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THE SYNTHESIS OF 7-HYDROXY-3, 9-DIAZABICYCLO[3.3.1]NONANE

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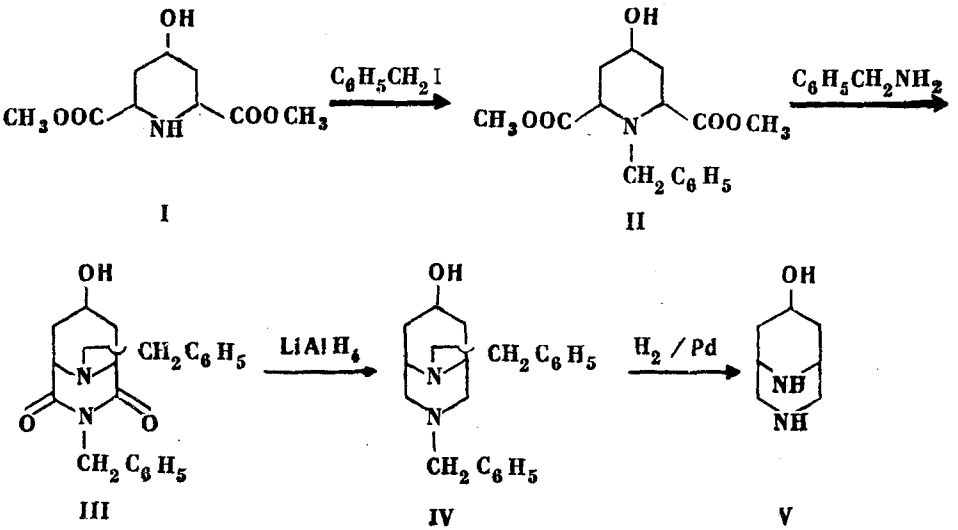
7-Hydroxy-3, 9-diazabicyclo[3.3.1]nonane is synthesized, starting from the dimethyl ester of the 4-hydroxypiperidine-2, 6-dicarboxylic acid, by preparing the N-benzyl derivative and cyclizing the latter with benzylamine to the benzylimide of the 1-benzyl-4-hydroxypiperidine-2, 6-dicarboxylic acid. On reduction of the given imide with lithium aluminum hydride and catalytic hydrogenolysis of the benzyl groups, the final 7-hydroxy-3, 9-diazabicyclo[3.3.1]nonane is obtained, the three-dimensional structure of which (chair-chair type) is proved by comparison of its methyl derivative with a known compound of demonstrated three-dimensional structure.

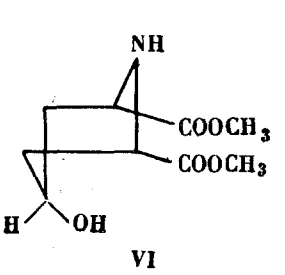
In a previous report the synthesis, structure and several derivatives of 7-hydroxy-9-methyl-3, 9-diazabicyclo-[3.3.1]nonane were described. In the present paper the synthesis of the first member of this series of compounds, unsubstituted 7-hydroxy-3, 9-diazabicyclo[3.3.1]nonane, is presented.

The starting crystalline isomer of the dimethyl ester of 4-hydroxypiperidine-2, 6-dicarboxylic acid (I), mp 134-135°, was used to obtain the 7-hydroxy-3, 9-diazabicyclo[3.3.1]nonane (V) in accordance with the scheme:

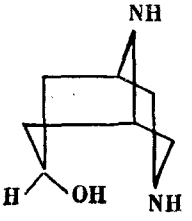


The benzylation of (I) with benzyl iodide gives the dimethyl ester of 1-benzyl-4-hydroxypiperidine-2, 6-dicarboxylic acid (II) which is cyclized with benzylamine to the benzylimide of 1-benzyl-4-hydroxypiperidine-2, 6-dicarboxylic acid (III) in 58% yield. Reduction of the latter with lithium aluminum hydride gives 7-hydroxy-3, 9-dibenzyl-3, 9-diazabycyclo[3.3.1]nonane (IV). The debenzylation of (IV) is accomplished by hydrogenation in the presence of palladium.

The structures of the crystalline dimethyl ester of 4-hydroxypiperidine-2, 6-dicarboxylic acid (I) and 7-hydroxy-3, 9-diazabicyclo[3.3.1]nonane (V) have been proved. By methylation of (I) with methyl iodide the crystalline isomer of the dimethyl ester of 1-methyl-4-hydroxypiperidine-2, 6-dicarboxylic acid, mp 92-94°, was obtained. This, as shown earlier [1], has cis carboxyl groups and the OH group on the same side of the plane of the molecule as the carbmethoxyl groups. Hence it follows that the diester (I) has the three-dimensional structure represented by formula (VI). As might be expected, this compound does not form a cyclic crystalline derivative with n-nitrobenzaldehyde [1] and its N-benzoyl derivative does not undergo a transacylation reaction (N → O), which confirms the structure given.

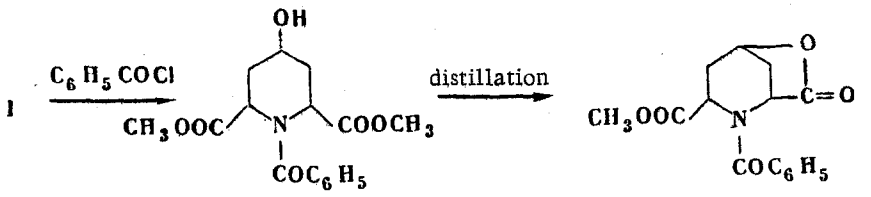


VI



IX

The dimethyl ester of 1-benzoyl-4-hydroxypiperidine-2, 6-dicarboxylic acid (VII), needed for the transacylation reaction, was synthesized by the reacting I with benzoyl chloride in pyridine in the cold. On distillation under vacuum the benzoyl derivative formed gives the lactone VIII. To prevent lactonization, the product of the reaction of (I) with benzoyl chloride, which is not distilled, is crystallized from ether.



VII VIII

On methylation of 7-hydroxy-3, 9-diazabicyclo[3.3.1]nonane (V), there is formed a compound identical with the 7-hydroxy-3, 9-dimethyldiazabicyclo[3.3.1]nonane formed on methylation of 7-hydroxy-9-methyl-3, 9-diazabicyclo-[3.3.1]nonane, the structure of which we proved earlier [1]. From this it follows that compound (V), like 7-hydroxy-9-methyl-3-9-diazabicyclo[3.3.1]nonane, has a chair-chair form and the OH group directed towards the nitrogen in position 3 (IX).

EXPERIMENTAL

Dimethylester of 1-benzyl-4-hydroxypiperidine-2, 6-dicarboxylic acid (II). A mixture of 5 g crystalline (I), 5 g benzyl iodide, and 4.75 g finely ground calcined potash is heated under the conditions described earlier in 65 ml anhydrous toluene [2]. 4.1 g (57.9%) of a thick, light-yellow, caramel mass, bp 200-202° (1 mm), are obtained. Found: C 62.41; H 6.91; N 4.85%. Calculated for $C_{16}H_{21}NO_5$: C 62.52; H 6.88; N 4.55%.

Hydrochloride – a white, finely crystalline substance, mp 210-212°. Found: Cl 13.83; N 5.45%. Calculated for $C_9H_{15}NO_5 \cdot HCl$: Cl 13.97; N 5.52%.

Benzylimide of 1-benzyl-4-hydroxypiperidine-2, 6-dicarboxylic acid (III). The reaction is carried out in an analogous manner to that described earlier [1]. The yield of technical imide is 57.6%. White, square plates, mp 162-164°. Found: C 71.92; H 6.37; N 7.64%. Calculated for $C_{21}H_{22}N_2O_3$: C 71.97; H 6.32; N 7.98%.

Hydrochloride – white, finely-crystalline deposit, mp 193-195°. Found: C 65.54; H 6.33; Cl 9.66; N 7.26%. Calculated for $C_{21}H_{22}N_2O_3 \cdot HC$: C 65.19; H 5.99; Cl 9.16; N 7.24%.

7-Hydroxy-3, 9-dibenzyl-3, 9-diazabicyclo[3.3.1]nonane (IV). 3.15 g (III) are reduced by 1.0 g lithium aluminum hydride in an ether-dioxane medium. 2.07 g (71%) of a colorless, caramel mass, mp 200-203° (0.3 mm), are obtained. Found: C 77.62; H 7.98%. Calculated for $C_{21}H_{20}N_2O$: C 78.22; H 8.12%.

7-Hydroxy-3, 9-diazabicyclo[3.3.1]nonane (V). 1.85 g (IV) are hydrogenated in 100 ml alcohol over 1 g palladium chloride. 1.13 g (91%) of the hydrochloride of 7-hydroxy-3, 9-diazabicyclo[3.3.1]nonane are obtained in the form of a white, finely crystalline substance, mp 274-276° (decomp.). Found: Cl 33.11; N 12.92%. Calculated for $C_{7\,14}N_2O \cdot 2HCl$: Cl 32.96; N 13.02%.

The base, which is isolated in the usual manner, exists as colorless, long needles, mp 206-208°. Found: C 58.68; H 9.73; N 19.78%. Calculated for $C_7H_{14}N_2O$: C 58.43; H 9.92; N 19.70%.

7-Hydroxy-3, 9-dimethyl-3, 9-diazabicyclo[3.3.1]nonane. 1.2 g of (V) are methylated with a mixture of 2.33 g formic acid, 1.57 g formalin, and 0.80 ml water under the conditions described earlier [1]. 1.05 g (73%) of a colorless, mobile liquid, bp 78-80° (0.6 mm), are formed. The liquid is converted into the methiodide, mp 274-276° (decomp.), and dihydrochloride, mp 247-248° (decomp.). In physicochemical properties the compounds obtained are identical with 7-hydroxy-3, 9-dimethyl-3, 9-diazabicyclo[3.3.1]nonane, it methiodide and dihydrochloride, as obtained earlier.

Dimethyl ester of 1-methyl-4-hydroxypiperidine-2, 6-dicarboxylic acid. 5 g (I) are heated in 25 ml absolute alcohol with 1.63 g methyl iodide at 40-45° for 6 hr. The precipitate (2.95 g), the hydroiodide of (I), is filtered off. The alcoholic mother liquor is driven off under vacuum, and the residue recrystallized from ethyl acetate. 2.61 g (49%) of a white crystalline substance, mp 92-94°, are obtained. Mixing the compound with the dimethyl ester of 1-methyl-4-hydroxypiperidine-2, 6-dicarboxylic acid, obtained earlier, gave no depression of the melting point.

Dimethyl ester of 1-benzoyl-4-hydroxypiperidine-2, 6-dicarboxylic acid (VII). 2 g benzoyl chloride are added with ice-cooling to 3 g (I) in 30 ml pyridine and stirred with cooling for 3 hr. The pyridine is driven off under vacuum, the residue treated with excess of a 50% potash solution, extracted with chloroform, the extract dried with anhydrous sodium sulfate, the chloroform driven off, and the residue dissolved in dry ether (15-20 ml) and left overnight in the refrigerator. 2.65 g (60%) of a white, finely crystalline substance, mp 81.83°, are obtained. Found: C 59.87; H 5.99; N 4.35%. Calculated for $C_{16}H_{19}NO_6$: C 59.80; H 5.96; N 4.35%.

If, after the chloroform is driven off, the residue is distilled under vacuum, a light-yellow, caramel mass is obtained, mp 222-224° (0.5-0.6 mm). This is the lactone VIII. Found: C 62.21; H 5.30; N 4.82%. Calculated for $C_{15}H_{15}NO_5$: C 62.27; H 5.22; N 4.84%.

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