THE SYNTHESIS OF TERTIARY AMINOARYL-PROPENE AND -PROPANE DERIVATIVES

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(Received March 30, 1960)

Some secondary amino derivatives of cinnamyl chloride have been prepared as compounds of potential physiological activity. Attempts have been made to decide about the configuration of the obtained stereoisomers by examining the possibility of mixed crystal formation.

During the course of our pharmacological investigations involving several groups of materials [1], [2], we have prepared also some tertiary aminocynnamyl-(1-phenylpropene-2) derivatives. The relationship between physiological activity and structure has been studied also in this case.

A general formula of the compounds to be described in detail in the following, may be given as

$$R \cdot CH_2 \cdot CH = CH \cdot C_6H_5$$

where R = a secondary amine group. Our syntheses involved the preparation of the derivatives of piperidine, pirrolidine, morpholine and diethylamine. The general course of the synthesis may be illustrated by the following formulas:

$$2R_1R_2NH + Cl \cdot CH_2CH = CH \cdot C_6H_5 \rightarrow R_1R_2 \cdot$$
$$\cdot NCH_2CH = CH \cdot C_6H_5 + R_1R_2N \cdot HCl$$

where R_1R_2NH = piperidine, pyrrolidine, morpholine or diethylamine.

The reactions are usually carried out in anhydrous solvents. The yield of the reaction is highly decreased by the formation of amine hydrochloride. This effect can often be eliminated by the use of pyridine as an acid binding agent.

Cinnamaldehyde, the first product of the synthesis leading to cinnamyl chloride, was prepared

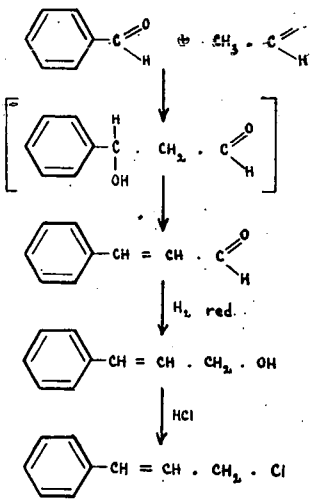

Fig. 1

by an aldol-type condensation of benzaldehyde and acetaldehyde [3]. Cinnamaldehyde was then converted to cinnamyl alcohol by means of aluminium isopropoxide [4], and the resulting alcohol was treated with hydrogen chloride to give cinnamyl chloride [5].

Since stereochemical relationships of the synthesis of cinnamyl chloride involving an aldol-type condensation are not clear, we tried to establish the cis or trans configuration, resp., of the derivatives obtained by the use of cinnamyl chloride.

First we attempted to apply BRUNI's rule, which was succesfully used by FODOR and KISS [6] for deciding about the cis-trans isomerism of sphingosine. 1-Phenyl-3-N-piperidino-propene-2 was hydrogenated, and the saturated and unsaturated derivatives were allowed to stand in a solvent in the molar ratios of 1:1. However, formation of mixed crystals did not take place, and only the unsaturated compound crystallized from the solvent. When these crystals were filtered, evaporation of the solution gave the saturated compound. In this case, of course, failure of the formation of mixed crystals affords no unequivocal proof for the cis configuration of the synthesized compound. BRUNI *et al.* [7] derived their rule from evidence obtained on model compounds having longer carbon chains.

Experimental

Materials

Piperidine: "Merck" piperidinium puriss. was used.

Acetaldehyde "pure for scientific use" was employed.

Benzaldehyde, puriss., was obtained from the Factory of Fine Chemicals "REANAL", Budapest.

Cinnamaldehyde prepared by the condensation of benzaldehyde and acetaldehyde [3] had b. p. 128—130°C/20 mm, m. p. 75°C.

Cinnamyl alcohol obtained by reduction with aluminium isopropoxide [4] had b. p. 100—102°C/15 mm.

Cinnamyl chloride was obtained by introducing hydrogen chloride into cinnamyl alcohol [5].

1-Phenyl-3-N-pirrolidinopropene-1

4 g of cynnamyl chloride dissolved in 5 ml of anhydrous benzene was slowly added to a solution of 4 g pirrolidine in 5 ml benzene. The mixture was allowed to stand half an hour, then the two layers were separated, the upper benzene layer dried over sodium sulphate, and the benzene distilled off under reduced pressure on the steam bath. The residue was fractionated to give 6,2 g product with b. p. 124—125°C/2 mm, $n_D^{25} = 1{,}5578$.

The *hydrochloride* of the compound was precipitated by means of hydrogen chloride dissolved in anhydrous ether. The finely dispersed precipitate was filtered and recrystallized from ethanol, m. p. 158°C. Analysis: Calculated C 69,77; H 8,11; Cl 15,86 %. Found C 69,51; H 7,96; Cl 15,62 %.

1-Phenyl-3-N-piperidinopropene-1

A solution of 20 g cinnamyl chloride in 30 ml anhydrous ether was slowly added to a stirred solution of 18 g piperidine in 30 ml anhydrous ether. When the addition was completed, the mixture was refluxed for 20 minutes, then it was allowed to stand for half an hour. The precipitate was filtered on a sintered glass filter, and the filtrate dried over sodium sulphate. After evaporating the ether, the oily residue was fractionated to give 21 g product, b. p. 130—132°C/2 mm, $n_D^{25} = 1{,}5572$. *The hydrochloride* of the compounds was precipitated by hydrogen-chloride dissolved in anhydrous ether. The finely dispersed precipitate was filtered and recrystallized from a mixture of ethanol acetone (1:6) m. p. 213°C. Analysis: Calculated C 70,70; H 8,48; Cl 14,93 %. Found C 70,70; H 8,68; Cl 15,10 %.

1-Phenyl-3-N-morpholinopropene-1

10 g of cinnamyl chloride was added under constant stirring to 8 g of morpholine. The mixture was allowed to stand one day, it was filtered from the precipitate, washed with anhydrous benzene, and the filtrate dried over sodium sulphate. The benzene was then evaporated, and the residue fractionated to give 10,5 g of the product, b. p. 133°/1 mm, $n_D^{25} = 1{,}5621$.

The *hydrochloride* of the compound was precipitated in the same way as described above, and recrystallized from a 1:10 mixture of ethanol and acetone. M. p. 215,5°C. Analysis: Calculated C 65,11; H 7,57; Cl 14,80 %. Found C 65,07; H 7,46; Cl 15,00 %.

1-Phenyl-3-N-diethylamino-propene-1

10 g of cinnamyl chloride was added to 7 g of diethylamine, the mixture was shaken vigorously and allowed to stand one day at room temperature. The precipitate was filtered and washed with anhydrous benzene, and the solution dried over sodium sulphate. The benzene was destilled off, and the residue fractionated to give 10,2 g of the product, b. p. 94°C/1 mm, $n_D^{25} = 1{,}5352$.

Its *hydrochlorid* was obtained as described above and recrystallized from anhydrous acetone. M. p. 149°C. Analysis: Calculated C 69,14; H 8,93; Cl 15,72 %. Found C 69,25; H 8,75; Cl 15,84 %.

1-Phenyl-3-N-piperidinopropane

4,5 g of 1-Phenyl-3-N-piperidinopropene-1 was dissolved in 20 ml of anhydrous ethanol, 2,5 ml of a 12 % hydrogen chloride solution in alcohol was added and the material was hydrogenated at atmospheric pressure and at room temperature in the presence of palladium charcoal catalyst. The theoretical amount of hydrogen (0,53 l) was taken up within half an hour. A calculated amount of alcoholic hydrogen chloride solution was added and the alcohol was evaporated at reduced pressure on the steam bath. The crystalline residue was recrystallized from a 1:6 mixture of ethanol and acetone.

M. p. 183°C. Analysis: Calculated C 70,11; H 9,25; Cl 14,80 %. Found C 69,97; H 9,35; Cl 14,92 %.

Experiment for mixed crystal formation

0,5 g of each of the saturated and unsaturated compounds (hydrochlorides) was dissolved in a 1:1 mixture of warm ethanol and acetone. The solution was allowed to stand in a refrigerator. A precipitation of crystal needles was obtained in 2 hours. After filtration and drying 0,55 g material was obtained, m. p. 212°C. Microhydrogenation showed the uptake of 1 mol of hydrogen. The formation of mixed crystals did not take place.

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The authors wish to thank the Analytical Laboratory of the Institute for carrying out the microanalyses, and Mr. J. FÜLÖP for preparing a part of the starting materials.

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СИНТЕЗ ТРЕТИЧНОГО-АМИНО-АРИЛ-ПРОПАНА И ПРОИЗВОДНЫХ ПРОПАНА

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Исходя из хлористого арил-пропена были изготовлены несколько секундерно-аминовых производных, ввиду их фармакологического значения. Кроме того авторы стремились установить пространственную структуру путем образования простого кристалла-смеси