STUDY OF THE CLEAVAGE OF THE N—N BOND IN THE REACTION OF BENZALDEHYDE PYRAZINYL-, PYRIDAZINYL-, AND PYRIMIDINYLHYDRAZONES WITH SODIUM ETHOXIDE

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The reaction of benzaldehyde pyrazinyl-, pyridazinyl-, and pyrimidinylhydrazones with sodium ethoxide was investigated by means of gas—liquid chromatography (GLC) and mass chromatometry. It was established that the previously discovered new type of cleavage of the N—N bond in pyridylhydrazones under the influence of alkali-metal alkoxides also takes place in a number of azine systems, but the yields of the corresponding N-monoalkylamino derivatives of pyrazine, pyrimidine, and pyridazine differ.

During a previous study of the indolization of pyridyl- and arylhydrazones with alkali-metal alkoxides we observed a new type of cleavage of the N—N bond that is accompanied by N-alkylation and leads to the formation of alkylaminopyridines (or, respectively, N-alkylanilines) and sodium derivatives of oximes of carbonyl compounds [1]. In order to establish the range of application of this reaction in the present research we examined the reaction of some benzaldehyde pyrazinyl-, pyridazinyl-, and pyrimidinylhydrazones with sodium ethoxide. As we have demonstrated in a previous study [2], the use of benzaldehyde as the carbonyl component makes it possible to exclude the possibility of the normal indolization reaction and to direct the process to favor cleavage of the N—N bond in hydrazones accompanied by N-alkylation.

In addition to unsubstituted benzaldehyde 2-pyrazinyl- and 3-pyridazinylhydrazones (I, II), benzaldehyde 6-chloro-2-pyridazinylhydrazone (III) and benzaldehyde 4-chloro-6-pyrimidinylhydrazone (IV) were subjected to reaction with sodium ethoxide. The stabilizing effect of the α-chloro atoms in the azine systems, which increase the stability of the pyridazine and pyrimidine rings (which are readily decomposed under when the reaction of hydrazones with alkali-metal alkoxides is carried out under severe conditions), was used in this case.

Starting hydrazones I-IV were obtained as follows: I from 2-hydrazinopyrazine (V) [3] and benzaldehyde, II from 3-chloropyridazine (VI) [4] through 3-hydrazinopyradazine (VII), which was converted to hydrazone II without isolation, III from chlorohydrazine by a previously described method [5], and IV from 4-chloro-6-hydrazinopyrimidine [6] by treatment with benzaldehyde.

The analysis of the reaction mixtures formed in the reaction of hydrazones I-IV with sodium ethoxide was accomplished by means of gas—liquid chromatography; in addition, the reaction products were isolated preparatively. All of the reaction products were obtained by alternative synthesis for their identification and for quantitative analysis of the reaction mixture by GLC.

As expected, the reaction of sodium ethoxide with hydrazone I, in which the hydrazone residue is in the α position relative to the azine nitrogen atom, gives results that are closer to those obtained in the analogous transformations of benzaldehyde 2-pyridylhydrazone than in the case of the isomeric 3-pyridyl- and 4-pyridylhydrazones, for which the reaction takes place at lower temperatures with the primary formation of monoethylaminopyridines [1]. As in the case of benzaldehyde 2-pyridylhydrazone, the character of the cleavage of the N—N bond in hydrazone I and the principal pathway of the reaction depend substantially on the

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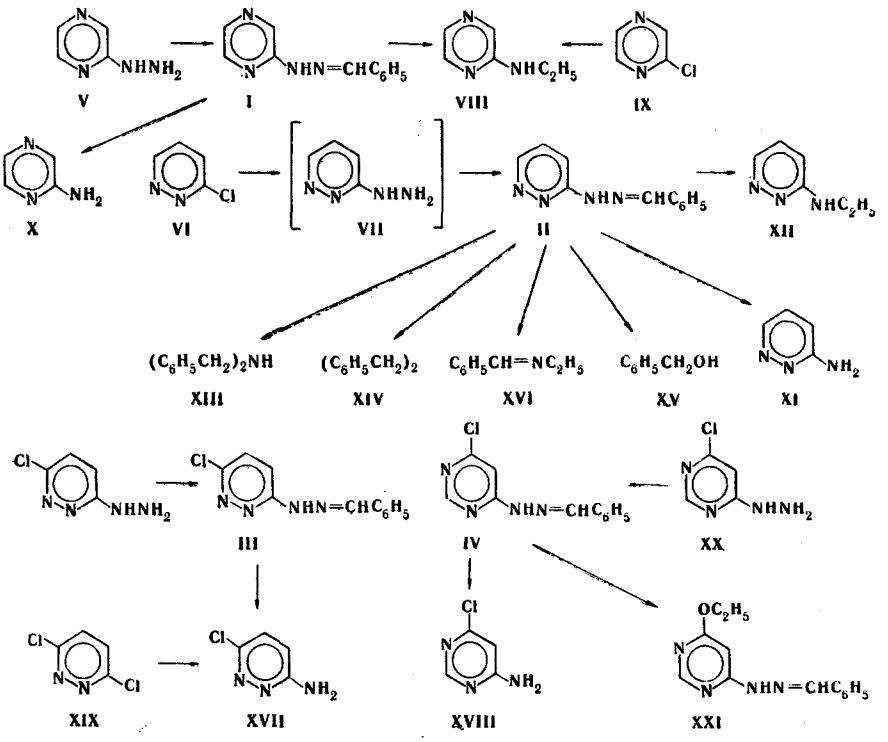

temperature: the process begins at 240°C and reaches its maximum intensity at 280°C in the direction of the formation of 2-ethylaminopyrazine (VIII), which was also obtained by alternative synthesis from 2-chloropyrazine (IX) and ethylamine. However, another reaction — thermolysis of hydrazone I to give unsubstituted 2-aminopyrazine (X) — also takes place at the same time as cleavage of the N—N bond, which evidently proceeds through a four-membered cyclic transition state [1] and leads to an N-alkylation product. As in the case of benzaldehyde 2-pyridylhydrazone, thermolysis is found to be the principal process, and its rate increases considerably more rapidly as the temperature is raised than does the rate of the reaction leading to monoalkylamino derivative VIII. Thus, for example, when the temperature is raised from 240°C (when up to 84% of starting I remains unchanged) to 250°C, the yield of amino VIII increases from 4% to 12%, and the yield of amine X increases from 11% to 77%. The maximum yield (17%) of ethylamino derivative VIII was observed in the case of brief (20 min) heating of the reaction mixture at 280°C.

The character (and evidently the mechanism) of the reaction changes substantially on passing from pyrazine derivative I to pyridazine derivative II. The reaction proceeds via many pathways to give an extremely complex mixture, the structures of the components of which could be established by means of mass chromatometry with the aid of authentic standards. In addition to the substances formed through the pyridazine portion of II — 3-aminopyridazine (XI, 4%) and 3-ethylaminopyridazine (XII, 25%) — dibenzylamine (XIII, 55%), dibenzyl (XIV, 7%), benzyl alcohol (XV, 5%), and benzylidenethylamine (XVI, 4%) were found among the reaction products and identified. The formation of XIII-XVI and, possibly, amines XI and XII in this case can be explained by assuming that when hydrazone II is heated with sodium ethoxide to 240-250°C, the N—N bond undergoes homolytic cleavage with the subsequent formation of other radicals (for example, benzyl and ethyl radicals) that undergo recombination, the products of which also may be all of the identified compounds (XI-XVI).

As we assumed, the introduction of chlorine atoms in the azine ring (pyridazine and pyrimidine) in III and IV increased their stabilities substantially. However, in addition to this, as we have already previously observed in the case of pyridine compounds [7], the introduction of chlorine atoms in the α position relative to the heterocyclic nitrogen atom shifts the process to favor thermolysis with the primary formation of amino-unsubstituted aminoazines. In fact, the principal products obtained when hydrazones III and IV were heated with sodium ethoxide were found to be precisely amino derivatives XVII and XVIII. Compound XVII was also obtained by alternative synthesis from 3,6-dichloropyridazine (XIX) and ammonia. The high lability of the chlorine atom in the 4 position of the pyrimidine ring was responsible for the formation from hydrazone IV of a side product, formed due to

nucleophilic substitution of this chlorine atom by an ethoxy group. Ethoxy hydrazone XXI was stable and was not cleaved by sodium ethoxide at high temperatures (up to 290°C).

EXPERIMENTAL

Analysis of GLC was carried out with a series 104 Pye–Unicam chromatograph with a flame-ionization detector and a 2.1 × 4 mm column filled with 10% SE-30 silicone elastomer on silanized diatomaceous earth (100-120 mesh); the nitrogen flow rate was 29 ml/min, the temperature was programmed from 160 to 245°C, the initial period was 5 min, and the temperature-rise rate was 32 deg/min. The retention times were as follows (in minutes): III 17, IV 18, XVII 6, XIX 6, XXI 19, and XXII 9. The retention times (in minutes) were as follows with the same apparatus with a catharometer (the helium flow rate was 30 ml/min, the temperature was programmed from 150 to 250°C, and the temperature-rise rate was 6 deg/min): I 18, II 20, VIII 7, X 6, XI 5, XII 6, XIII 12, XIV 9, XV 1.5, and XVI 2.5. The mass chromatometric measurements were made with a Varian MAT-112 apparatus at 70 eV and an emission current of 1.5 mA; the 2.1-m long column was filled with 3% SE-30 on Chromosorb W, and the helium flow rate was 20 ml/min.

Benzaldehyde 3-Pyridazinylhydrazone (II). A solution of 11.4 g (0.1 mole) of VI and 15 ml of hydrazine (obtained by distillation of 60 ml of hydrazine hydrate over 60 g of granulated potassium hydroxide) in 50 ml of anhydrous ethanol was refluxed for 3 h, after which it was cooled, and the product was removed by filtration and treated, without additional purification, with 10.6 g (0.1 mole) of benzaldehyde. The mixture was heated to the boiling point and allowed to stand overnight at room temperature. The precipitate of hydrazone II was removed by filtration and recrystallized from alcohol to give 13.7 g (69%) of a product with mp 210-211°C. Found: C 66.5; H 5.0; N 28.2%. $C_{11}H_{10}N_4$. Calculated: C 66.6; H 5.1; N 28.3%.

Benzaldehyde 2-Pyrazinylhydrazone (I). This compound, with mp 206.5-207.5°C, was similarly obtained in 70% yield from equimolar amounts of 2-pyrazinylhydrazine and benzaldehyde in anhydrous ethanol. Found: C 66.8; H 5.3; N 28.6%. $C_{11}H_{10}N_4$. Calculated: C 66.6; H 5.1; N 28.3%.

2-Ethylaminopyrazine (VIII). A mixture of 1 g (8.7 mmole) of 2-chloropyrazine (IX), 3 ml of distilled ethylamine, and 10 ml of anhydrous ethanol was heated in a sealed glass tube at 120-130°C for 11 h, after which it was subjected to vacuum evaporation, and the residue was treated with 20 ml of water. The aqueous mixture was made alkaline with potassium carbonate and extracted with chloroform. The chloroform extract was dried with magnesium sulfate and vacuum distilled to give 0.8 g (75%) of amine VIII in the form of a colorless liquid that was quite soluble in ordinary organic solvents and had bp 103-104°C (20 mm) and n_D^{20} 1.5635. Found: C 58.5; H 7.5; N 34.5%. $C_6H_9N_3$. Calculated: C 58.5; H 7.4; N 34.1%.

The alternative synthesis of 2-aminopyrazine was accomplished by the method in [8].

Reaction of Benzaldehyde 2-Pyrazinylhydrazone (I) with Sodium Ethoxide. A mixture of 0.6 g (3 mmole) of hydrazone I and 0.5 g (7.5 mmole) of sodium ethoxide was heated at 240°C for 20 min, after which it was cooled and dissolved in water. The aqueous solution was extracted with chloroform, and the chloroform extract was dried with magnesium sulfate and evaporated. The residue was analyzed by GLC. 2-Ethylaminopyrazine (VIII), 2-aminopyrazine (X), and unchanged hydrazone I were obtained in 4, 11, and 84% yields, respectively. When the same reaction was carried out at 250°C for 2 h, the yield of VIII was 8%, the yield of X was 56%, and the yield of I was 24%, as compared with 12, 77, and 9%, respectively, after 5 h at 250°C. When the same reaction was carried out at 280°C for 20 min, the yield of VIII was 17%, the yield of X was 55%, and the yield of I was 16%.

Reaction of Benzaldehyde 3-Pyradazinylhydrazone with Sodium Ethoxide. A mixture of 3 g (15 mmole) of hydrazone II and 2 g (30 mmole) of sodium ethoxide was heated at 250°C for 60 min, after which it was cooled and dissolved in water. The aqueous solution was extracted with chloroform, and the chloroform extract was dried with magnesium sulfate and evaporated. The residue (2.3 g) contained, according to the GLC data, the following principal products (the yields based on the theoretical values are indicated): dibenzylamine (XIII) 55%, 3-ethylaminopyridazine (XII) 25%, 2-aminopyridazine (XI) 4%, dibenzyl (XIV) 7%, benzylideneethylamine (XVI) 4%, and benzyl alcohol (XV) 5%. The residue (1.1 g) obtained after extraction of the mixture with hot heptane and removal of the solvent by distillation

was vacuum distilled at 79-80°C (0.5 mm) to give 0.55 g (36%) of dibenzylamine, which was identical to a genuine sample with respect to its IR spectrum and retention time in GLC.

When the same reaction was carried out at 240°C for 20 min, the yields according to the GLC data were: XII 7%, XI 3%, and II 85%. The yields at 280°C after the same time were: XII 14%, XI 8%, XIII 24%, and II 40%. The yields at 310°C were: XII 6% and XI 8%.

The alternative synthesis of 3-ethylaminopyridazine (XII) and 3-aminopyridazine (XI) was accomplished by the methods in [9, 10], dibenzyl (XIII) was synthesized alternatively by the method in [11], and benzylideneethylamine (XVI) was synthesized alternatively by the method in [12].

3-Ethylamino-6-chloropyridazine (XXII). A 0.5-g (3.3 mmole) sample of 3,6-dichloropyridazine (XIX) was heated with 1 ml of 33% aqueous ethylamine at 98°C for 1 h, after which the mixture was cooled and extracted with ether. The ether extract was dried with potassium carbonate and vacuum evaporated, and the residue was recrystallized from cyclohexane to give 0.4 g (72%) of amine XXII with mp 127-128°C. The product was quite soluble in ordinary organic solvents but insoluble in water. Found: C 45.7; H 5.2; Cl 22.4; N 26.6%. $C_6H_8ClN_3$. Calculated: C 45.7; H 5.1; Cl 22.5; N 26.7%.

Reaction of Benzaldehyde 6-Chloro-3-pyridazinylhydrazone (III) with Sodium Ethoxide. A mixture of 1 g (5 mmole) of hydrazone III [5] and 0.7 g (10 mmole) of sodium ethoxide was heated at 300°C for 15 min, after which the markedly resinified mixture was dissolved in methanol. The methanol solution was refluxed with charcoal and evaporated, and the residue was recrystallized from aqueous methanol (1:2) to give 0.09 g (18%) of 3-amino-6-chloropyridazine (XVII) with mp 209-210°C. No melting-point depression was observed for a mixture of this product with a genuine sample obtained from 3,6-chloropyridazine and ammonia [13], and the IR spectra and retention times of the two samples were identical.

Considerable amounts (up to 36%) of starting III were detected in the resinified reaction mass when the same reaction was carried out at 200 and 240°C for 15 min, but 3-amino-6-chloropyridazine (XVII) and 3-ethylamino-6-chloropyridazine (XXII) were absent according to the GLC data.

Benzaldehyde 6-Chloro-4-pyrimidinylhydrazone (IV). A total of 10 ml of 50% acetic acid was added to 1 g (11 mmole) of 6-chloro-4-hydrazinopyrimidine (XX) [6] and 1 ml (11 mmole) of benzaldehyde in 50 ml of ethanol, and the mixture was refluxed for 1.5 h and allowed to stand at room temperature overnight. The precipitated IV was removed by filtration and recrystallized from ethanol to give 1.12 g (70%) of a product with mp 213-214°C. The product was quite soluble in chloroform and DMF but only slightly soluble in other ordinary organic solvents and water. Found: C 56.9; H 3.7; Cl 15.2; N 23.9%. $C_{11}H_9ClN_4$. Calculated: C 56.8; H 3.8; Cl 15.2; N 24.1%.

Reaction of Benzaldehyde 6-Chloro-4-pyrimidinylhydrazone (IV) with Sodium Ethoxide. A mixture of 1 g (5 mmole) of hydrazone IV and 0.7 g (10.5 mmole) of sodium ethoxide was heated at 230-240°C for 1 h, after which it was cooled and treated with water. The aqueous solution was extracted with chloroform, and the chloroform extract was dried with magnesium sulfate and evaporated. According to the GLC data, the residue contained the following compounds in the indicated yields: benzaldehyde 6-ethoxy-4-pyrimidinylhydrazone (XXI) 76%, starting hydrazone IV 7%, and 4-amino-6-chloropyrimidine (XVIII) 4%. Chromatography on aluminum oxide (activity II) with elution with 400 ml of ether yielded 0.67 g (64%) of hydrazone XXI with mp 177-178°C (from alcohol). The product was soluble in chloroform and DMF, only slightly soluble in other ordinary organic solvents, and insoluble in water. Found: C 64.4; H 5.6; N 23.1%. $C_{13}H_{14}N_4O$. Calculated: C 64.4; H 5.8; N 23.1%.

When the same reaction was carried out at 220°C for 30 min, the yields according to the GLC data were as follows: XXI 72%, XVIII 4%, and IV 12%. Pronounced resinification was observed when the reaction was carried out at 280°C (10 min), and the yields were as follows: XXI 8%, IV 7%, and XVIII 10%.

Compound XXI was recovered quantitatively when 0.1 g (0.5 mmole) of hydrazone XXI was heated with 0.3 g (4.5 mmole) of sodium ethoxide at 240°C.

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HETEROCYCLIC ANALOGS OF PLEIADIENE.

XXXVI.* EFFECT OF N-SUBSTITUENTS ON THE RECYCLIZATION OF PERIMIDINES

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Electron-acceptor substituents (phenyl, benzyl, methoxymethyl, acetonyl, and phenacyl) in the 1 position of perimidine do not have an appreciable effect on the ease of opening of the perimidine ring under the influence of aroyl chlorides in the presence of mild bases. However, some of them (C_6H_5 and CH_3OCH_2) substantially hinder the step involving the cyclization of the pseudo bases to arylperimidines under the influence of alkalis. It was shown by kinetic measurements that substituents in the N-aroyl group of N-methyl-N-formyl-N'-aroyl-1,8-naphthalenediamines have virtually no effect on the rate of cyclization in alkaline media. A mechanism for the alkaline and acidic cyclization of the pseudo bases is proposed on the basis of the regularities observed. 1,2-Diarylperimidines were synthesized for the first time.

We have recently observed a new recyclization reaction that makes it possible to introduce virtually any aromatic, heteroaromatic, or vinylaromatic substituent [2, 3] in the 2 position of N-substituted perimidines. The reaction consists of two steps: the first step involves treatment of the N-substituted perimidine (I) with the chloride of the corresponding carboxylic acid, the radical of which one desires to incorporate in the μ position of the perimidine, in the presence of a mild base (triethylamine, diethylamine, and sometimes potassium carbonate). In this case a highly reactive N-acylperimidinium salt (VII), which is readily converted in the presence of hydroxide ions to pseudo base VIII (which exists in acyclic form IX), is formed. In the second step of the reaction pseudo base IX is refluxed with aqueous alkali, as a result of which the formyl group is split out, and 1,2-disubstituted perimidine XII is formed in high yield.

The aim of the present research was to study the effect of N-substituents on both steps of the recyclization reaction. Phenyl, benzyl, acetonyl, phenacyl, and methoxymethyl groups were used as N-substituents in the starting compound (the reaction for 1-methyl- and 1-dialkylaminoalkylperimidines was previously studied in [2, 3]). All of these substituents

*See [1] for communication XXXV.

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