SYNTHESIS OF CYCLIC α -AMINO KETONES

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Chemical Institute, Academy of the Rumanian Peoples' Republic Translated from Izvestiya Akademii Nauk SSSR, Otdelenie Khimicheskikh Nauk, No. 1, pp. 149-151, January, 1961 Original article submitted June 4, 1960

In a previous communication [1] we showed that saturated azlactones (1) react with aromatic compounds in the presence of aluminum chloride, behaving like acid anhydrides. This yields α -acylamino ketones according to the scheme:



In this investigation it was observed that like acid chlorides [2], azlactones of the type (II) (n = 1, 2, and 3) give cyclic α -acetylamino ketones (III) when treated with aluminum chloride in carbon disulfide, as a result of an intramolecular condensation.



Azlactones of this type are prepared smoothly by treatment of appropriate α -amino acids with acetic anhydride [3]:



By this method we synthesized: 2-acetylaminoindanone, which is usually obtained from indanone through 2-nitrosoindanone with subsequent reduction with stannic chloride [4]; 2-acetylaminotetralone-1, which was first obtained by Neber by rearrangement of tetralone oxime arylsulfonate [5], and was recently obtained from 1,2,3,4-tetrahydro-1naphthylamine by conversion to the dichloramine with subsequent treatment with sodium methylate [6]; 4-acetylaminobenzosuberone, whose synthesis has not been given in the literature. Hydrolysis yielded the hydrochlorides of these α -amino ketones. In view of the ease with which the azlactones of this series are obtained, this method is a simple route to the synthesis of cyclic α -amino ketones.

EXPERIMENTAL

The azlactones were obtained by heating appropriate amino acids with five parts of acetic anhydride on a water bath for 10-15 min. The excess acetic anhydride was removed at as low a pressure as possible (1-2 mm Hg) and with gentle heating on a water bath ($35-40^\circ$). A 0.1 mole portion of the azlactone was dissolved in a five- or

tenfold amount of carbon disulfide. Into a flask fitted with a mechanical stirrer were placed 0.3 mole of anhydrous aluminum chloride and approximately 5 parts of carbon disulfide, and the azlactone solution was added dropwise at room temperature. The reaction was weakly exothermal. The reaction mixture was boiled on a water bath for an hour and left at room temperature overnight. After decomposition of the complex with iced water, the carbon disulfide was separated and the aqueous layer extracted continuously with ether. Removal of the ether yielded the crystalline α -acetylamino ketone, which was recrystallized from water. The yield was approximately 65%.

<u>2-Acetylaminoindanone</u> (III, n = 1) had m. p. 155-156°. It was prepared from 2-methyl-4-benzyl-5-oxazolone (II, n = 1), which, in its turn, was synthesized from α -phenylalanine and acetic anhydride [7]. Found: C 69.76; H 6.12; N 7.42%. C₁₁H₁₁O₂N. Calculated: C 69.80; H 5.80; N 7.41%.

The 2,4-dinitrophenylhydrazone had m. p. 254° (from acetic acid). Found: N 18.80%. C₁₇H₁₅O₅N₅. Calculated: N 18.96%.

Hydrolysis with dilute hydrochloric acid (1:1) yielded α -aminoindanone hydrochloride with m. p. 237-238° (with decomposition), which was identical with that described in the literature [4]. In the same way we obtained benzoylaminoindanone from N-benzoyl- α -phenylalanine through the azlactone; it had m. p. 190°. Found: C 76.32; H 5.24; N 5.58%. C₁₆H₁₃O₂N. Calculated: C 76.49; H 5.17; N 5.57%.

<u>2-Acetylaminotetralone-1</u> (III, n = 2) had m. p. 127-128° and was synthesized from 2-methyl-4-phenylethyl-5oxazolone [b. p. 138-139° (2 mm)], which was prepared from γ -phenyl- α -acetylaminobutyric acid and acetic anhydride [8]. The yield of the cyclization was 63%. Found: C 71.11; H 6.62; N 6.85%. C₁₂H₁₃O₂N. Calculated: C 70.91; H 6.45; N 6.89%.

The 2,4,-dinitrophenylhydrazone had m. p. 256° (from acetic acid). Found: N 18.34%. $C_{18}H_{17}O_5N_5$. Calculated: N 18.27%. The hydrochloride, which was obtained as a result of hydrolysis with hydrochloric acid, crystallized with one molecule of water and melted at 203-204°, in contrast to the anhydrous product of Neber, which melted at 117°. This has recently been pointed out by other authors [16].

<u>4-Acetylaminobenzosuberone-3</u> (III, n = 3). δ-Phenyl-α-aminovaleric acid was obtained by condensation of cinnamaldehyde with acetylglycine [9], and then reduced with sodium amalgam to butene-4-phenyl-1-acetylamino-1-carboxylic acid (m. p. 116°). Catalytic hydrogenation of the latter in alcohol in the presence of platinized charcoal (5%), removal of the solvent in vacuum, and recrystallization from water gave an acetylamino acid with m. p. 149-150° in a yield of 70%, calculated on cinnamaldehyde. Found: C 66.36; H 7.28%. C₁₃H₁₇O₃N. Calculated: C 66.43; H 7.51%. The azlactone was obtained by the method given and recrystallized after removal of the excess acetic anhydride; it had m. p. 59-60° and the yield was 92-93%. Treatment with aluminum chloride in carbon disulfide gave the acetylamino ketone (III) with m. p. 137° in 64% yield. Found: C 71.57; H 6.94; N 6.50%. C₁₃H₁₅O₂N. Calculated: C 71.86; H 6.96; N 6.40%. The 2,4-dinitrophenylhydrazone had m. p. 237° (from ethanol). Found: N 17.64%. C₁₀H₁₉O₅N₅. Calculated: N 17.81%.

SUMMARY

A simple method is described for synthesizing cyclic α -amino ketones by intramolecular cyclization of azlactones under the action of aluminum chloride.

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