ness. The residue was dissolved in 3 ml of water, and the solution was acidified to pH 5 with concentrated HCl and cooled. The precipitate was removed by filtration and crystallized from water. The yield was 0.1 g.

5,5'(4,4')-Ureylenebis[imidazole-4(5) sulfonamide] (X). A 0.21-g (0.97 mmole) sample of VI was refluxed in 10 ml of 80% dioxane or water for 10 min, after which the mixture was vacuum evaporated to dryness, and the residue was crystallized from water. The yield was 0.11 g.

3,4-Dihydro-3-oxoimidazo[4, 5-e]-1,2,4-thiadiazine 1,1-Dioxide (XI). A 1-g (4.63 mmole) sample of VI was added in portions to 10 ml of refluxing pyridine, and the mixture was allowed to stand for 5 min. It was then cooled and treated with 10 ml of ethanol, and the resulting precipitate was removed by filtration and crystallized from water acidified to pH 4. The yield was 0.7 g.

LITERATURE CITED

1. V. S. Mokrushin, V. I. Ofitserov, T. V. Rapakova, A. G. Tsaur, and Z. V. Pushkareva, Khim. Geterotsikl. Soedin., No. 4, 556 (1976).
2. L. L. Bennett and H. T. Baker, J. Am. Chem. Soc., 79, 2188 (1957).
3. M. H. Fisher, W. H. Nickolson, and R. S. Stuart, Can. J. Chem., 31, 501 (1961).
4. V. S. Mokrushin, V. I. Nifontov, Z. V. Pushkareva, and V. I. Ofitserov, Khim. Geterotsikl. Soedin., No. 10, 1421 (1971).
5. V. I. Ofitserov, V. I. Nifontov, V. S. Mokrushin, Z. V. Pushkareva, and E. A. Shtokareva, Inventor's Certificate No. 437,764 (1972); Byul. Izobr., No. 28, 53 (1974).

1,4-DIAZABICYCLO[2.2.2]OCTANES

III*. SYNTHESIS AND PROPERTIES OF 1,4-DIAZABICYCLO[2.2.2] OCTANE-2-CARBOXYLIC ACID BIS(METHYLBROMIDE)

L. B. Mrachkovskaya, K. F. Turchin, and L. N. Yakhontov

UDC 547.895'861.3.8.07:542.944

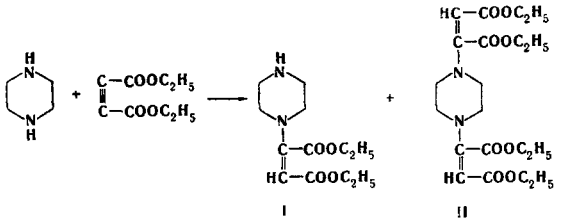
1,4-Diazabicyclo[2.2.2]octane-2-carboxylic acid bis(methylbromide), which is readily converted with splitting out of hydrogen bromide to the corresponding quaternary betaine, was synthesized.

1,4-Diazabicyclo[2.2.2]octane-2-carboxylic acid derivatives are of interest in connection with the pharmacological activity of the corresponding deaza analogs – quinuclidine-2-carboxylic acid derivatives and primarily diokhin (diethylaminoethyl quinuclidine-2-carboxylate dimethiodide). Moreover, 1,4-diazabicyclo[2.2.2]-octane-2-carboxylic acid and its derivatives are unknown, and attempts to obtain them have been unsuccessful: intramolecular fragmentation occurs during the synthesis through 4-(β,β-diethoxycarbonylethyl)piperazines [2, 3], 1,1,4,4-tetramethylpiperazinium bromide is formed in reactions of 1,4-dimethylpiperazine with methyl α,β-dibromopropionate or α,β-dibromopropionitrile [4], and monothiooxalic acid bis(N-methylpiperazide) is obtained in the synthesis from 3-(N-methylpiperazinyl)propionic acid through its α-bromo derivative.

Our experiments on the condensation of piperazine with diethyl acetylenedicarboxylate also gave negative results. Instead of the bicyclic derivative we obtained a mixture of products, from which we isolated 1-(α,β-diethoxycarbonylethylene)piperazine (I) and 1,4-bis(α,β-diethoxycarbonylethylene)piperazine (II).

* See [1] for communication II.

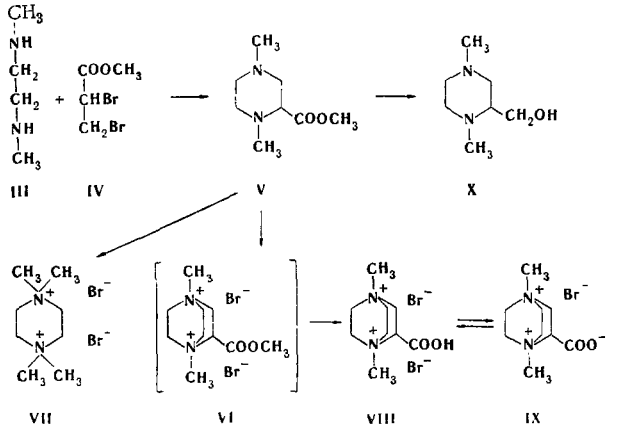
S. Ordzhonikidze All-Union Scientific-Research Pharmaceutical-Chemistry Institute, Moscow. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 8, pp. 1123-1126, August, 1976. Original article submitted September 19, 1975.



I II

Compounds I and II display the properties of enamines and are hydrolyzed by the action of an alcohol solution of hydrogen chloride on the starting components. However, I and II are not reduced at the double bond by catalytic hydrogenation with platinum or by the action of sodium in alcohol, and, in contrast to 1-(β,β-diethoxycarbonylethylene)-4-methylpiperazine [3], do not undergo reductive fragmentation. Heating I in refluxing xylene does not lead to closing of the 1,4-diazabicyclic system but is accompanied by disproportionation to give unsubstituted piperazine and 1,4-disubstituted derivative II.

1,4-Diazabicyclo[2.2.2]octane-2-carboxylic acid bis(methylbromide) was synthesized by the general method for the preparation of 1,4-diazabicyclic systems with functional substituents [5]. N,N'-Dimethylethylenediamine (III) and methyl α,β-dibromopropionate (IV), from which methyl 1,4-dimethylpiperazine-2-carboxylate (V)* was obtained, were used as the starting materials.



III IV V X

VII VI VIII IX

The reaction of piperazine ester V with 1,2-dibromoethane led to methyl 1,4-diazabicyclo[2.2.2]octane-2-carboxylate bis(methylbromide) (VI), along with a small amount of 1,1,4,4-tetramethylpiperazinium dibromide (VII), the formation of which was also observed in the reaction of 1,4-dimethylpiperazine with substituted 1,2-dibromoalkanes. Compound VI was subjected, without isolation directly to saponification to 1,4-diazabicyclo[2.2.2]octane-2-carboxylic acid bis(methylbromide) (VIII). A carbonyl band is observed in the IR spectrum of VIII at 1710 cm^{-1}. The PMR spectrum contains two singlets at 3.42 and 3.52 ppm affiliated with the protons of the $N-CH_3$ group. The signal of the proton in the α position relative to the COOH group is a triplet at 4.63 ppm. The remaining signals form a multiplet at 3.93-4.28 ppm. The ratio of the intensities of the indicated protons is 3:3:1:10.

An interesting feature of 1,4-diazabicyclo[2.2.2]octane-2-carboxylic acid bis(methylbromide) (VIII) is its ability to split out a molecule of hydrogen bromide to give inner quaternary salt IX on treatment with water and alcohol or on heating. Compound IX is reconverted to bis(methylbromide) VIII when it is reprecipitated from hydrobromic acid by the addition of acetone. Thus the conversion of bis(methylbromide) VII to betaine IX is reversible.

EXPERIMENTAL

The PMR spectra of D_2O solutions of the compounds were recorded with a JNM-4H-100 spectrometer with $(CH_3)_3COOH$ as the internal standard (δ_{CH_3} 1.23 ppm). The IR spectra of mineral oil suspensions of the compounds were recorded with a Perkin-Elmer 457 spectrometer. Thin-layer chromatography (TLC) was carried out on Silufol UV-254 plates in a methanol-25% ammonium hydroxide system (10:1) with development by o-chlorotolidine (blue coloration). Analysis by gas-liquid chromatography (GLC) was carried out with a Pye Unicam-104 chromatograph with a flame-ionization detector and a 2.1 m by 4 mm column filled with 10%

*1,4-Dimethyl-2-hydroxymethylpiperazine (X), identical to the compound previously obtained [7], was obtained by reduction of V with lithium aluminum hydride.

SE-30 silicone elastomer on silanized diatomite (100-120 mesh). The carrier gas (nitrogen) flow rate was 30 ml/min, and the column temperature was 150°. The retention times were 2.3 min for piperazine, 6 min for diethyl acetylenedicarboxylate and 12.5 and 16.2 min, respectively, for I and II (with temperature programming from 150 to 250° with an initial period of 6 min and a temperature-rise rate of 32 deg/min).

Condensation of Piperazine with Diethyl Acetylenedicarboxylate. A 10-g (59 mmole) sample of diethyl acetylenedicarboxylate was added with stirring to a solution of 11.4 g (59 mmole) of piperazine in 400 ml of anhydrous ether. After 48 h, colorless crystals of 1,4-bis(α,β-diethoxycarbonylethylene)piperazine (II) were removed by filtration and washed with ether to give 3.92 g (23%) of II with mp 152-153° (from ethanol). The product was quite soluble in chloroform, less soluble in alcohols and acetone, and insoluble in water and ether; R_f = .78. IR spectrum: 1685 and 1735 cm^{-1} (C=C). Found: C 56.4; H 7.1; N 6.7%. $C_{20}H_{30}N_2O_8$. Calculated: C 56.4; H 7.0; N 6.6%.

The ether solution remaining after separation of II was washed with three 30-ml portions of water. The ether was removed by distillation, and the residue was vacuum fractionated to give 6.5 g (43%) of 1-(α,β-diethoxycarbonylethylene)piperazine (I) with bp 140-141° (0.5 mm). The product was an oil that was quite soluble in ordinary organic solvents and only slightly soluble in water; R_f = 0.55. IR spectrum: 1695 and 1740 cm^{-1} (C=O). Found: C 56.0; H 7.3; N 10.5%. $C_{12}H_{20}N_2O_4$. Calculated: C 56.3; H 7.8; N 10.9%.

The aqueous extract was saturated with alkali and extracted with ether to give 3.58 g (31%) of piperazine hexahydrate.

Attempted Cyclization of 1-(α,β-Diethoxycarbonylethylene)piperazine (I). A) A solution of 1 g (39 mmole) of I in 100 ml of anhydrous xylene was refluxed for 20 h, after which the xylene was removed by vacuum distillation. According to GLC data, the analyzed sample contained 5.5% piperazine and 5.5% II.

B) A 0.5-g (2 mmole) sample of I was added to a solution of 0.15 g (2.2 mmole) of sodium ethoxide in 15 ml of anhydrous ethanol, and the mixture was refluxed for 5 h. It was then vacuum evaporated, the residue was dissolved in 5 ml of water, and the aqueous solution was extracted with chloroform. According to GLC data, the extract contained 46% I, and piperazine and II peaks were absent.

Methyl 1,4-Dimethylpiperazine-2-carboxylate (V). A mixture of 17 g (107 mmole) of the dihydrochloride of III, 25.9 g (107 mmole) of IV, 27 g (215 mmole) of anhydrous sodium carbonate, 21.3 g (215 mmole) of triethylamine, and 250 ml of methanol was refluxed with stirring for 4 h, after which it was cooled, and the precipitate was removed by filtration and washed with methanol. The combined filtrate was vacuum evaporated, and the residue was dissolved in 30 ml of water. The aqueous solution was extracted with benzene, and the benzene extract was dried with $MgSO_4$ and vacuum evaporated. The residue was distilled at 115-116° (20 mm) to give 11.75 g (64%) of V as a colorless oil with a weak amine odor and n_D^{20} 1.4610. The product was quite soluble in ordinary organic solvents but less soluble in water. Found: C 56.0; H 9.2; N 16.1%. $C_8H_{16}N_2O_2$. Calculated: C 55.8; H 9.3; N 16.3%.

1,4-Dimethyl-2-hydroxymethylpiperazine (X). A solution of 1.72 g (10 mmole) of V in 20 ml of ether was added to a suspension of 1.5 g of lithium aluminum hydride in 20 ml of ether, and the mixture was refluxed for 3 h. It was then worked up in the usual manner to give 0.9 g (60%) of X with bp 81-82° (0.6 mm) and n_D^{20} 1.4862. The product was identical (according to its IR spectrum) to a sample synthesized by the method in [5].

1,4-Diazabicyclo[2.2.2]octane-2-carboxylic Acid Bis(methylbromide) (VIII). A mixture of 6.88 g (40 mmole) of V and 7.52 g (40 mmole) of 1,2-dibromoethane was heated at 125-130° for 3 h, after which it was cooled and triturated with 50 ml of methanol. The mixture was then filtered to give 1.3 g (11%) of 1,1,4,4-tetramethylpiperazinium dibromide (VII) with mp 324-325° (dec.); no melting-point depression was observed for a mixture of this product with an authentic sample of VII. The IR and PMR spectra of the two samples were identical.

The methanol solution remaining after separation of VII was vacuum evaporated, and the residue was dissolved in 120 ml of 10% HBr and refluxed for 9 h. It was then vacuum evaporated to dryness, and the residue was triturated by heating with 20 ml of anhydrous ethanol and recrystallized from methanol. It was then dissolved in 20 ml of 48% HBr, and the solution was diluted with acetone until precipitation ceased. The VIII was removed by filtration, washed with acetone and anhydrous ether, and dried at room temperature to give 2.1 g (15%) of colorless crystals with mp 194-195° (dec.). The product was quite soluble in water, less soluble in alcohols, and insoluble in the other ordinary organic solvents. Found: Br 46.4; N 8.1%. $C_9H_{18}Br_2N_2O_2$. Calculated: Br 46.3; N 8.1%.

A 0.2-g sample of bis(methylbromide) VIII was dried in vacuo at 130° for 10 h over sodium hydroxide. It underwent conversion to IX, during which it darkened somewhat and became hygroscopic. The product had mp 175-177° (dec.). Found: Br 29.9; N 10.0%. $C_9H_{17}BrN_2O_2$. Calculated: Br 30.2; N 10.0%.

Bis(methylbromide) VIII, with mp 194-195° (dec.), precipitated when IX was dissolved in 48% HBr, and the solution was diluted with acetone. The product was identical to that described above with respect to the results of elementary analysis and the PMR and IR spectra.

LITERATURE CITED

1. L. B. Mrachkovskaya, and L. N. Yakhontov, Khim. Geterotsikl. Soedin., No. 6, 845 (1976).
2. L. N. Yakhontov, L. B. Mrachkovskaya, A. I. Ermakov, K. F. Turchin, and T. F. Vlasova, Zh. Orgn. Khim., No. 10, 868 (1974).
3. L. B. Mrachkovskaya, K. F. Turchin, and L. N. Yakhontov, Zh. Org. Khim., 11, 420 (1975).
4. L. B. Mrachkovskaya and L. N. Yakhontov, Khim. Geterotsikl. Soedin., No. 6, 856 (1975).
5. L. B. Mrachkovskaya, K. F. Turchin, and L. N. Yakhontov, Khim. Geterotsikl. Soedin., No. 2, 272 (1976).