PREPARATION OF 1-BROMOADAMANTANE

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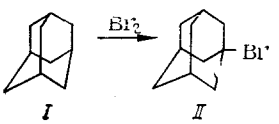
Derivatives of adamantane (I) have been introduced into pharmacological use on an increasingly larger scale over the last 10-15 years. One of the existing preparations in this series is aminoadamantane hydrochloride (midantane), an effective agent for the treatment of Parkinson's disease. The starting material for the synthesis of midantane is 1-bromoadamantane (II), which is prepared by bromination of I.



The literature [1-4] describes methods of preparing II by bromination of I with liquid bromine. The disadvantage of these methods is that they are all based on bromination without solvent. But since I is a solid product, bromination does not begin until the greater part of the liquid phase (bromine) has been added and the reaction mixture has become homogeneous; the process is then extremely rapid and is accompanied by vigorous evolution of hydrogen bromide. This makes control of the process difficult and causes complications in recovering the hydrogen bromide. Consequently the literature methods of [1-3] can be used to prepare II only on the laboratory scale, while scaling up [4] gives rise to difficulties in the operating procedure and in equipment design (special dispensers operating in aggressive media are required).

Our intention was to develop an easily controllable, safe, and technically feasible method for preparing II, which could be implemented on a commercial scale, using existing standard equipment. We found that bromination of I can be carried out in an inert organic solvent (for example in carbon tetrachloride). Bromination goes smoothly in this solvent though the rate of reaction is sharply reduced. If copper turnings (1-1.5 wt. % of I) are used as catalyst, the reaction goes at the normal rate and is complete after the reaction mixture has been refluxed for 5 h [5].

We carried out the bromination process in an air-tight vessel under slightly reduced pressure (700-720 mm Hg). These conditions promote the more complete evolution of hydrogen bromide from the reaction mixture and also improve its absorption in the cold traps containing alkali and sodium metabisulfite solutions (to trap the bromine vapor entrained with the hydrogen bromide).

When the reaction was complete, we removed the mixture of bromine and carbon tetrachloride by distillation through the traps under 100-150 mm Hg and at a distillard temperature not exceeding 100°C.

The residual bromine after distillation was removed from the reaction mixture by addition of a small quantity of carbon tetrachloride followed by distillation. The distilled solvent was used for subsequent brominations. Thus the consumption of bromine in preparing II exceeded the theoretical by only 10%.

The resulting technical II was crystallized from ethyl or isopropyl alcohol; traces of free bromine were removed by adding a small quantity of dry sodium metabisulfite. The yield

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of crystalline II was 87% of theoretical, based on I.

Our results have been used as the basis for the production of II and the commercial output of midantane in the USSR has begun on a scale commensurate with the national requirements.

EXPERIMENTAL

The reaction was carried out in an air-tight reaction vessel fitted with an efficient reflux condenser and stirrer and containing I (300 g, 2.2 mole), copper turnings (5-6 g), and carbon tetrachloride (200 ml). The reaction mixture was refluxed on a water bath while bromine (1410 g, 8.8 mole) was added over a period of 1.5 h. The reaction mixture was then refluxed for 5 h. The bromination was carried out under 700-720 mm Hg, while the evolved hydrogen bromide and the traces of entrained bromine were absorbed in cold traps containing sodium metabisulfite and alkali solutions.

Unreacted bromine was removed with the carbon tetrachloride by distillation under 100-150 mm Hg and at a distillant temperature not exceeding 100°C. The residual bromine was removed from the reaction mixture by distillation with fresh carbon tetrachloride (150 ml). The residue was recrystallized in the presence of sodium metabisulfite (2-3 g), yielding II (413 g, 87% of theoretical, based on I), mp 116-118°C (from ethyl alcohol).

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PREPARATION OF β-(5-NITRO-2-FURYL)ACROLEIN

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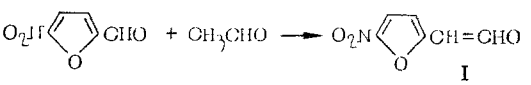
β-(5-Nitro-2-furyl)acrolein I is a key intermediate in the synthesis of several preparations possessing antibacterial properties (furagin, solafur, nifuron, and letilan) that are widely used in medicine.

The synthesis of I is based on the reaction of 5-nitrofurfural with acetaldehyde:



I

The literature [1-8] describes methods for preparing I based on this reaction in the presence of a catalyst (pyridine acetate or morpholine acetate). The disadvantage of these methods is that they all stipulate the use of benzene as reaction solvent. This causes the industrial hygiene to deteriorate in the preparation of I, copious (up to 30%) resinification, and a number of additional difficulties.

The aldehyde resins that are formed are poorly soluble in benzene, while I, conversely,

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