproate, and, in addition to the formation of a monoquaternary derivative, a significant amount of starting III remains after heating for 12 h. Bisquaternary derivatives and esters involving the hydroxymethyl group (according to data from the IR spectra) were not detected in the reaction products in either case, although it is known that 1,4-diazabicyclo-[2.2.2]octane is capable of catalyzing the acylation of alcohols [9, 10].

EXPERIMENTAL

The IR spectra of KBr pellets of the compounds were recorded with a UR-20 spectrometer. The PMR spectra were recorded with a Varian A60/56A spectrometer with tetramethylsilane as the external standard. The mass spectrum was obtained with an MS-902 spectrometer at an ionizing voltage of 13 eV. Thin-layer chromatography (TLC) was carried out on Silufol in ethanol—ammonia (5:1) (system A) with detection of the spots by a modification of Dragendorf's method. Paper chromatography was carried out on Leningrad Slow paper in butanol saturated with ammonium hydroxide—methanol (4:1) (system B) with detection of the spots with Dragendorf's reagent.

2-Hydroxymethyl-1,4-diazabicyclo[2.2.2]octane Dihydrobromide (VI). A) From 1,4-Diazabicyclo[2.2.2]octane-2-carboxylic Acid Dihydrobromide (I). A 0.22-g (0.7 mmole) sample of acid I was added in small portions to a suspension of 0.32 g (8.4 mmole) of lithium aluminum hydride in 10 ml of absolute THF, and the mixture was maintained at room temperature for 1 h with constant stirring. It was then refluxed for 6 h, after which it was decomposed with ethyl acetate and evaporated to dryness. The residue was treated with a saturated solution of potassium carbonate and extracted with ether. The extract was evaporated and the residue was dissolved in 2 ml of 48% hydrobromic acid. The solution was evaporated, and the precipitate was washed with absolute ethanol and recrystallized from methanol with the addition of a few drops of water to give 0.05 g (24%) of dihydrobromide VI with mp 266-271°C (decomp.) and R_f 0.7 (system B). The IR spectrum did not contain vibrations of the C=O group. PMR spectrum (in D_2O): 3.8-4.5 ppm (m, ring and CH_2 protons). Found: C 27.5; H 5.4; Br.52.6; N 9.1%. $C_7H_{14}N_2O \cdot 2HBr$. Calculated: C 27.7; H 5.3; Br 52.6; N 9.2%.

B) From Methyl 1,4-Diazabicyclo[2.2.2]octane-2-carboxylate (V). A suspension of 0.28 g (1.64 mmole) of methyl ester V in 20 ml of absolute THF was added to a suspension of 0.49 g (12.9 mmole) of lithium aluminum hydride in 15 ml of absolute THF, and the mixture was maintained at room temperature for 30 min. It was then worked up as described above to give 0.3 g (60%) of dihydrobromide VI with mp 264-271°C (decomp.).

C) By Hydrolysis of 2-Benzyloxymethyl-1,4-diazabicyclo[2.2.2]octane Dihydrochloride (II). A 1-g (3.28 mmole) sample of benzyl derivative II was refluxed in 5 ml of 48% hydrobromic acid for 1 h, after which the solution was evaporated to dryness, and the residue was treated with 5 ml of absolute ethanol. The precipitate was removed by filtration, washed with ether, and recrystallized from methanol with the addition of a few drops of water to give 0.9 g (91%) of dihydrobromide VI with mp 267-271°C (decomp.).

The IR and PMR spectra, as well as the chromatographic behavior in systems A and B, were identical for all three samples.

2-Hydroxymethyl-1,4-diazabicyclo[2.2.2]octane Dihydrochloride (VII). A mixture of 1 g (3.28 mmole) of benzyl derivative II, 1 g of 10% palladium on charcoal, and 15 ml of methanol was stirred in a hydrogen atmosphere at normal pressure. After the theoretical amount of hydrogen had been absorbed, the catalyst was removed by filtration and washed with methanol and water, and the filtrate was evaporated. The residue was triturated with alcohol to give 0.53 g (75%) of dihydrochloride VII with mp 225-230°C (decomp., from aqueous methanol). The PMR spectrum of a solution in D_2O was in agreement with the PMR spectrum of dihydrobromide VI.

2-Hydroxymethyl-1,4-diazabicyclo[2.2.2]octane (III). Base III was obtained by alkalization of salt VII with sodium methoxide in methanol, evaporation, and subsequent extraction with ether. The extract was evaporated, and the residue was sublimed *in vacuo* (5 mm) at 100°C to give base III with mp 70-72°C. PMR spectrum (in CCl_4): 2.58 (m, 11H, ring protons), 3.37 (m, 2H, CH_2O), and 3.82 ppm (s, 1H, OH). Found: M^+ 142. $C_7H_{14}N_2O$. Calculated: M 142.

2-Acetoxymethyl-1,4-diazabicyclo[2.2.2]octane Dihydrochloride (VIII). A 0.11-g (0.78 mmole) sample of base III was dissolved in 5 ml of acetic anhydride, and the solution was allowed to stand at room temperature for 65 h. The acetic anhydride was removed almost completely by distillation *in vacuo*, and the residue was dissolved in ethanol. Hydrogen chloide was passed into the solution, and the mixture was treated with ether. The liberated oil was triturated with ether to give 0.17 g (85%) of VIII with mp 177-184°C (decomp.). IR spectrum: 1745 cm^{-1} (C=O). PMR spectrum (in D_2O): 2.48 (s, 3H, $CH_3C{=}O$), 4.13 (m, 11H, ring protons), and 4.78 ppm (m, 2H, CH_2O). Found: Cl 27.2; N 10.8%. $C_9H_{16}N_2O_2 \cdot 2HCl$. Calculated: Cl 27.5; N 10.9%.

2-Hydroxymethyl-1,4-diazabicyclo[2.2.2]octane Bis(methiodide) (IX). A 0.9-ml (threefold excess) sample of methyl iodide was added to a solution of 0.34 g (2.39 mmole) of base III in 15 ml of absolute methanol, and the mixture was allowed to stand overnight. It was then refluxed for 2 h, after which it was evaporated until crystallization commenced. It was then treated with ether, and the precipitate was removed by filtration and recrystallized three times from absolute ethanol with the addition of a few drops of water to give 0.33 g (29%) of bis(methiodide) IX with mp 188°C (decomp.). The IR spectrum did not contain bands of C—O—C groups. The PMR spectrum is similar to the PMR spectrum of bis(methobromide) IV described in [4]. Found: C 27.9; H 5.7; I 55.0; N 6.0%. $C_9H_{20}I_2N_2O \cdot C_2H_5OH$. Calculated: C 28.0; H 5.6; I 54.0; N 5.9%. The product gave one spot at the start in system B. A small amount of monoquaternary derivative X was isolated from the mother liquor.

2-Hydroxymethyl-1,4-diazabicyclo[2.2.2]octane Mono(methochloride) Hydrochloride (X). A) From III and Methyl Iodide. An equimolar amount (0.16 ml) of methyl iodide was added to a solution of 0.36 g (2.53 mmole) of base III in 5 ml of absolute dioxane. The solution became turbid instantaneously, and an oil was liberated. The mixture was maintained at room temperature for 2 h, after which it was evaporated to dryness. The residue was dissolved in absolute methanol, and ether was added. The resulting oil solidified upon standing. The product gave two spots in system B: one at the start, and one with R_f 0.4. The product was recrystallized from absolute ethanol to give 0.05 g of bisquaternary derivative IX (the spot at the start in system B). The filtrate was evaporated, and the residue (R_f 0.4 in system B) was dissolved in methanol saturated with hydrogen chloride. The solution was evaporated, and the residue was reprecipitated several times from solution in absolute methanol by the addition of ether to give 0.14 g (25%) of hydrochloride X with mp 243-245°C (decomp., in a capillary). PMR spectrum (in D_2O): 3.65 (s, 3H, CH_3N), 3.84-5.25 ppm (m, 13H, ring and CH_2 protons).

B) From III and the Methyl Ester of Benzoic or Caproic Acid. A mixture of 0.38 g (2.67 mmole) of III and 1 ml (a threefold excess) of methyl benzoate was heated at 135-155°C for 3 h until the starting compound vanished (as monitored by TLC). The mixture was treated with ether, and the liberated oil (R_f 0.4 in system B) was reprecipitated several times from methanol by the addition of ether. This product was then dissolved in methanol and treated with hydrogen chloride. The mixture was evaporated to dryness, and the residue was dissolved in methanol and reprecipitated with ether to give 0.09 g (15%) of X with mp 244-247°C (decomp., in a capillary). Found: C 41.3; H 7.9; Cl.30.8; N 12.2%. $C_8H_{17}ClN_2O \cdot HCl$. Calculated: C 41.9; H 7.9; Cl 30.9; N 12.2%. Workup of the mother liquor gave 0.09 g (27%) of benzoic acid. When a mixture of 0.3 g (2.1 mmole) of base III and 2.1 ml of methyl caproate was heated at 140-160°C for 12 h, X was formed, and a significant amount of starting III remained, according to the chromatographic data (in system B). Workup of the reaction mixture as in the case of methyl benzoate gave 0.02 g (4%) of X with mp 243-246°C (decomp., in a capillary). The IR and PMR spectra of X obtained by the different methods were identical.

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