LABILITY OF THE β-DIETHYLAMINOETHYL GROUP UNDER THE CONDITIONS OF THE FORMATION OF A PYRROLE RING VIA THE KNORR SYNTHESIS

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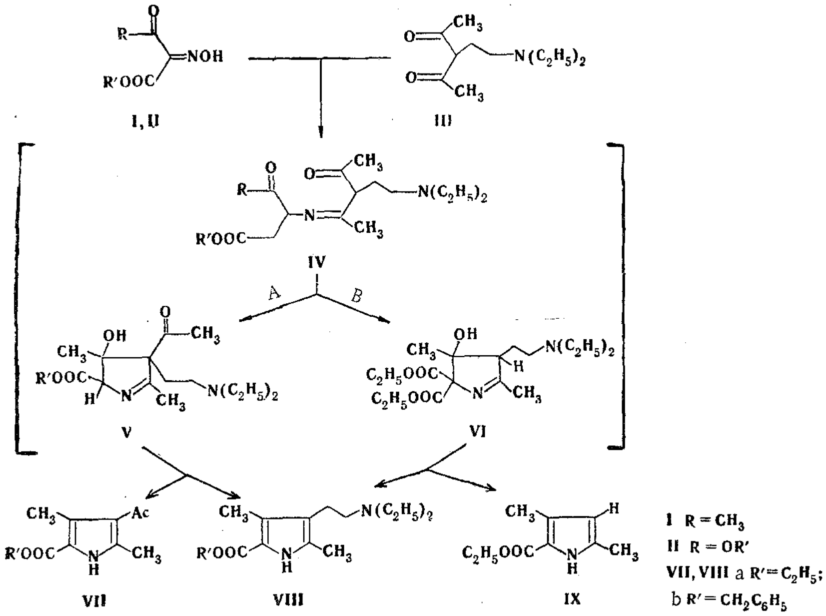
The corresponding 3-acetyl- and 3-H-pyrroles are formed along with 2,4-dimethyl-3-(β-diethylaminoethyl)-5-carbethoxypyrrole in the condensation of 3-(β-diethylaminoethyl)pentane-2,4-dione with isonitrosoacetoacetic (I) and isonitrosomalonic (II) esters.

3-(β-Diethylaminoethyl)pyrroles are widely used in the preparation of porphyrins with vinyl groups [1, 2]. The starting ethyl and benzyl esters of 2,4-dimethyl-3-(β-diethylaminoethyl)pyrrole-5-carboxylic acid in the synthesis of such pyrroles are obtained by Knorr condensation of 3-(β-diethylaminoethyl)pentane-2,4-dione (III) with the appropriate acetoacetic or diethylmalonic esters [3, 4]. In connection with the fact that the yield in this step was relatively low, we undertook a more detailed study of this reaction. Analysis of the reaction products formed in the condensation of acetoacetic ester with pentanedione III made it possible to establish that 2,4-dimethyl-3-acetyl-5-carbethoxypyrrole (VIIa) is present in considerable amounts in the reaction mixture, along with β-diethylaminoethyl-substituted pyrrole VIIIa. Replacement of acetoacetic ester by the corresponding benzyl ester (Ib) leads to an increase in the yield of acetylpyrrole (from 8 to 17%).



At the same time, the amount of pyrrole VIII decreases from 29 to 19%. Small amounts of 2,4-dimethyl-3,5-dicarbalkoxypyrroles and 2,5-dimethyl-3,6-dicarbalkoxypyrazine are also detected. The former are apparently

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formed as a result of condensation of isonitrosoacetoacetic ester with acetoacetic ester, while the latter is the product of self-condensation of aminoacetoacetic ester.

However, the formation of pyrrole VII naturally seems of greatest interest. 3-Alkylpentane-2,4-diones of the III type usually give only 3-alkylpyrroles on Knorr condensation. The reaction may proceed via either path A with splitting out of an acetyl group or via path B, in which the acetyl group participates in the construction of the heteroring. When methyl 4-acetyl-5-oxohexanoate was used, it was shown [5] that the reaction proceeds primarily via the second path. However, our results are evidence that cyclization in the case of a pentanedione with a β-diethylaminoethyl group is realized via mechanism A. In addition, the facile loss of a β-diethylaminoethyl radical by V is unusual in this reaction.

The ease of splitting out of a β-diethylaminoethyl group was also demonstrated thoroughly in the condensation of pentanedione III with diethylmalonic ester. In this case, as it is easy to note, the formation of a pyrrole ring can proceed only via path B. Despite the fact that competition between the acetyl and β-diethylaminoethyl substituents is absent here, the latter is split out at a sufficiently high rate. The yield of pyrroles VIIIa and IX were 32 and 25%, respectively.

EXPERIMENTAL

The IR spectra were recorded with a Perkin-Elmer model 257 spectrometer. The PMR spectra of deuterochloroform solutions were obtained with a JEOL S-60-HL spectrometer with tetramethylsilane as the internal standard.

3-(β-Diethylaminoethyl)pentane-2,4-dione was obtained by the method in [3] and was vacuum-distilled several times to give a product with bp 131-133° (10 mm) and n_D^{20} 1.4700 (n_D^{20} 1.4670 [3]). Found: C 66.2; H 10.7; N 6.7%. $C_{11}H_{21}NO_2$. Calculated: C 66.3; H 10.6; N 7.0%.

Condensation of Pentanedione III with Acetoacetic Ester. A solution of 64 g of sodium nitrite in 80 ml of water (8-10°) was added with stirring to a solution of 81 g of acetoacetic ester in 400 ml of acetic acid, and the resulting solution was stirred for 5 h and then gradually added to a mixture of 122 g of pentanedione III, 25 g of zinc dust, and 50 g of sodium acetate in 300 ml of acetic acid. Zinc dust (100 g) and 50 g of sodium acetate were then added by sprinkling in small portions simultaneously in such a way that the temperature was maintained at 60-65°. At the end of the addition of the isonitrosoacetoacetic ester, the reaction mixture was stirred for 30 min and poured into 2.5 liter of ice water. The precipitate was removed by filtration, and the solution was neutralized to pH 6 with 10% sodium hydroxide solution and extracted with chloroform. The extract was dried with magnesium sulfate and evaporated to dryness. The residue was treated with ether, and the insoluble material was removed by filtration and added to the first precipitate. The oxalate of pyrrole VIIIa was precipitated from the ether solution. The yield of a product with mp 179-180° (from water) was 63 g (29%). No melting-point depression was observed for a mixture of this product with an analytical sample [3].

The combined precipitates were passed through a layer of Al_2O_3 and subjected to fractional crystallization from aqueous acetic acid to give 11 g (8.5%) of pyrrole VIIa with mp 143° (from alcohol) (mp 143° [6a]). The yield of 2,4-dimethyl-3,5-dicarbethoxypyrrole with mp 136° (from alcohol) was 1.2 g. No melting-point depression was observed for a mixture of this product with an analytical sample [6b].

Condensation of Pentanedione III with Benzyl Acetoacetate. This reaction and the isolation of the compounds obtained were carried out as in the first experiment. The yield of the oxalate of pyrrole VIIIb, with mp 179-180° (mp 179.5-180° [4]), was 19%. The yield of pyrrole VIIb, with mp 134-136° (mp 135° [7]), was 17%. IR spectrum (KBr): 3180 (NH), 1682 (ester C = O), 1630 cm^{-1} ($COCH_3$).

2,4-Dimethyl-3,5-dicarbobenzoxypyrrole. This compound, the yield of which was 1 g (2%), had mp 137-137.5° (mp 137° [8]).

2,5-Dimethyl-3,6-dicarbobenzoxypyrazine. This compound was isolated, after separation of the mother liquors, with a column filled with Al_2O_3. The yield of product with mp 108° (from alcohol–hexane) (mp 108° [9]) was 0.6 g. IR spectrum: 1705 (in KBr) and 1725 (in CCl_4) (ester C=O). PMR spectrum in CCl_4, δ, ppm: 745 (10H), 5.35 (4H, singlet), 2.73 (6H, singlet).

Condensation of Pentanedione III with Isonitrosomalonic Ester. Zinc dust (20 g) was added in portions at 85-90° to a solution of 24 g of isonitrosomalonic ester, 24 g of pentanedione III, and 50 g of fused sodium acetate in 200 ml of acetic acid, after which the mixture was heated at 110° for 3 h and poured into

1.5 liter of water. The reaction mixture was then worked up as in the first experiment to give 13.8 g (32%) of the oxalate of pyrrole VIIIa with mp 179-180°.

Pyrrole IX was isolated in a yield of 5 g (24.8%) and had mp 125°. No melting-point depression was observed for a mixture of this product with an analytical sample [6c].

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