

EXPERIMENTAL

2-Methyl-3-carbethoxy-4H,8H,5,6-dihydrothieno[2,3-d]thia[1]pyrano[4,3-b]pyrrole (VI).

A mixture of 1 g (4 mmole) of hydrazine hydrochloride I, 0.53 g (4.5 mmole) of ketone II, and 5 ml of absolute alcohol was refluxed for 5 min, after which it was cooled, and the precipitate was removed by filtration and washed with water to give 1 g of pyrrole VI. To obtain VII, the reaction mixture was refluxed in absolute alcohol for 20 min. The condensation of hydrochloride I with ketones III and V was carried out in a 2% alcohol solution of hydrogen chloride in equimolar amounts; the solutions were refluxed for 1 h and 5 h, respectively. An increase in the concentration of the alcohol solution of hydrogen chloride led to resinification of the mixture. The data for VI-IX are presented in Table 1.

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PYRROLES FROM KETOXIMES AND ACETYLENE

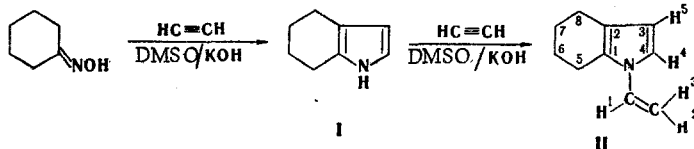
8.\*SYNTHESIS OF 4,5,6,7-TETRAHYDROINDOLE AND ITS 1-VINYL DERIVATIVE

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4,5,6,7-Tetrahydroindole or 1-vinyl-4,5,6,7-tetrahydroindole was obtained in 81 and 93% yields, respectively, by reaction of cyclohexanone oxime with acetylene at 90-140°C in the presence of alkali metal hydroxides or alkoxides in dimethyl sulfoxide (DMSO) or mixtures of DMSO with low-polarity or nonpolar solvents. The reaction is effective both in an autoclave (initial pressure 8-16 gage atm) and at atmospheric pressure.

In our previous communications [2, 3] we reported that 4,5,6,7-tetrahydroindole (I) and 1-vinyl-4,5,6,7-tetrahydroindole (II) were synthesized by the reaction of cyclohexanone oxime with acetylene:



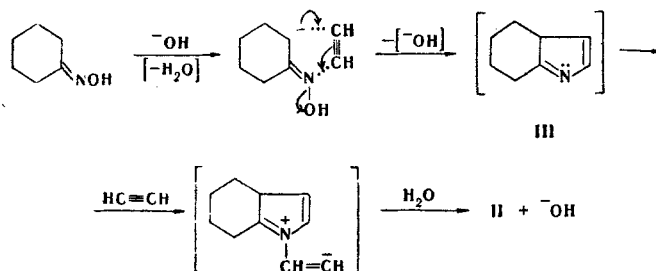
\*See [1] for communication 7.

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Indoles I and II were obtained in 81 and 93% yields, respectively.

The fundamental peculiarities and experimental details of this synthesis are discussed in the present paper.

The fact that vinylindole II is formed from tetrahydroindole I is confirmed by the facile vinylation of the latter under the conditions of this reaction (the product is obtained in no less than 85% yield). However, a comparison of the yields of I and II under comparable conditions makes it possible to assume that the production of II in one step does not exclude its direct synthesis by reaction of acetylene with some reactive intermediate (since the yield of II is always appreciably higher than the yield of tetrahydroindole I). Structure III, in which the nitrogen atom, because it is not included in the aromatic system, should have increased nucleophilicity and therefore should react more vigorously with a second molecule of acetylene than the "pyrrole" nitrogen atom of tetrahydroindole I, may serve as an intermediate of this type, according to the mechanism proposed in the preceding communications of this series:



Not even traces of O-vinylcyclohexanone oxime, which could have been postulated as an intermediate, could be detected even under mild conditions and at low degrees of conversion of cyclohexanone oxime. This pathway is evidently not realized under the conditions of this condensation (in contrast to the reaction of cyclohexanone oxime with acetylenedicarboxylic acid [4]).

The synthesis of indoles I and II proceeds successfully at a cyclohexanone oxime to acetylene molar ratio of 1:2-5 at 90-140°C; the reaction proceeds very slowly below 90°C, and the rate of side processes increases markedly above 140°C.

Bases (alkali metal hydroxides and alkoxides) taken in 10-50% amounts relative to the weight of the cyclohexanone oxime serve as catalysts. Potassium, rubidium, and tetrabutylammonium hydroxides catalyze the reaction efficiently; the last two catalysts have a selective effect on the step involving the construction of the tetrahydroindole ring (in the synthesis of indole I), and the first catalyst is also active in the vinylation step.

The condensation proceeds well in both polar aprotic solvents (sulfoxides and amidophosphates) and in mixtures of these aprotic solvents with nonpolar or low-polarity solvents (dioxane and benzene) taken in a volume ratio of 1-25:1-10 with cyclohexanone oxime. In the case of the reaction of cyclohexanone oxime with acetylene it was established that the most effective of the aprotic solvents in this reaction is DMSO, and that DMSO-dioxane is the most effective of the mixed solvents. This was subsequently also confirmed for other ketoximes. The use of the mixed DMSO-dioxane solvent system makes it possible to carry out the reaction absolutely selectively, i.e., to obtain either indole I (in the case of a DMSO content on the order of 5-10%) or vinylindole II (in pure DMSO). It is not expedient to use more than a 25-fold excess of the solvent, while an increase in the reaction temperature, which leads to resinification, is required in the case of insufficient solvent (below the indicated limit).

The reaction can be carried out equally successfully not only in an autoclave at an initial acetylene pressure of 8-16 atm but also in an apparatus or flask with a stirrer with continuous admission of acetylene at a slightly increased (1.5-2 atm) or atmospheric pressure.

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Chromatographic analysis was accomplished with a Khrom-4 chromatograph with a catharometer as the detector; the 2.5-m long column had a diameter of 3 mm, the solid phase was

Chromaton N-AW-DMCS, the liquid phase was 15% DS 550 silicone, the thermostat temperature was 170°C, and the carrier gas was helium. The IR spectra of liquid films of the compounds were recorded with a UR-20 spectrometer. The PMR spectra of solutions of the compounds in CCl<sub>4</sub> were recorded with a Tesla BS-487B spectrometer with hexamethyldisiloxane as the internal standard.

4,5,6,7-Tetrahydroindole (I). 1) Cyclohexanone oxime (50 g), 5 g of KOH, and 300 ml of DMSO were placed in a 2-liter steel rotating autoclave, and acetylene was fed in from a cylinder (the initial pressure was 16 gage atm). The autoclave was then sealed, and the contents were heated with stirring at 120°C for 1 h. The autoclave was cooled to room temperature, and the reaction mixture was removed and washed with 20% aqueous potassium or sodium hydroxide solution to remove the unchanged cyclohexanone oxime. The aqueous alkaline solutions were extracted with ether, and the ether extracts were combined with the reaction mass, and the mixture was dried with K<sub>2</sub>CO<sub>3</sub>. The ether was removed by distillation, and residual indole I, which began to crystallize, was purified by recrystallization from hexane, heptane, or octane to give 39.4 g (74%) of I with mp 50°C. IR spectrum: 1550 and 1590 (pyrrole ring); 1665 and 3370 cm<sup>-1</sup> (deformation and stretching vibrations of an associated NH grouping). PMR spectrum: 7.22 (NH, markedly split because of the effect of the quadrupole moment of nitrogen); 5.74 (3-H), 6.15 (2-H); 2.42 (4-H and 7-H); 1.67 ppm (5-H and 6-H). Found: C 79.2; H 8.9; N 11.3%. C<sub>6</sub>H<sub>11</sub>N. Calculated: C 79.3; H 9.1; N 11.6%.

2) Dimethyl sulfoxide (5 kg) and 5 kg of dioxane were placed in a 25-liter reactor with a turbine-driven stirrer, after which 1500 g of cyclohexanone oxime and 500 g of KOH were added with stirring. The apparatus was sealed, the reaction mixture was heated with stirring to 100°C, and acetylene was admitted from a cylinder (1.2-1.5 gage atm; the flow rate was determined by the rate of absorption and was ~ 30 liters/h) for 4-6 h. The entire process was carried out at 110-120°C. Samples (the first after 3 h and the subsequent samples every hour) were removed from the reaction mixture during the reaction to determine the percentages of cyclohexanone oxime and indoles I and II by gas-liquid chromatography (GLC). When traces of II (up to 1%) appeared on the chromatogram, the acetylene flow was stopped, the reactor was allowed to cool to room temperature, and the reaction mixture was removed and worked up as described in method 1 to give 799 g (50%) of I.

3) Dimethyl sulfoxide (200 ml), 25 g of cyclohexanone oxime, and 3 g of KOH were placed in a flask equipped with a stirrer, a reflux condenser, a thermometer, and a bubbler, the reaction mixture was heated with stirring to 90-95°C, and acetylene was admitted from a cylinder at atmospheric pressure for 2-2.5 h (until traces of vinylindole II appeared on the chromatogram). The mixture was then cooled to room temperature and worked up by the standard procedure (see method 1) to give 12 g (45%) of I.

1-Vinyl-4,5,6,7-tetrahydroindole (II). 1) Cyclohexanone oxime (5 g), 1.5 g of KOH, and 120 ml of DMSO were placed in a 1-liter steel autoclave, and acetylene was admitted from a cylinder (initial pressure 16 gage atm). The autoclave was sealed, and the contents were heated with stirring at 120°C for 1 h. The autoclave was cooled to room temperature, and the reaction mass was removed and washed with aqueous DMSO. The aqueous solutions were extracted with ether, the ether extracts were combined with the reaction mass, and the mixture was dried with K<sub>2</sub>CO<sub>3</sub>. The ether was removed by distillation, and the residue was subjected to vacuum distillation to give 5.5 g (93%) of II with bp 85-86°C (3 mm), n<sub>D</sub><sup>20</sup> 1.5562, and d<sub>4</sub><sup>20</sup> 1.0010. IR spectrum: 585, 850, 970, 1180, 1320, 1550, 1600, 1650, 3020, and 3070 cm<sup>-1</sup> (N-vinyl group). PMR spectrum: 1.47 and 2.24 (4H, two m, 6-H and 7-H; 5-H and 8-H) and five signals of different multiplicities at 4.10-6.60 ppm (five protons): The number of the olefin proton,  $\delta$  ( $\pm$  0.01 ppm), and the spin-spin coupling constants ( $\pm$  0.1 Hz) are given: 1, 6.43, <sup>3</sup>J<sub>12</sub> = 8.9, <sup>3</sup>J<sub>13</sub> = 15.6, <sup>4</sup>J<sub>14</sub> = 0.4; 2, 4.21, <sup>2</sup>J<sub>23</sub> = 0.8, <sup>3</sup>J<sub>24</sub> = 8.9; 3, 4.66, <sup>2</sup>J<sub>32</sub> = 0.8, <sup>3</sup>J<sub>31</sub> = 15.6; 4, 6.54, <sup>3</sup>J<sub>45</sub> = 3.0, <sup>4</sup>J<sub>41</sub> = 0.4; 5, 5.76, <sup>3</sup>J<sub>54</sub> = 3.0, <sup>5</sup>J<sub>51</sub> = 0.4. Found: C 81.6; H 8.7; N 9.4%. C<sub>10</sub>H<sub>13</sub>N. Calculated: C 81.6; H 8.9; N 9.5%.

2) Dimethyl sulfoxide (3 kg) was placed in a 5-liter equipped with a turbine-driven stirrer, after which 600 g of cyclohexanone oxime and 240 g of KOH were added with stirring. The reactor was sealed, and the contents were heated with stirring to 100°C as acetylene was admitted from a cylinder (at 1.2-1.5 gage atm; the flow rate was determined by the rate of absorption and was ~ 30 liters/h) until absorption was complete (usually 9-12 h). The entire process was carried out at 110-120°C. The reactor was then allowed to cool to room temperature, and the contents were subjected to the standard workup (see method 1) to give 545.3 g (70%) of II.

3) Cyclohexanone oxime (25 g), 12.5 g of KOH, and 200 ml of DMSO were placed in a flask equipped with a stirrer, reflux condenser, thermometer, and bubbler, the mixture was heated with stirring to 90-95°C, and acetylene was admitted at atmospheric pressure for 4-5 h (until cyclohexanone oxime disappeared on the chromatogram). Standard workup gave 28.9 g (90%) of II.

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#### BEHAVIOR OF N-ALKOXYBENZIMIDZOLES WITH RESPECT TO NUCLEOPHILIC REAGENTS.

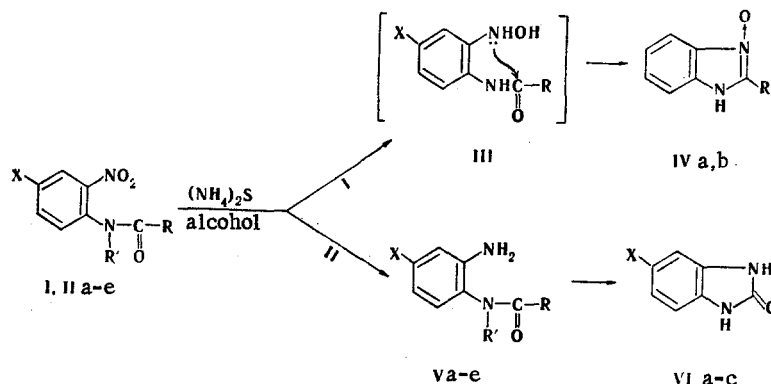
#### ATTEMPTS TO SYNTHESIZE N-HYDROXY-2-AMINOBENZIMIDAZOLES

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Various possibilities for the synthesis of N-hydroxy- and N-alkoxy derivatives of 2-aminobenzimidazoles — reductive cyclization of o-nitrophenylureas, the action of sodium amide on 1-alkoxybenzimidazoles, the ammonolysis of 1-alkoxy-2-iodobenzimidazoles, etc. — were investigated. Organometallic compounds of 1-alkoxybenzimidazoles were obtained for the first time, and their reactivities with respect to benzophenone, iodine, and 1-substituted benzimidazoles were studied. 2,2'-Di-benzimidazolyls that contain an alkoxy group in the 1 position were synthesized.

The present research was undertaken in order to synthesize N-oxides of 2-aminobenzimidazoles — a class of compounds that heretofore has not been described in the literature. Two approaches based on the cyclization of suitable o-phenylenediamine derivatives and on the direct incorporation of an amino group in N-hydroxybenzimidazoles were studied.



I R=H, Alk, Ar; R'=H; II a R=NH<sub>2</sub>, X=H, R'=H; b R=NH<sub>2</sub>, X=CH<sub>3</sub>, R'=H; c R=NH<sub>2</sub>, X=NO<sub>2</sub>, R'=H; d R=NH<sub>2</sub>, X=NO<sub>2</sub>, R'=CH<sub>3</sub>; e R=NH<sub>2</sub>, X=CH<sub>3</sub>, R'=CH<sub>3</sub>; IV a R=H, Alk, Ar; b R=NH<sub>2</sub>; V a X=H, R'=H, R=NH<sub>2</sub>; b X=CH<sub>3</sub>, R'=H, R=NH<sub>2</sub>; c X=NH<sub>2</sub>, R'=H, R=NH<sub>2</sub>; d X=NH<sub>2</sub>, R'=CH<sub>3</sub>, R=NH<sub>2</sub>; e X=CH<sub>3</sub>, R'=CH<sub>3</sub>, R=NH<sub>2</sub>; VI a X=H; b X=CH<sub>3</sub>; c X=NH<sub>2</sub>

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