SYNTHESIS OF AMANTADINE VIA THE NITRATE OF 1-ADAMANTANOL

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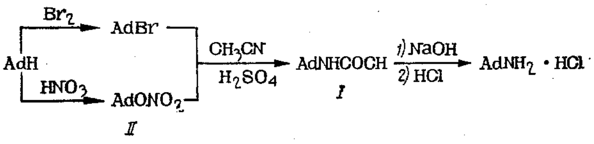
Amantadine, the hydrochloride salt of 1-aminoadamantane, serves as an effective prophylatic agent against diseases of the virus groups [1]. The known method of its preparation [2, 3] is based on reaction of 1-bromoadamantane with acetonitrile with subsequent basic hydrolysis of the formed 1-acetylaminoadamantane [1].



We have carried out the synthesis starting from the nitrate of adamantanol (II), more accessible than 1-bromoadamantane, the reaction of which with acetonitrile in the presence of sulfuric acid leads to compound (I).

Optimal conditions were selected by the method of mathematical systematization of the experiment, permitting the preparation of compound (I) in a yield of 80% (see Table 1).

Nitroester (II) was obtained by treatment of adamantane with 94% nitric acid at a temperature of 30°.

EXPERIMENTAL

Nitrate of 1-Adamantanol (II).* To 12.5 ml of 94% nitric acid was added at room temperature 1 g of adamantane at such a rate that the temperature did not exceed 30°, the mixture was maintained at this temperature for 30 min, and the reaction mixture was poured onto ice. The precipitate was filtered, washed repeatedly with water, and dried. We obtained 1.2 g (83%) of (II), mp 104-5° (from methanol). IR spectrum (KBr pellets), cm^{-1}: 1615, 1284, 1300, 1312. Found, %: No. 7, 18. $C_{10}H_{15}NO_3$. Calculated, %: No. 7, 1.

TABLE 1. Results of Sudden Ascent during Synthesis of 1-Acetylaminoadamantane (I)

Factors	X_1	X_2	X_3	X_4	X_5	Y
Levels						
0	5	0,75	4	45	13	—
—1	0,5	0,5	3	20	2	—
+1	9,5	1	5	70	24	—
Intervals of variation	4,5	0,25	1	25	11	—
Coefficient b_i	—11,98	5,03	14,72	—2,77	—3,97	—
$b_i\varepsilon_i$	—53,91	1,26	14,71	—69,25	—43,67	—
Changes ΔX_i corresponding to $\Delta X_1=4$	—4	0,1	1	—5	—3	—
Sudden ascent experiment	1	0,83	5	40	10	78,3

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*Compounds of such type should be regarded with great care – Editor.

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1-Acetylaminoadamantane (I). To obtain the maximum yield we set a fractional factorial experiment 2^{5-2} with generating relations $X_4 = X_1X_2X_3$, $X_5 = -X_1X_2$. As the main factors determining yield and quality of product we selected: quantity of sulfuric acid in the reaction mixture (X_1, ml); amount of (II) (X_2, g); amount of acetonitrile (X_3, ml); reaction temperature (X_1, deg); time of maintaining the reaction mass (X_5, h).

Values of coefficients calculated from experimental results were found to be equal to: $b_0 = 43.59$, $b_1 = -11.98$; $b_2 = 5.03$; $b_3 = 14.72$; $b_4 = -2.77$; $b_5 = -3.97$. A linear model was inadequate, since the value $F_{3.2\text{calc}} = 49.5 > F_{3.2\text{tab}} = 19.2$ at a 5% level of significance.

Despite this, we decided to use the found coefficients for calculation of experiments of sudden ascent.

Further motion along the gradient was not expedient from the point of view of restrictions imposed on the region of variation.

The optimal yield of (I) with satisfactory mp was obtained under the following conditions: to 0.85 ml of 95% sulfuric acid at room temperature was added in drops 1 g of (II) in 5 ml of acetonitrile. After maintaining for 10 h at 40° and cooling, the reaction mass was poured onto ice, extracted with benzene, and washed with water. The benzene was evaporated to give 0.82 g (80%) of (I), mp 149-150° (from methanol). From GLC data, the content of main material was 98%.

Hydrochloride Salt of 1-Aminoadamantane. With stirring and heating, 150 g of sodium hydroxide was dissolved in 1520 ml of diethylene glycol. To the solution was added 76 g of (I) and the mixture was heated for 15 h on an oil bath. After cooling, the reaction mass was poured into 3 liters of water and extracted repeatedly with ether. The calculated amount of gaseous hydrogen chloride was passed into the ether solution. Aminoadamantane hydrochloride (48.1 g, 87%) precipitated, which did not melt up to 360°. Content of main material was 99%, from potentiometric titration data.

LITERATURE CITED

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