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STRUCTURE AND SYNTHETIC UTILITY OF β,β-DISUBSTITUTED AMINOETHYLENES

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INTRODUCTION

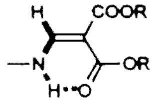
In the synthesis of nalidixic acid-type drugs, the key step is the thermal cyclization of N,N-dialkylsubstituted aminomethylene malonates – aminoethylene with two alkoxycarbonyl groups in the β-position. Typical for this type of therapeutics is the rigid structure of 4-oxo-1,4-dihydropyridine-3-carboxylic acid. The Gould-Jacobs type reaction or other reactions, which serve for preparation of these drugs, are principally only cyclizations of aminoethylenes [1, 2]. The study of structure of the aminoethylene substituents has as yet not received appropriate attention. Only a few works deal with the structure of aminoethylenes with two electron withdrawing groups in β-positions.

RESULTS

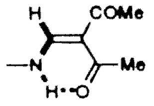
We studied symmetric aminoethylenes, such as N,N,-dialkyl- or N-isopropylidene aminomethylene malonates aminomethyleneacetylacetone, malononitrile as well as unsymmetrically substituted with various combinations of cyano, acetyl, and ester group. Aminomethylene malonates were reviewed [3].

DISCUSSION

Aminoethylenes with at least one carbonyl group exhibit an intramolecular hydrogen bond between an imino hydrogen and a carbonyl oxygen, and the bond is especially strong with acetyl group. This intramolecular hydrogen bond stabilizes an antiperiplanar conformation of the aminomethylene grouping (I, II) [4-10].



I



II

According to x-ray analysis, the aminoethylene substituent in compound III is planar, and the population of both conformers (rotation around (het) aryl-NH bond) is about the same. The phenyl rings are twisted out of the plane of the quinoxaline ring system by 46.7 and 38.0 degrees, respectively [10]. There also exists an interaction between nitrogen of the tautomeric benzazole ring (IV) and the ethylenic proton when the substituent is in position 4 [4-6, 9].

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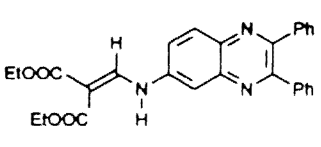
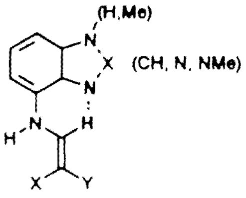


III

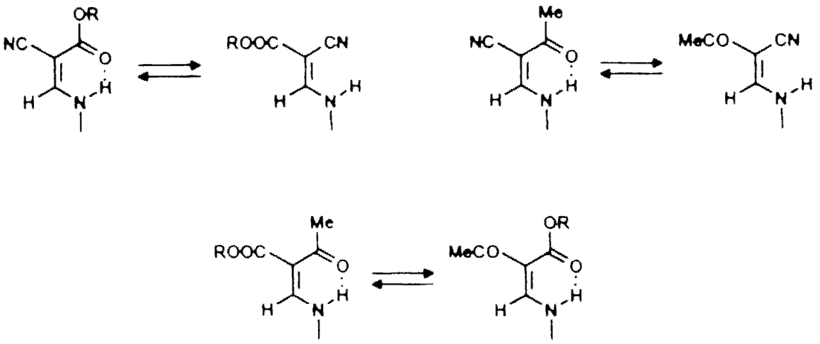


IV

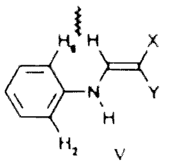
It is not so simple to establish the structure of aminomethylenemalononitrile systems because there exists no stabilization by intramolecular hydrogen bond. We have found that rotation around the C – N bond is hindered, the lone electron pair of nitrogen being in conjugation with the π-electron system of the double bond, and both hydrogen atoms of the amino group are nonequivalent. In proton spectra we observed 2 doublets instead of a triplet. The structure of alkylated analogues is the same. All these facts were also confirmed by *ab initio* calculations and spectral measurements [11].

All unsymmetrically substituted aminoethylenes also show geometrical isomerism at the double bond in which the isomer with acetyl carbonyl engaged in intramolecular hydrogen bond or the sterically less hindered isomer is preferred (Scheme 1) [4-9, 12].

Scheme 1



For the study of the influence of the aminoethylene substituent on chemical shifts of carbon atoms, we studied 14 anilinoethylenes in liquid and solid states using the CP MAS technique. We confirmed that in the solid state the aminoethylene substituent is planar without rotation around the C – N bond and there exists a steric hindrance between the methylene proton and the phenyl proton in *ortho*-position (V) [12].



V

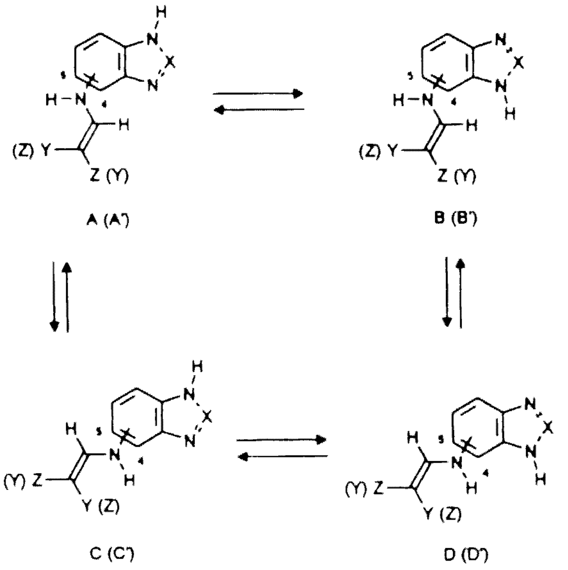
X, Y = COOMe, COOEt, COMe, CN, COOCMe$_2$OCO, CONHCONHCO, COCH$_2$CMe$_2$CH$_2$CO, CO(CH$_2$)$_3$CO

In the solid state we have also studied the tautomerism of the azole ring of benzimidazole or benzotriazole. We have found (Scheme 2) that 5-substituted isomers exist like structure (C) and 4-substituted isomers exist predominantly like structures (B), but also like (A) and (D) [5].

Among many reactions of aminoethylenes, the best known one is the Gould-Jacobs reaction of aminomethylene malonates, cyanoacetates, and acetoacetates [1-3, 6, 8, 13-15].

Only one work [16] deals with the cyclization of aminomethylene derivatives of β-dicarbonyl compounds in PPA and two papers appeared on the cyclization of aminomethylene malononitrile derivatives with aluminium chloride to afford fused 3-cyano-4-aminopyridine derivatives [13, 17].

Scheme 2



The alkylation of aminoethylene systems takes place on nitrogen and it is also preferred in the case of polycentric benzimidazole or benzotriazole aminoethylene derivatives [7].

EXPERIMENTAL

There exist many methods for the syntheses of aminoethylenes, but the most frequently used is the reaction of amine with dialkyl 1-alkoxymethylene compounds, the latter being commercially available or easily prepared.

In our laboratory we developed the synthesis of 2-ethoxymethylene-3-oxobutanenitrile, starting from 3-amino-2-butenenitrile.

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