

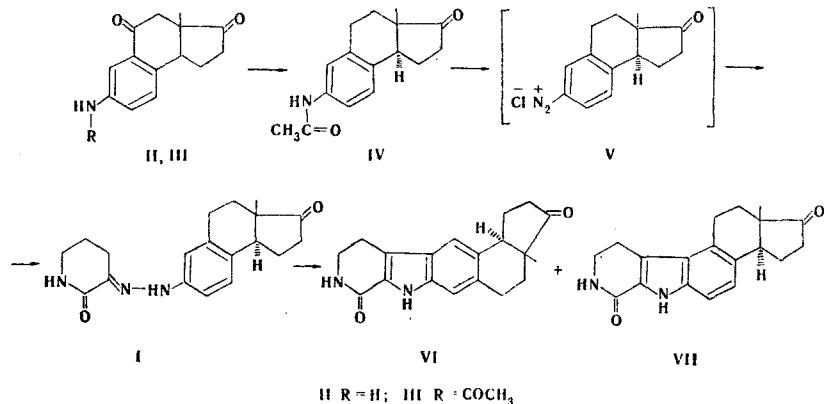
INVESTIGATION OF THE DIRECTION OF THE FISCHER  
CYCLIZATION OF ARYLHYDRAZONES THAT ARE  
DERIVATIVES OF HEXAHYDROBENZ[e]INDENE  
CYCLIZATION OF A PIPERIDINE-2,3-DIONE 3-HYDRAZONE

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The cyclization of the piperidine-2,3-dione 3-hydrazone obtained from the three-ring steroid BCD fragment proceeds with the primary formation of a p-substitution product. According to the PMR spectral data, the ratio of the para and ortho isomers is 3.3:2.

We have previously shown [1] by PMR spectroscopy that an o-substitution product is primarily formed in the Fischer cyclization of ethyl pyruvate trans-3a-methyl-1,2,3a,4,5,9b-hexahydro-3H-benz[e]inden-3-on-7-ylhydrazone; the ratio of o- and p-substitution products is 3:2. In the present research we studied the direction of the Fischer cyclization of piperidine-2,3-dione 3-hydrazone I, which contains the same three-ring BCD fragment. Hydrazone I, which was obtained from amine II, was refluxed in alcohol with sulfuric acid, and a mixture of (73% yield) of isomeric tetrahydro- $\beta$ -carbolinones VI and VII was obtained; this mixture was separated by crystallization.



Bands of indole NH stretching vibrations at 3380 and 3340  $\text{cm}^{-1}$ , respectively, and bands of a tetrahydropyridone ring NH bond at 3320  $\text{cm}^{-1}$ , as well as bands of stretching vibrations of a carbonyl group in a cyclopentane ring at 1720  $\text{cm}^{-1}$  in the spectrum of VI and at 1725  $\text{cm}^{-1}$  in the spectrum of isomer VII, are observed in the IR spectra of VI and VII. The bands at 1650  $\text{cm}^{-1}$  in the IR spectrum of VI and the band at 1660  $\text{cm}^{-1}$  in the spectrum of VII correspond to the absorption of the amide carbonyl group of the tetrahydropyridone ring.

The mass spectra of isomeric VI and VII are practically identical and are characterized by intense molecular ion peaks at 308 $\dagger$  and by peaks of  $[\text{M} - \text{CH}_3]^+$ ,  $[\text{M} - \text{CO}]^+$ ,  $[\text{M} - \text{HCO}]^+$ ,  $[\text{M} - \text{NCO}]^+$ ,  $[\text{M} - \text{CONHCH}_2]^+$ , and  $[\text{M} - \text{CO} - \text{C}_2\text{H}_4]^+$  fragments due to fragmentation of the cyclopentane and tetrahydropyridone rings. The peaks at 293, 280, 279, 265, and 251 correspond to these fragments.

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† Here and subsequently, the m/e values are presented.

Two singlets at 7.18 and 7.29 ppm belonging to the protons of the phenyl ring are observed at weak field in the PMR spectrum of VI. The absence of spin-spin coupling between these protons constitutes evidence for their mutual para orientation. A singlet of a  $\text{CH}_3$  group (0.53 ppm) and multiplets of aliphatic protons at 1.0-3.5 ppm are observed at strong field. The broad singlets at 7.47 and 11.37 ppm belong to the protons of the NH groups. A quartet of the AB type (6.96 ppm, 7.22 ppm) belonging to the protons of the phenyl ring is observed at weak field in the PMR spectrum of VII. The spin-spin coupling constant (SSCC) of these protons ( $J = 8.7$  Hz) attests to their mutual ortho orientation. A singlet of a methyl group (0.64 ppm) and a multiplet of protons of  $\text{CH}_2$  and CH groups at 1.0-3.5 ppm are observed in the strong-field region. The broad singlets at 7.52 and 11.50 ppm belong to the protons of the NH groups.

Analysis of the PMR spectra of the products showed that 45.5% of isomer VI and 27.5% of isomer VII are formed in the cyclization of hydrazone I. On the basis of an examination of Dreiding and Stuart models it can be assumed that the decrease in the percentage of isomer VII as compared with the percentage of the o-substitution product formed in the cyclization of the ethyl pyruvate hydrazone is explained by steric hindrance associated with the drawing together of the atoms in the 4 and 5 positions. This conclusion is in good agreement with the available data regarding the cyclization of hydrazones of unsymmetrical ketones [2, 3].

## EXPERIMENTAL

The IR spectra of mineral oil suspensions of the compounds were recorded with a Perkin-Elmer 457 spectrometer. The UV spectra of alcohol solutions of the compounds were recorded with an ESPS-3 spectrophotometer. The PMR spectra of  $d_6$ -DMSO solutions of the compounds containing six drops of  $\text{CCl}_4$  were recorded with a JNM 4H-100 spectrometer with tetramethylsilane as the standard. The mass spectra were obtained with an MKh-1303 spectrometer with direct introduction of the samples into the ion source at an ionizing voltage of 50 eV.

7-Acetamido-trans-3a-methyl-1,2,3a,4,5,9b-hexahydro-3H-benz[e]indene-3,5-dione (III). Acetic anhydride [2 ml (8.8 mmole)] was added to a suspension of 2 g (8.8 mmole) of amine II in 50 ml of concentrated KOH at pH 8, and the mixture was stirred at 20°C for 3 h. The resulting precipitate was removed by filtration and washed with water and alcohol to give 1.94 g of III, with mp 258-260°C (from alcohol), in 82% yield. UV spectrum,  $\lambda_{\text{max}}$  (log  $\epsilon$ ): 240 (3.62) and 325 nm (3.02). IR spectrum: 3295, 3460 (NH); 1660, 1680; 1690, and 1740  $\text{cm}^{-1}$  (CO). Found: C 70.8; H 6.3; N 5.2%.  $\text{C}_{16}\text{H}_{17}\text{NO}_3$ . Calculated: C 70.8; H 6.3; N 5.2%.

7-Acetamido-trans-3a-methyl-1,2,3a,4,5,9b-hexahydro-3H-benz[e]inden-3-one (IV). A solution of 1.62 g (6 mmole) of acetamido derivative III was hydrogenated over 1.6 g of 20%  $\text{PdCl}_2$  and 0.16 g of 10% Pd/Cl in a mixture of 162 ml of acetic acid and 16 ml of HCl. After 20 h, the catalyst was removed by filtration and washed with acetic acid, and 28 g of sodium acetate was added to the filtrate. The solvent was removed by vacuum evaporation, and the residue was washed with water and dried to give 1.52 g of crude product, from which 0.14 g of starting III, which was identical to an authentic sample with respect to its IR spectrum and melting point, was isolated by fractional crystallization from alcohol. No melting-point depression was observed for a mixture of this product with an authentic sample. Workup of the mother liquor yielded 0.94 g (61%) of IV with mp 163° (from benzene-hexane). UV spectrum,  $\lambda_{\text{max}}$  (log  $\epsilon$ ): 246 (4.22) and 280 nm (3.10, shoulder). IR spectrum: 3320, 3440 (NH); 1665, 1680, and 1735  $\text{cm}^{-1}$  (CO). Found: C 74.5; H 7.4; N 5.3%.  $\text{C}_{16}\text{H}_{19}\text{NO}_2$ . Calculated: C 74.7; H 7.4; N 5.4%.

3-Piperidine-2,3-dione trans-3a-Methyl-1,2,3a,4,5,9b-hexahydro-3H-benz[e]inden-3-on-7-ylhydrazone (I). A 0.72-g (2.8 mmole) sample of acetamido derivative IV was refluxed in a mixture of 1.3 ml of HCl and 4.5 ml of water for 15 min, after which the solution was cooled to 0°C and treated with a solution of 0.23 g (2.9 mmole) of  $\text{NaNO}_2$  in 0.55 ml of water. The diazonium solution was treated with 10% sodium acetate solution to bring it up to pH 4. A mixture of 0.5 g (1.7 mmole) of 3-carbethoxy-2-piperidone, 0.2 g (3.6 mmole) of KOH, and 2.7 ml of water was stirred at 20°C for 1 h, after which it was acidified to pH 5 with acetic acid.

The solution of the diazonium compound was added at 0°C to the resulting solution of 3-carboxy-2-piperidone, and the mixture was stirred at 25° for 30 h. The resulting precipitate was removed by filtration, washed with water, and dried to give 0.7 g (78%) of hydrazone I with mp 238°C (from acetone). UV spectrum,  $\lambda_{\text{max}}$  (log  $\epsilon$ ): 240 (2.94) and 330 nm (3.58). IR spectrum: 3200, 3382 (NH); 1660, 1735  $\text{cm}^{-1}$  (CO). Found: C 70.1; H 7.2; N 12.6%; M 325 (by mass spectrometry).  $\text{C}_{19}\text{H}_{23}\text{N}_3\text{O}_2$ . Calculated: C 70.1; H 7.1; N 12.9%; M 325.

trans-8a-Methyl-1,2,3,4,5b,6,7,8a,9,10-decahydro-8H-indeno[5,4-g][9H-pyrido[3,4-b]indole]-1,8-dione (VI). A 0.13-g (0.4 mmole) sample of hydrazone I was refluxed for 2 h in a mixture of 5.4 ml of alcohol and 0.276 ml of concentrated  $\text{H}_2\text{SO}_4$ , after which the mixture was cooled, and the resulting precipitate was removed by filtra-

tion, washed with alcohol and water, and dried to give 0.05 g (40.6%) of VI with mp 355°C (from alcohol). Found: C 74.0; H 6.6; N 9.1%; M 308 (by mass spectrometry).  $C_{19}H_{20}N_2O_2$ . Calculated: C 74.0; H 6.5; N 9.1%; M 308.

trans-3a-Methyl-1,2,3,4,5,6,6a,8,9,9a-decahydro-7H-indeno[5,4-h][9H-pyrido[3,4-b]indole]-1,7-dione (VII). Workup of the filtrate yielded 0.042 g (32.6%) of a mixture, which, according to the PMR spectrum, contained 85% isomer VII and 15% isomer VI. Crystallization of the mixture from alcohol yielded VII with mp 325°C. Found: C 73.8; H 6.5; N 9.1%; M 308 (by mass spectrometry).  $C_{19}H_{20}N_2O_2$ . Calculated: C 74.0; H 6.5; N 9.1%; M 308.

#### LITERATURE CITED

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#### RESEARCH ON 1-AZA TWO-RING SYSTEMS

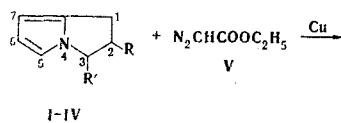
#### XVI.\* SYNTHESIS OF 5-, 6-, AND 7-CARBETHOXYMETHYL-1,2-DIHYDROPYRROLIZINES AND METHOD FOR THE ISOLATION OF 5-CARBETHOXYMETHYL-1,2-DIHYDROPYRROLIZINES FROM MIXTURES WITH OTHER ISOMERS

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Mixtures of isomeric 5-, 6-, and 7-carbethoxymethyl-1,2-dihydropyrrolizines were obtained by reaction of 1,2-dihydropyrrolizines with ethyl diazoacetate. The effect of the position of the alkyl groups in the two-membered ring on the ratio of isomers in the reaction products is demonstrated. A method for the isolation of 5-carbethoxymethyl-1,2-dihydropyrrolizines from the mixtures of isomers based on the difference in their reactivities in diazo coupling is described. The preferred conformations of the two-membered rings in the 5-carbethoxymethyl-1,2-dihydropyrrolizines are judged from the PMR spectral data.

We have previously demonstrated that mixtures of compounds with a carbethoxymethyl group in the 5 and 7 positions are obtained as a result of the reaction of 1,2-dihydropyrrolizines with ethyl diazoacetate (in contrast to the analogous reaction of the simplest pyrroles, which leads to products of substitution of the  $\alpha$ -carbon atoms [2]) [3]. In the present paper we describe the results of further studies of the products of the reaction of 1,2-dihydropyrrolizines (I-IV) with ethyl diazoacetate (V) and present new data on the preparation of 6-carbethoxymethyl-1,2-dihydropyrrolizines (XIV-XVII) in addition to 5- (VI-IX) and 7-carbethoxymethyl (X-XIII) derivatives:



\* See [1] for communication XV.

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