NEW METHOD FOR THE SYNTHESIS OF AZOLIDONES

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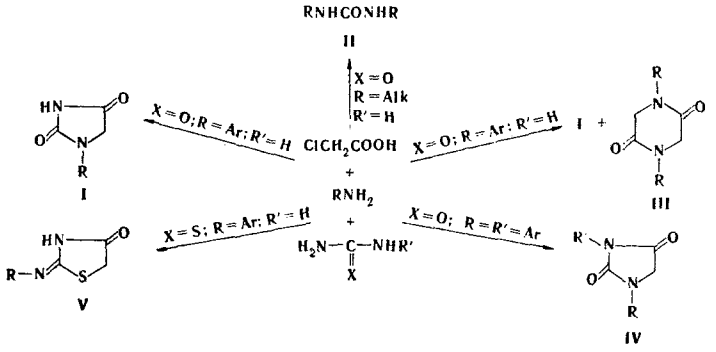
A new method for the synthesis of azolidones by direct condensation of chloroacetic acid and aromatic amines was developed. sym-Dialkylureas are formed in the case of aliphatic amines.

The known methods for the synthesis of monosubstituted hydantoins, which consist in the condensation of aromatic amines with chloroacetylurethane [1], of amino acids with urea [2] or potassium cyanate [3, 4], or of monosubstituted urea with glyoxal [5], are laborious in most cases and lead to the formation of the final products in low yields.

In this connection we attempted to develop a simple and preparatively convenient method for the synthesis of substituted hydantoins based on the use of readily accessible starting materials.

We have found [6] that 1-arylhydantoins I are formed in 50-60% yields in the direct condensation of anilines with chloroacetic acid and urea in the absence of a solvent. The basicities of the amines have a substantial effect on the direction of the reaction and the character of the products. Thus monoalkylhydantoins are not formed in the case of aliphatic amines, and N,N'-dialkylureas II are the principal products. However, aromatic amines – aniline, anisidine, and toluidine – give primarily 1-arylhydantoins. In the case of anilines with electron-acceptor substituents (bromine and chlorine) diketopiperazine derivatives III are formed along with I. The condensation with N-phenylurea or thiourea under similar conditions leads to, respectively, 1,3-diphenylhydantoin (IV) and 2-arylimino-2-thiazolidones V.



We have advanced the assumption that aniline (which is a stronger base than urea) in the monochloroacetic acid–aniline–urea system primarily participates in an acid–base equilibrium with monochloroacetic acid. This is also confirmed by the fact that the introduction of previously prepared aniline monochloroacetate into reaction with urea does not have an appreciable effect on the trend of the reaction or the character of the products. Urea subsequently deprotonates adduct VI because of leveling of the basicities of the aromatic amine and urea in acidic media, thereby facilitating its conversion to arylglycine VII. The resulting urea hydrochloride (VIII) reacts with the arylglycine either directly or through its decomposition product – isocyanic acid (IX) – to give the arylhydantoin:

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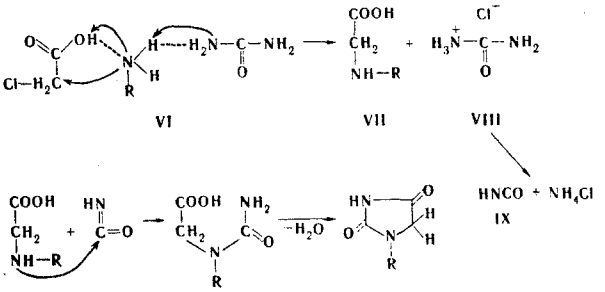
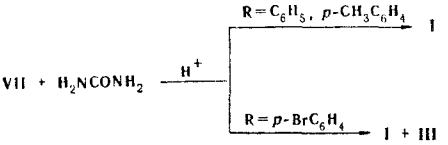


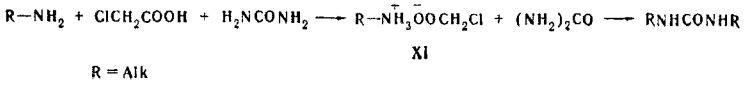
This pathway is confirmed by the fact that the condensation of previously prepared arylglycines and the urea salts postulated as intermediates in this reaction is equivalent to the process described above and leads to the formation of 1-substituted hydantoins.



It should be noted that in both the former and latter cases diketopiperazine derivatives are formed as side products along with the 1-arylhydantoins when less basic aromatic amines are used. This again confirms the correctness of the proposed scheme, in which the process actually reduces to the formation of arylglycines and protonated urea. In the case of anilines that contain electron-acceptor substituents the rate of formation of isocyanic acid prevails over the rate of formation of the arylglycine because of the reduced basicity of the amino group. Because of the volatility of isocyanic acid, this leads to a decrease in the yields of the 1-arylhydantoins and to the formation of diketopiperazines III as side products. The rates of formation of the arylglycine and isocyanic acid are approximately equal for anilines having donor substituents, and this also leads to the formation of exclusively 1-monosubstituted hydantoins I.

If one takes into account the available data that the condensation of arylglycines with ureas is a slow process that is realized at 160°C, our observed acid catalysis of this reaction facilitates the preparation of a hydantoin via the amino acid method considerably.

The fact that the condensation of unsubstituted glycine with urea and sulfuric acid leads to the formation of a hydantoin (X) in high yield while an attempt to synthesize an unsubstituted hydantoin directly from monochloroacetic acid, ammonium carbonate, and urea was unsuccessful, was unexpected. This also pertains to aliphatic amines, in which case the change in the direction of the reaction, as we have already noted above, is due to the difficulty in the deprotonation of the aliphatic amine monochloroacetate by urea in connection with its higher basicity [7, 8]. The conversion reduces to the formation of saltlike product XI, which on heating reacts with urea in the same way as in the case of the reaction of amine hydrochlorides with ureas, which gives primarily substituted ureas.



EXPERIMENTAL

1-Phenylhydantoin. A mixture of equimolar amounts of aniline, urea, and chloroacetic acid was heated at 120-130°C for 20-30 min. The reaction is exothermic and is accompanied by vigorous gas evolution. At the end of the process the mixture solidified completely. The 1-phenylhydantoin obtained in this way was crystallized successively from alcohol to give a product with mp 193-194°C (in agreement with the literature value) in 60% yield.

1-(p-Tolyl)- (in 55% yield, mp 213°C), 1-(p-anisyl)- (in 57% yield, mp 196-197°C), and 1-(p-phenylethyl)-hydantoin (in 56% yield, mp 165°C) were obtained by a similar method.

1-(p-Bromophenyl)hydantoin. A) A mixture of stoichiometric amounts of p-bromoaniline, chloroacetic acid, and urea was heated without a solvent on a water bath at 120-130°C. The exothermic reaction was complete after 20-30 min, and the reaction mixture solidified. The mixture was then refluxed successively in water and methanol, and the methanol mixture was filtered. The methanol filtrate was cooled, and the precipitated 1-(p-bromophenyl)hydantoin was removed by filtration to give a product with mp 234-235°C (in agreement with the

literature value) in 60% yield. The undissolved portion was crystallized from acetic acid to give a colorless product with mp 300°C in 19% yield. No melting-point depression was observed for a mixture of this product with 1,4-bis(p-bromophenyl)-2,5-diketopiperzine obtained by condensation of p-bromophenylglycine.

1-(p-Chlorophenyl)hydantoin with mp 230-231°C was similarly obtained in 53% yield.

B) A mixture of 1-(p-bromophenyl)glycine, urea, and sulfuric acid in a molar ratio of 1:1:0.5 was heated at 120-130°C for 15-20 min, after which it was worked up as described above to give 1-(p-bromophenyl)-hydantoin (58%) and 1,4-bis(p-bromophenyl)2,5-diketopiperazine (20%).

Hydantoin. A mixture of glycine, urea, and sulfuric acid (molar ratio 1:1:0.5) was heated at 120-130°C for 15-20 min. At the end of the reaction the solidified mass was refluxed in acetic acid for 30 min, and the mixture was filtered. The filtrate was cooled and worked up to give acicular crystals of hydantoin with mp 220°C in 70% yield.

1,3-Diphenylhydantoin. A mixture of equimolar amounts of chloroacetic acid, N-phenylurea, and aniline was heated on an oil bath at 110-120°C for 20-30 min, after which it was refluxed in benzene, and the benzene solution was filtered to remove the undissolved material. The benzene filtrate was treated with hexane, and the precipitated colorless plates of 1,3-diphenylhydantoin were removed by filtration to give a product with mp 138-139°C (from ethanol) in 60-70% yield. No melting-point depression was observed for a mixture of this product with a genuine sample.

Thiazolidine-2,4-dione. A mixture of equimolar amounts of thiourea, chloroacetic acid, and aniline was heated on an oil bath at 115-120°C for 20 min. At the end of the reaction, a solution of hydrochloric acid (1:1) was added to the solidified reaction mass, and the mixture was refluxed for 30-40 min. It was then cooled and worked up to give 3-phenylthiazolidine-2,4-dione with mp 144°C in 12% yield. The filtrate from the separation of the precipitate was evaporated, and the resulting thiazolidine-2,4-dione was crystallized from water to give a product with mp 122°C in 65% yield.

sym-Dibenzylurea. A mixture of monochloroacetic acid, benzylamine, and urea in a ratio of 1:1:1 was heated to 100-120°C for 20-30 min, after which the reaction mass was crystallized from alcohol to give colorless needles with mp 167-168°C in 46% yield.

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