1,4-BENZODIAZEPINES AND THEIR CYCLIC HOMOLOGS AND ANALOGS

VIII.* NEW METHOD FOR THE SYNTHESIS OF 1,5-BENZODIAZOCINE DERIVATIVES

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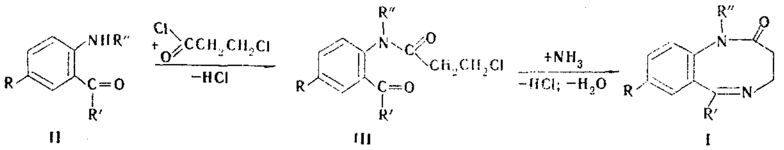
A new method, consisting in the reaction of o-aminobenzophenones with β-chloropropionyl chloride and subsequent treatment of the resulting 2-(β-chloropropionylamino)benzophenones with ammonia, is proposed for the synthesis of 1,2,3,4-tetrahydro-1,5-benzodiazocin-2-ones.

The advances in the chemistry of 1,4-benzodiazepines [2], which are used in medicine as minor tranquilizers, are stimulating the study of related condensed nitrogen heterocycles, including 1,5-benzodiazocines. Two methods for the preparation of 1,2,3,4-tetrahydro-1,5-benzodiazocin-2-ones (I) have been described [3,4]. According to one of them, compounds of the I type are obtained by a laborious multistep route starting from quinazolines [3]. In the second method, compounds of the I series are synthesized by reaction of o-aminobenzophenones with carbobenzoxy-β-alanyl chloride and subsequent splitting out of the carbobenzoxy group from the condensation product and cyclization of the 2-(β-aminopropionylamino)benzophenones to substances of the I type in refluxing toluene [4]. However, this method is extremely inconvenient, since 16-membered heterocyclic systems with four nitrogen atoms are formed when R = H.

We propose a simple method for the preparation of compounds of the I series. The method consists in the treatment of o-aminobenzophenones (II) with β-chloropropionyl chloride and subsequent reaction of an alcoholic ammonia solution with the resulting 2-(β-chloropropionylamino)benzophenones (III) at room temperature.



The IR spectra of compounds of the I series contain the characteristic absorption bands of carbonyl groups (1660 cm^{-1}) and C = N groups conjugated with the benzene ring (1615-1620 cm^{-1}). The absorption band characteristic for the I system is observed at 240 nm in the UV spectra of these substances [3].

EXPERIMENTAL†

The UV spectra of ethanol solutions of the compounds were recorded with an SF-4A spectrophotometer. The IR spectra of methylene chloride solutions were recorded with an IKS-14A spectrophotometer.

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† N. E. Yasinenko participated in the experimental work.

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The individuality of benzodiazocines I was monitored by chromatography in a loose thin layer of activity II aluminum oxide with toluene–methanol (5 : 1).

2-(β-Chloropropionylamino)-5-chlorobenzophenone. A solution of 5.7 g (0.045 mole) of β-chloropropionyl chloride in 10 ml of dioxane and 20 ml of 3 N sodium hydroxide solution were added dropwise simultaneously at 15° to a solution of 7 g (0.03 mole) of 2-amino-5-chlorobenzophenone in 30 ml of dioxane. At the end of the addition, the mixture was stirred for another 30 min. The reaction mass was diluted with water, and the resulting oil was dissolved in ether or methylene chloride. The solvent was removed by distillation, and the residue was crystallized from hexane to give 7.7 g (80%) of colorless needles with mp 75-77°. Found,%: C 59.4; H 4.3; N 4.6. $C_{16}H_{13}Cl_2NO_2$. Calculated,%: C 59.6; H 4.0; N 4.3.

A similar procedure was used to obtain 2-(β-chloropropionylamino)-5-bromobenzophenone with mp 97-99° in 80% yield. Found,%: C 52.5; H 3.7; N 3.9. $C_{16}H_{13}BrClNO_2$. Calculated,%: C 52.4; H 3.5; N 3.8.

6-Phenyl-8-chloro-1,2,3,4-tetrahydro-1,5-benzodiazocin-2-one. A solution of 4 g of 2-(β-chloropropionylamino)-5-chlorobenzophenone in 85 ml of a 22% solution of ammonia in anhydrous methanol was held at room temperature for 6 days, after which the ammonia was evaporated while heating on a water bath, and the methanol was removed by vacuum distillation at 20-25°. Methylene chloride was added to the oily residue, and the resulting precipitated ammonium chloride was removed by filtration. The filtrate was washed with water, dried with anhydrous sodium sulfate, and treated with ether to precipitate 1.8 g (51%) of a substance with mp 264-266° (from ethanol). Found,%: C 67.3; H 4.7; N 9.7. $C_{16}H_{13}ClN_2O$. Calculated,%: C 67.1; H 4.6; N 9.8.

A similar procedure was used to obtain 6-phenyl-8-bromo-1,2,3,4-tetrahydro-1,5-benzodiazocin-2-one with mp 270-272° in 45% yield. Found,%: C 58.2; H 4.2; N 8.4. $C_{16}H_{13}BrN_2O$. Calculated,%: C 58.3; H 3.9; N 8.5.

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