PREPARATION OF 1-BROMOADAMANTANE AND ADAMANTANE-1-CARBOXYLIC ACID FROM 1-ADAMANTYL NITRATE

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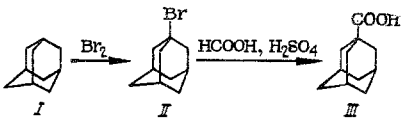
Some amino derivatives of the adamantane (I) series have found application in medical practice. The most well-known derivatives of this type include 1-aminoadamantane hydrochloride (Midantan), which is being used as an effective agent for the treatment of Parkinsonism, and α-methyl-α-(1-adamantyl)methylamine (Remantadin), which is being used successfully as an anti-influenza preparation.

The key intermediates for the synthesis of Midantan and Remantadin are 1-bromoadamantane (II), which is obtained by bromination of I, and adamantane-1-carboxylic acid (III), which is synthesized by Koch–Haaf carboxylation of II.



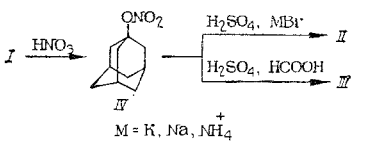
Methods for the preparation of II by bromination of I in excess liquid bromine [1-4] or in an inert solvent such as carbon tetrachloride [5] have been described. In the latter case the use of copper filings (1-1.5% of the mass of I) as the catalyst accelerates the reaction substantially [6].

A drawback of the indicated methods [1-6] is the use, as the principal reagent, of liquid bromine, the toxicity of which constitutes an industrial hazard and causes difficulties in both the technological arrangement and in the apparatus design of the process.

In our opinion, a method involving the use, as the starting compound, of 1-adamantyl nitrate (IV), which, like other nitrates of the adamantane series, is already being used in organic synthesis [7-9], should be considered to be a more promising method for the preparation of Midantan and Remantadin. As compared with II, it is more accessible and is formed by the action of I of concentrated nitric acid [10] or a mixture of the latter with acetic acid [11]. To verify our assumption we developed a new method for the synthesis of II, as well as III, on the basis of IV.

The preparation of III via the Koch–Haaf reaction from II or 1-adamantanol (V) was described in [12-14]. The use of IV (instead of the expensive II) for the synthesis of III is of undoubted interest.

We have found that the synthesis of II can be realized by the reaction of IV with salts of hydrobromic acid in sulfuric acid and that the synthesis of III can be realized by carboxylation of the same IV under the conditions of the Koch–Haaf reaction.



It has been shown [15] that V is formed in up to 9% yield [according to the results of thin-layer chromatography (TLC)] as a side product in the preparation of IV; recrystallization was used to remove the accompanying impurities from IV. In connection with this fact we became interested in how the presence of V would affect the yields and quality of final products II and III.

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TABLE 1. Synthesis of 1-Bromoadamantane (II)

Starting compound	Bromide	Composition of the reaction mixture			Yield of II, %
		starting compound, mole	bromide, mole $\cdot 10^{-1}$	H_2SO_4, ml	
IV	KBr	0,01	0,83	10	89,1
IV	NaBr	0,01	0,85	10	88,7
IV	NH_4Br	0,01	1,01	10	88,2
V	KBr	0,075	0,60	8	89,3
IV+V (1:1)	KBr	0,01+0,013	0,9	11	88,8
IV+V (9:1)	KBr	0,01+0,001	0,85	10,5	89,2
IV*	KBr	0,021	1,70	20	89,0
		0,02	1,68	20	88,2

*Without recrystallization.

TABLE 2. Synthesis of Adamantane-1-carboxylic Acid (III)

Starting compound	Composition of the reaction mixture			Yield of III, %
	starting compound, mole	HCOOH, mole	H_2SO_4, ml	
I*	0,075	1,1	20	62,7
II	0,03	0,7	100	78,6
IV	0,03	0,36	20	98,2
V	0,025	0,3	20	94,1
IV+V (1:1)	0,01±0,013	0,27	16	93,0
IV+V (9:1)	0,01+0,001	0,13	8	92,8
IV†	0,028	0,36	20	92,6
	0,029	0,36	20	93,0

*Oleum and nitric acid were added to the reaction mixture [16-17].
†Without recrystallization.

Special experiments showed that V and a mixture of IV and V are converted to II and III in high yields under similar reaction conditions (similar to pure IV). This behavior of V made it possible to do away with the recrystallization of IV (which simplified the process) and to increase the yields and quality of the desired products.

The results of the experiments on the synthesis of II and III are presented in Tables 1 and 2, respectively.

The synthesis of II, III, and IV was carried out in a flask equipped with a reflux condenser, a stirrer, a thermometer, and, for free-flowing reagents, a dispenser (or dropping funnel) at 0-30°C and atmospheric pressure.

Absorbers filled with a solution of alkali were used to trap the oxides of nitrogen and hydrogen bromide liberated in the synthesis of IV and II.

Thus, we have demonstrated the possibility of a new approach to the synthesis of II and III through 1-adamantyl nitrate (we will call it the "nitrate method"). From the results obtained in this research it can be concluded that the use of the nitrate method is a promising method for the preparation of Midantan and Remantadin.

EXPERIMENTAL

Adamantane conforming to TU-6-02-7-39-78, technical-grade nitric acid with d_4^{20} 1.500-1.515, analytical-grade anhydrous formic acid, concentrated sulfuric acid, and pure-grade potassium, sodium, and ammonium bromides were used in the research. The purity of the synthesized substances was monitored by chromatography on Silufol UV-254 plates (Czechoslovakian SSR). The constants of the compounds were in agreement with the literature data. The compositions and structures were confirmed by the results of elementary analysis and the IR spectra (obtained with UR-20 and Spektromom-2000 spectrometers).

1-Adamantyl Nitrate (IV). A 20.4-g (0.15 mole) sample of I was added with stirring to 250 ml of nitric acid at such a rate that the temperature did not exceed 30°C. The mixture was stirred until I had dissolved completely, after which the solution was allowed to stand for 30 min and poured over ice. The resulting precipitate, which contained IV and V in a

ratio of 9:1, was removed by filtration, washed many times with water, and dried in air. The product was used for the preparation of II and III.

Extraction of the reaction product with hexane gave IV (83%) with mp 103-104°C (from methanol). The residue remaining after extraction with hexane was V (9%) with mp 283-285°C.

1-Bromoadamantane (II). A 4.1-g (0.021 mole) sample of IV was dissolved with stirring in 20 ml of sulfuric acid, and 20.2 g (0.17 mole) of potassium bromide was sprinkled into the mixture in portions as the hydrogen bromide evolution ceased. The reaction mixture was allowed to stand for 1 h, after which it was poured into ice water. The resulting precipitate was removed by filtration, washed with water, and dried in air to give II (89%) with mp 116-118°C (from ethanol).

Adamantane-1-carboxylic Acid (III). A 5.7-g (0.029 mole) sample of IV was dissolved in 20 ml of sulfuric acid with stirring at no higher than 10°C, and 17 g (0.36 mole) of formic acid was added in the course of an hour, during which the temperature of the mixture rose to 20-22°C. The mixture was stirred for 1 h, after which it was poured into ice water. The resulting precipitate was removed by filtration, washed with water, and dried in air to give III (93%) with mp 178-179°C (from hexane).

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