QUATERNARY AMMONIUM SALTS OF BIS-3-AZATRICYCLO[5,3,0,$1^{1,5}$]UNDECANE

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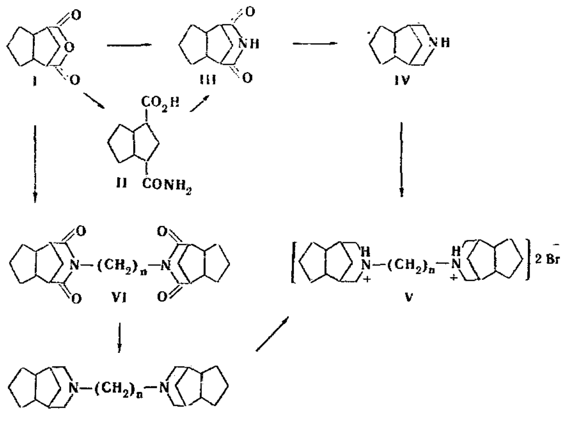
The reaction of the anhydride of exo-cis-bicyclo[3,3,0]octane-2,4-dicarboxylic acid with ammonia followed by the reduction of the resulting imide with lithium aluminum hydride has yielded 3-azatricyclo[5,3,0,$1^{1,5}$]undecane, from which a number of quaternary bisammonium salts have been obtained with dihaloalkanes. These salts have also been synthesized from the anhydride of exo-cis-bicyclo[3,3,0] octane-2,4-dicarboxylic acid and polymethylenediamines.

It is known from the information in the literature that quaternary ammonium salts of azabicyclo[3,3,0] octane [1] and azabicyclo[4,3,0]nonane [2] possess a considerable ganglion-blocking activity and also a curaremimetic activity combined with low toxicity. Continuing investigations in the field of the chemistry of bicyclooctane [3], we have obtained 3-azatricyclo [5,3,0,$1^{1,5}$]undecane (IV) and have isolated its quaternary salts, which should also possess the activity mentioned. The synthesis of IV was effected by the reaction of the anhydride of bicyclo[3,3,0]octane-2, 4-dicarboxylic acid (I) with an aqueous solution of ammonia. The first stage of this reaction is the formation of the amino acid II, which, on being heated to 200–220° C, is converted into the imide III. The reduction of the imide with lithium aluminum hydride leads to IV in good yield. The behavior and properties of this tricyclic amine are similar to those of piperidine. Thus, it readily gives stable salts with acetic, hydrochloric, and sulfuric acids. On standing in the air, it is rapidly converted into a solid product which is identical with the carbonate obtained by the treatment of the amine with carbon dioxide. On heating, the carbonate decomposes with the liberation of carbon dioxide and the initial tricyclic amine. Without the access of air, the amine remains unchanged for a long time. Compound IV reacts with mono- and dihaloalkanes and gives the corresponding salt-like products in good yield. In this way we synthesized salts of bis(3-azatricyclo[5, 3, 0, $1^{1,5}$]-3-undecyl)alkanes (V, n = 2, 4, 6). Similar salts of bisammonium compounds were obtained from the anhydride and polymethylenediamines with subsequent reduction of the imides formed by means of lithium aluminum hydride and their quaternization with alkyl halides. The salts synthesized are being sent for testing as relaxants.



EXPERIMENTAL

The anhydride of exo-cis-bicyclo[3,3,0]octane-2,4-dicarboxylic acid (I) was obtained by boiling the acid with acetic anhydride by the method described previously [3]. Bp 55–156° C (3 mm).

Monoamide of exo-cis-bicyclo[3,3,0]octane-2,4-dicarboxylic acid (II). Over 30 min, 13 g of the anhydride I was added in small portions with stirring to 50 ml of 25% aqueous ammonia. After the anhydride had dissolved completely, the mixture was allowed to stand for 1 hr. The excess of ammonia was eliminated by means of a water pump, and the residual solution was acidified with concentrated HCl with cooling. The crystals that deposited were filtered off on a Büchner funnel and washed with a small amount of ice water. This gave 14.0 g of reaction product. Mp 210–211° C (from water). Found, %: C 60.34; H. 7.72; N 7.13. Calculated for $C_{10}H_{15}NO_3$, %: C 60.91; H 7.61; N 7.10.

Imide of exo-cis-bicyclo[3,3,0]octane-2,4-dicarboxylic acid (III). With stirring, 15 g of the anhydride I was added in small portions to 60 ml of 25% aqueous ammonia. After the complete dissolution of the anhydride, the excess of ammonia and the water were distilled off and the temperature of the reaction mixture was gradually raised to 200–220° C and kept there for 1 hr. The resulting melt was crystallized from water, giving 13.0 g of imide. Mp 135–136° C. Found, %: N 7.96. Calculated for $C_{10}H_{13}NO_2$, %: N 7.82.

When the amido acid (II) was fused under the same conditions (200–220° C, 1 hr), the imide was obtained with a yield of 90%. Mp 136–137° C.

3-Azatricyclo[5,3,0,$1^{1,5}$]undecane (IV). With stirring, 25 g of the imide III in 250 ml of absolute tetrahydrofuran was added dropwise over 30 min to 500 ml of a 0.5 M ethereal solution of $LiAlH_4$, and then the mixture was kept at 40° C for 3 hr. The excess of $LiAlH_4$ was decomposed with a small amount of water, and the ethereal layer was separated off and dried over $MgSO_4$. The ether was driven off under vacuum, and the residue was distilled to give 16 g of the tricyclic amine. Bp 99° C (13 mm); n_D^{14} 1.5100.

Ethiodide of IV, mp 192–194° C (from methanol). Found, %: N 4.26, I 39.96. Calculated for $C_{12}H_{22}IN$, %: N 4.16, I 39.06.

The carbonate of IV decomposes at 70° C. Found, %: C 69.41; H 9.89; N 7.69. Calculated for $C_{21}H_{36}N_2O_3$, %: C 69.23; H 9.89; N 7.69.

Acetate of IV, mp 112° C (from methanol). Found, %: C 68.46; H 10.27; N 6.64. Calculated for $C_{12}H_{21}NO_2$, %: C 68.24; H 9.95 N 6.63.

Preparation of quaternary salts of the bis(3-azatricyclo[5,3,0,$1^{1,5}$]-3-undecyl)alkanes (V). 0.02 mole of the tricyclic amine was added to 0.01 mole of a dibromoalkane in absolute acetone, and the mixture was left for 1 hr. Then it was boiled for 1 hr and left overnight. The crystals of the hydrobromide V that had deposited were filtered off, washed with ether, and recrystallized from absolute methanol. Bis(3-azatricyclo[5,3,0,$1^{1,5}$]-3-undecyl)butane hydrobromide, mp 253–254° C (decomp.). Found, %: N 5.64, Br 33.89. Calculated for $C_{24}H_{40}N_2 \cdot 2HBr$, %: N 5.94, Br 34.58. Bis(3-azatricyclo[5,3,0,$1^{1,5}$]-3-undecyl)hexane hydrobromide, mp 255° C (decomp.). Found, %:

N 4.93, Br 28.88. Calculated for $C_{26}H_{44}N_2 \cdot 2HBr$, %: N 5.12, Br 29.30.

Preparation of bis(3-azatricyclo[5,3,0,$1^{1,5}$]undecane-2,4-dion-3-yl)alkanes (VI). To 0.02 mole of I was added 0.011 mole of a polymethylenediamine in benzene. The temperature was slowly raised to 220–230° C, and the reaction mixture was kept at this temperature for 1 hr. After cooling, the VI obtained was recrystallized from aqueous ethanol. Bis(3-azatricyclo[5,3,0,$1^{1,5}$]undecane-2,4-dion-3-yl)ethane, mp 92–93° C. Found, %: N 8.01. Calculated for $C_{22}H_{28}N_2O_4$, %: N 7.29. Bis(3-azatricyclo[5,3,0,$1^{1,5}$]undecane-2,4-dion-3-yl(hexane, mp 134–135° C. Found, %: C 70.42; H 8.24; N 6.20. Calculated for $C_{26}H_{35}N_2O_4$, %: C 70.90; H 8.18; N 6.36.

Reduction of bis(3-azatricyclo[5,3,0,$1^{1,5}$]undecane-2,4-dion-3-yl)alkanes with lithium aluminum hydride. In drops, with stirring, 0.01 mole of VI in tetrahydrofuran was added to 100 ml of an ethereal solution of $LiAlH_4$, and the reaction mixture was stirred for 4 hr. The excess of $LiAlH_4$ was decomposed with a small amount of water, and the ethereal layer was separated off and dried over $MgSO_4$. The ether was distilled off in vacuum and the crude product was used directly for the preparation of the quaternary salts V. Bis(3-azatricyclo[5,3,0,$1^{1,5}$]-3-undecyl)ethane hydrobromide, mp 277° C (decomp.). Found, %: N 5.65, Br 32.40. Calculated for $C_{22}H_{36}N_2 \cdot 2HBr$, %: N 5.71, Br 32.60. Bis)3-azatricyclo[5,3,0,$1^{1,5}$]-3-undecyl) hexane hydrobromide, mp 256° C (decomp.). Found, %: N 5.02, Br 29.03. Calculated for $C_{26}H_{44}N_2 \cdot 2HBr$, %: N 5.12, Br 29.30.

REFERENCES

1. L. Rice and C. Grogan, J. Org. Chem., 24, 7, 1959.

2. L. Rice and C. Grogan, J. Am. Chem. Soc., 77, 616, 1955.

3. L. I. Vereshchagain, L. D. Gavrilov, T. A. Alesina, G. A. Nikolaiko, and I. V. Kalechits, Neftekhimiya, 6, 355, 1966.

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