1,4-DIAZABICYCLO[2.2.2]OCTANES.

II.* SYNTHESIS OF 1,4-DIAZABICYCLO[2.2.2]OCTANE METHYLCHLORIDE

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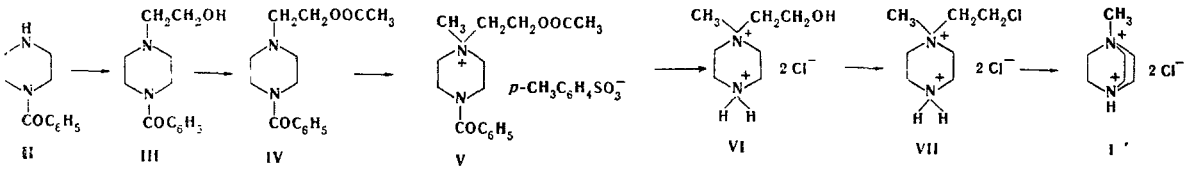
1,4-Diazabicyclo[2.2.2]octane hydrochloride methylchloride was obtained from N-benzoylpiperazine through 1-(2'-hydroxyethyl)-4-benzoylpiperazine, 1-(2'-acetoxyethyl)-4-benzoylpiperazine methyltosylate, 1-(2'-hydroxyethyl)piperazine methylchloride, and 1-(2'-chloroethyl)piperazine methylchloride.

1,4-Diazabicyclo[2.2.2]octane hydrochloride methylchloride (I) has been described [2] as the product of thermal cyclization of 1-methyl-4-(2'-chloroethyl)piperazine methylchloride at 250-254°C. The yield of I in this reaction was not indicated, and it was reported only that it had mp 288-289° after two recrystallizations.

In order to exclude the high-temperature pyrolytic process, which is accompanied by pronounced resinification of the products, we synthesized I from the accessible N-benzoylpiperazine (II) via the scheme



It has previously been shown in the case of 2,2,5,5-tetramethyl-1-(2'-haloethyl)piperazine that tertiary-secondary amines of this type cannot be converted to 1,4-diazabicyclic products, inasmuch as the prevailing reaction gives a spiroimmonium cation, which subsequently either undergoes polymerization or is converted to a hydroxyethyl derivative [3, 4]. 2,2,5,5-Tetramethyl-1-(2'-hydroxyethyl)piperazine was converted through the corresponding O,N-diacetyl derivative and its methyltosylate and methylchloride to 1-(2'-chloroethyl)-2,2,5,5-tetramethylpiperazine methylchloride, which was found capable of undergoing cyclization to the 1,4-diazabicyclic compound. We used a similar principle to eliminate the possibility of spiroimmonium cyclization. The reaction of benzoyl derivative II with ethylene oxide proceeded in a different manner and required chromatographic separation of hydroxyethyl derivative III from the accompanying minor side products. The acetylation of alcohol III with acetic anhydride proceeded smoothly to give the product in 84% yield, but difficulties were encountered in the conversion to the corresponding quaternary salt – methyltosylate V. The reaction in this case involves quaternization of the sterically shielded nitrogen atom and therefore required severe conditions – heating of a mixture of ester IV and methyl p-toluenesulfonate without a solvent for 25 h. Under these conditions, in addition to the formation of quaternary acetoxy derivative V, we observed partial transacylation to give the corresponding O-tosyl ester, which hindered the isolation of V in pure form but did not affect the subsequent synthesis of quaternary alcohol VI. Replacement of the tosyl anion by the Cl^- ion in V was required for the isolation in pure form and the subsequent transformations of monoquaternary alcohol VI. To achieve this, we treated quaternary salt V with the Cl^- form of IRA-400 ion-exchange resin. The substances were eluted from the ion-exchange resin with distilled water until the eluate gave a negative reaction for chloride ions. The benzoic acid and a certain amount of p-toluenesulfonic acid that were liberated after

*See [1] for communication I.

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subsequent saponification of the ester and amide groups by refluxing with 6 N HCl were extracted with ether, and evaporation of the aqueous hydrochloric acid solution gave 1-methyl-1-(2'-hydroxyethyl)piperazinium chloride hydrochloride (VI). Compound VI was obtained in 58% yield based on acetoxy base IV. The subsequent replacement of the hydroxyl group in VI by chlorine under the influence of thionyl chloride proceeded smoothly only on refluxing in an equimolar amount of pyridine that had been thoroughly dried over barium oxide. The resulting chloride hydrochloride methylchloride (VII) was readily cyclized on treatment with aqueous sodium bicarbonate solution at room temperature to the corresponding 1,4-diazabicyclo[2.2.2]octane derivative (I). 1,4-Diazabicyclo[2.2.2]octane hydrochloride methylchloride (I), with mp 289-290°, was obtained in 68% yield after separation from the side products of polycondensation, etc., and also from sodium chloride and recrystallization from alcohols; this made this compound accessible for subsequent studies.

EXPERIMENTAL

1-(2'-Hydroxyethyl)-4-benzoylpiperazine (III). A 4.4-g (100 mmole) sample of ethylene oxide was added to a solution of 19 g (100 mmole) of benzoylpiperazine (II) in 20 ml of methanol, and the mixture was refluxed for 3 h. It was then vacuum evaporated, and the residue was subjected to chromatography with a column (d 30 mm, h 500 mm) filled with silica gel (0.25-0.5 mesh). The impurities were initially eluted with ethyl acetate, and base III was then eluted with ethyl acetate–methanol (3 : 1) with monitoring of the elution process by thin-layer chromatography (TLC) on Silufol in a methanol–ethyl acetate (1 : 1) system (detection by means of o-chlorotolidine); III had R_f 0.5, and the impurities had R_f values > 0.55. A total of 16.8 g (71.5%) of III was obtained in the form of a viscous yellowish oily substance that was soluble in water, alcohols, acetone, ether, benzene, and chloroform and only slightly soluble in heptane, cyclohexane, and petroleum ether. The product had bp 219-220° (0.7 mm) and n_D^{20} 1.5539. Found: C 66.3; H 7.9; N 11.6%. $C_{13}H_{18}N_2O_2$. Calculated: C 66.7; H 7.7; N 12.0%.

s-(2'-Acetoxyethyl)-4-benzoylpiperazine (IV). An 8.4-g (36 mmole) sample of III was dissolved in 80 ml of acetic anhydride, and the solution was allowed to stand at room temperature for 12 h. It was then vacuum evaporated, and the residue was dissolved in 20 ml of water. The aqueous solution was made alkaline with sodium carbonate and extracted with ether. The ether extract was dried with magnesium sulfate and evaporated to give 8.3g (84%) of colorless crystals of IV with mp 58-59° (from hexane). The product was quite soluble in water and most ordinary organic solvents but only slightly soluble in heptane and petroleum ether. Found: C 65.4; H 7.5; N 10.0%. $C_{15}H_{20}N_2O_3$. Calculated: C 65.3; H 7.3; N 10.0%

1-Methyl-1-(2'-hydroxyethyl)piperazinium Chloride Hydrochloride (VI). A mixture of 6 g (27.6 mmole) of IV and 12 g (64.5 mmole) of methyl p-toluenesulfonate was heated at 120-125° for 25 h, after which the viscous mass was triturated with ether (three 20-ml portions) and dissolved in 30 ml of water. The aqueous solution was subjected to anion exchange with a column (d 10 mm, h 300 mm) filled with 15 g of the Cl^- form of IRA-4000 ion-exchange resin. The column was washed with 150-200 ml of distilled water after the solution had been applied to the column until the eluate gave a negative reaction for Cl^- ions (with $AgNO_3$ solution). The combined eluate was vacuum evaporated, the residue was dissolved in 20 ml of 6 N hydrochloric acid, and the acid solution was refluxed for 19 h. The benzoic acid and traces of p-toluenesulfonic acid were extracted with ether, the aqueous solution was evaporated to dryness, and the residue was triturated with 20 ml of methanol to give 2.73 g (58% based on IV) of colorless crystals of hydrochloride VI with mp 210-211° (from ethanol). The hydrochloride was quite soluble in water, only slightly soluble in alcohols, and insoluble in ether and acetone. Found: C 38.5; H 8.5; Cl 32.2; N 12.5%. $C_7H_{17}ClN_2O \cdot HCl$. Calculated: C 38.7; H 8.3; Cl 32.7; N 12.9%.

1,4-Diazabicyclo[2.2.2]octane Methylchloride Hydrochloride (I). A solution of 2.73 g (12.5 mmole) of hydrochloride VI, 2.3 ml (31.5 mmole) of purified thionyl chloride, and 1.07 g (12.5 mmole) of dry (fractionated over barium oxide) pyridine was refluxed for 4 h, after which it was vacuum evaporated. The residue was triturated with 10 ml of absolute ethanol, and the mixture was filtered to give 1.81 g (61%) of hydrochloride VII with mp > 350° (dec.). A total of 15 ml of 6% sodium bicarbonate solution was added dropwise with stirring in the course of an hour to a solution of 1.3 g of hydrochloride VII in 13 ml of water, after which the mixture was allowed to stand at room temperature for 24 h. It was then acidified to pH 3 with concentrated hydrochloric acid and evaporated to dryness. The residue was triturated with 10 ml of absolute ethanol and recrystallized from a mixture of equal volumes of methanol and absolute ethanol to give 0.75 g (68%) of colorless crystals of I with mp 289-290°. The product was quite soluble in water and methanol, slightly soluble in ethanol, and insoluble in acetone, ether, chloroform, and benzene. Found: C 42.4; H 8.3; Cl 35.3; N 14.1%. $C_7H_{15}ClN_2 \cdot HCl$. Calculated: C 42.2; H 8.0; Cl 35.6; N 14.1%.

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SYNTHESIS OF 3-SUBSTITUTED AND 1,3-DISUBSTITUTED 4,7-DIAZAINDOLES

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On the basis of a study of electrophilic substitution reactions (the Mannich reaction and bromination) it was shown that 4,7-diazaindoles react with greater difficulty with "soft" electrophilic agents than indoles or 4- and 7-monoazaindoles. 3-Substituted and 1,3-disubstituted 4,7-diazaindoles containing amino(dialkylamino)alkyl substituents in the 1 or 3 positions were synthesized.

It has previously been shown in the case of a series of electrophilic substitution reactions that the incorporation of a nitrogen heteroatom in the six-membered ring of the indole molecule reduces the ability of the compounds to react with "soft" electrophilic agents (Vilsmeier complexes and cyanomethylation and dialkylaminomethylation intermediates), and the location of the introduced heteroatom has practically no effect on the course of the process [1]. The aim of the present research was a comparison of the reactivities of 4,7-diazaindoles [2], indoles, and 4- and 7-monoazaindoles in electrophilic substitution reactions. For this, we carried out the bromination of 4,7-diazaindole (I) and its reaction with paraformaldehyde and N-methylpiperazine (the Mannich reaction) under the same conditions as those used in the monoazaindole series [3].

The results of the bromination of indoles, the isomeric azaindoles, and 4,7-diazaindole were practically identical, but 4,7-diazaindole displayed even lower reactivity than monoazaindoles in the Mannich reaction. The reaction of I with paraformaldehyde and N-methylpiperazine hydrochloride in refluxing butanol proceeded very slowly, and a certain amount of starting I remained in the reaction products, according to thin-layer chromatography (TLC), even after refluxing for 15 h. (In the case of the monoazaindoles, the reaction was complete after refluxing for 15 min in butanol.)

The location of the substituents at the $C_{(3)}$ atom in the products of the electrophilic reaction was confirmed by a comparison of the PMR spectra of I, II, and IV. When a bromine atom or an N-methylpiperazinomethyl group is introduced in the I molecule, the stronger-field signal of the proton in the 3 position vanishes in the PMR spectrum. [PMR spectrum of I: 6.76 (d, 3-H) and 7.81 ppm (d, 2-H).* PMR spectrum of II: 7.49 ppm (s, 2-H). PMR spectrum of IV: 8.05 ppm (s, 2-H).]

As in the case of indole and monoazaindole derivatives, the formation of small amounts of a disubstituted methane – bis(4,7-diaza-3-indolyl)methane (III) – which we were able to isolate and confirm the structure of by mass spectroscopy, was observed in the Mannich reaction.

The decrease in the reactivities on passing from indoles and their monoaza analogs to 4,7-diazaindole was exhibited not only in thereaction with "soft" electrophilic agents but also in the condensation of 3-formyl-4,7-diazaindole (V) [4] with nitroalkanes.

* The misprint in [2] was not corrected: the 2-H and 3-H signals were erroneously interchanged.

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