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SYNTHESIS OF SUBSTITUTED BENZO[g]ISOQUINOLINES AND 8-AZABENZO[a]FLUORANTHENES

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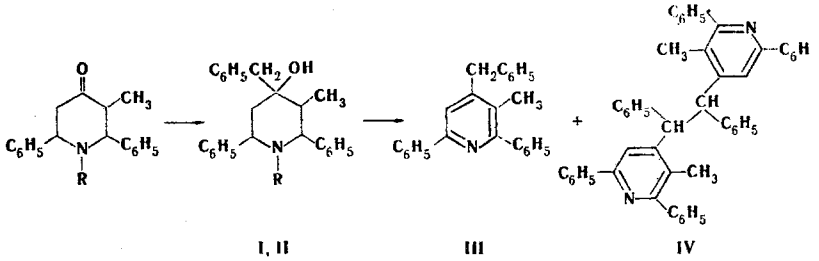
The conversion of 1,3-dimethyl-2,6-diphenyl-4-benzyl-4-piperidol and its N-unsubstituted analog by means of pyridine N-oxide to 3-methyl-2,6-diphenyl-4-benzylpyridine (I) is accompanied by the formation of 1,2-diphenyl-1,2-bis(3'-methyl-2',6'-diphenyl-4'-pyridyl)ethane, which was obtained under the same conditions directly from γ-benzyl-substituted pyridine I. The initial product in the catalytic dehydrocyclization of pyridine base I is 1,3-diphenylbenzo[g]isoquinoline, which is subsequently partially converted to 7-phenyl-8-azabenzo[a]fluoranthene. Spectral data for these heterocyclic compounds and the characteristics of the substances obtained by oxidation of them are presented.

Little study has been devoted to heterocyclic system of the benzoisoquinoline and benzoazafluoranthene heterocyclic systems because of the lack of methods for their synthesis. The possibility of the conversion of substituted aryl-γ-pyridylmethanes to benzoisoquinolines by dehydrocyclization was demonstrated in [1, 2]. The present research is a continuation of our studies in this area. 1,3-Dimethyl-2,6-diphenyl-4-benzyl-4-piperidol (I) and its N-unsubstituted analog (II) were obtained for the synthesis of the corresponding pyridine base from 1,3-dimethyl- and 3-methyl-2,6-diphenyl-4-piperidones. The conversion of these piperidols to 3-methyl-2,6-diphenyl-4-benzylpyridine (III) was accomplished by means of pyridine N-oxide, as described in [3]. A peculiarity of this reaction in this case is the fact that, in addition to pyridine base III, approximately the same amount of 1,2-diphenyl-1,2-bis(3'-methyl-2',6'-diphenyl-4'-pyridyl)ethane (IV) is formed; the latter is evidently the product of oxidative condensation at the methylene groups of molecules of pyridine base III. This assumption is confirmed by the synthesis of IV from substituted pyridine III when it is treated with pyridine N-oxide under the same conditions.



I, II III IV

I R=CH_3; II R=H

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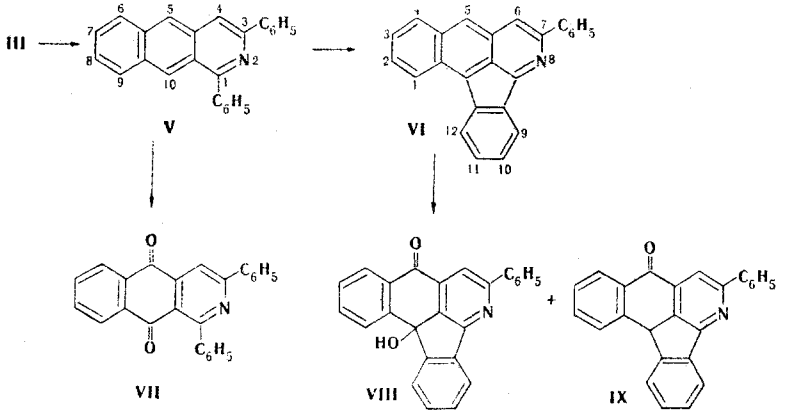
3-Phenyl-1-benzyl-4-azafluorene, 1,3-diphenyl-2-azabenzo[g]isoquinoline (V), and the products of their subsequent dehydrocyclization may be formed in the catalytic dehydrocyclization of substituted pyridine base III. The first of these compounds is not formed according to the data from the PMR spectrum of the substances present in the catalyzate. The PMR spectrum of the reaction mixture at strong field contains only two singlet signals of the protons of the methyl and methylene groups of starting III with δ 1.81 and 3.61 ppm, respectively, the integral intensity ratio of which is 3:2.

When the dehydrocyclization was carried out under optimal conditions (at 530-535°C), benzo[g]isoquinoline V (in 7% yield) and 7-phenyl-8-azabenzo[a]fluoranthene (VI) (in 21% yield, as compared with 11% yield at 570-580°C) were isolated from the catalyzate by means of chromatography.

The first step in the dehydrocyclization of pyridine base III is the formation of benzoisoquinoline V, which is subsequently converted to benzoazafluoranthene VI. This sequence of reactions is confirmed by an experiment involving the direct conversion of heterocyclic system V to VI under the conditions of catalytic dehydrocyclization.



In addition to the analytical and spectral data, the structures of the resulting condensed systems are confirmed by their transformations by oxidation with potassium dichromate. 1,3-Diphenyl-2-azaanthraquinone (VII) was obtained from azaanthracene V, while 12b-hydroxy-5-oxo-7-phenyl-8-aza-5,12b-dihydrobenzo[a]fluoranthene (VIII) was obtained from VI. In addition to VIII, a small amount of 5-oxo-7-phenyl-8-aza-5,12b-dihydrobenzo[a]fluoranthene (IX) was isolated from the oxidation products.

EXPERIMENTAL

The IR spectra of KBr pellets of the compounds were obtained with a UR-20 spectrometer. The PMR spectra were obtained with a Tesla BS-487C spectrometer with tetramethylsilane as the internal standard. The mass spectra were measured with an MKh-1303 mass spectrometer. Chromatography with a column and in a thin layer were accomplished on activity II aluminum oxide; a mixture of ethyl acetate and hexane (1:4) was used for thin-layer chromatography (TLC).

1,3-Dimethyl-2,6-diphenyl-4-benzyl-4-piperidol (I). A 69.7-g (0.25 mole) sample of 1,3-dimethyl-2,6-diphenyl-4-piperidone was added to benzylmagnesium chloride, obtained from 12.2 g (0.5 g-atom) of magnesium and 63.3 g (0.5 mole) of benzyl chloride in 450 ml of absolute ether at 0°C after 1 h, after which the mixture was refluxed for 2 h. It was then decomposed with 250 ml of a saturated solution of ammonium chloride, and the residue from the ether layer was crystallized from heptane–ethyl acetate (20:1) to give 56.4 g (61%) of piperidol I with mp 155.5-156°C and R_f 0.44. Found: C 84.3; H 7.8; N 3.6%. $C_{26}H_{29}NO$. Calculated: C 84.1; H 7.8; N 3.8%. The picrate of piperidol I had mp 213-215°C (from alcohol). Found: N 9.0%. $C_{26}H_{29}NO \cdot C_6H_3N_3O_7$. Calculated: N 9.3%.

3-Methyl-2,6-diphenyl-4-benzyl-4-piperidol (II). Similarly, 40 g (75%) of piperidol II, with mp 176-177°C (from heptane) and R_f 0.28, was obtained from 14.4 g (0.6 mole of magnesium, 76 g (0.6 mole) of benzyl chloride, and 50 g (0.2 mole) of 3-methyl-2,6-diphenyl-4-piperidone. Found: C 84.0; H 8.8; N 4.0%. $C_{25}H_{27}NO$. Calculated: C 84.0; H 8.8; N 3.9%.

3-Methyl-2,6-diphenyl-4-benzylpyridine (III) and 1,2-Diphenyl-1,2-bis(3'-methyl-2',6'-diphenyl-4'-pyridyl)ethane (IV). A) A mixture of 13.5 g (0.037 mole) of piperidol II and

10.5 g (0.11 mole) of pyridine N-oxide was heated in a Claisen flask at 255-265°C in a stream of nitrogen for 35 min, after which the reaction products were extracted repeatedly with boiling heptane. The heptane was then removed by distillation, and the residue was chromatographed with a column (H = 30 cm, d = 3.0 cm, elution with heptane). The initial product to be eluted was 5 g (39%) of pyridine base III with mp 119-120°C (from heptane) and R_f 0.63. PMR spectrum (in $CDCl_3$), δ: 3.61 (2H, s, CH_2), 1.81 (3H, s, CH_3) ppm. Found: C 89.3; H 6.2; N 4.2%; M^+ 335. $C_{25}H_{21}N$. Calculated: C 89.6; H 6.3; N 4.2%; M 335. The next substance to be eluted was 4 g (32%) of tetrasubstituted ethane IV with mp 272-274°C (from benzene) and R_f 0.37. PMR spectrum (in $CDCl_3$), δ: 4.93 (2H, s, CH), 2.35 (6H, s, CH_3) ppm. Found: C 89.6; H 6.1; N 4.0%; M^+ 668. $C_{50}H_{40}N_2$. Calculated: C 89.8; H 6.0; N 4.2%; M^+ 668.

B) Similarly, 2.6 g (39%) of pyridine base III, with mp 119-120°C, and 1.3 g (19%) of IV, with mp 271-273°C, were obtained from 7.4 g (0.02 mole) of piperidol II and 9.5 g (0.1 mole) of pyridine N-oxide.

C) A mixture of 2 g (6 mmole) of substituted pyridine III and 1.14 g (0.012 mole) of pyridine N-oxide was heated in a Claisen flask in a stream of nitrogen for 35 min. Similar workup yielded 1.1 g of starting pyridine III and 0.5 g (25%) of tetrasubstituted ethane IV, with mp 274-275°C, R_f 0.37, and M^+ 668.

Dehydrocyclization of 3-Methyl-2,6-diphenyl-4-benzylpyridine. The reaction was carried out in a flow system with a contact tube, quartz packing, and K-16 catalyst (20 ml). A solution of 5 g (0.015 mole) of pyridine base III in 30 ml of benzene was passed at a constant rate in the course of 50 min through the contact tube. The temperature in the catalyst zone was 530-535°C. The residue (3 g) after removal of the benzene from the catalyzate was chromatographed with a column (H = 50 cm, d = 2.5 cm, elution with heptane) to give initially 1.06 g of starting unsubstituted pyridine III (mp 118-120°C) and subsequently 0.37 g (7%) of benzoisoquinoline V as yellow crystals with mp 151.5-152.5°C (from heptane) and R_f 0.61. PMR spectrum (in $CDCl_3$), δ: 8.56 (1H, s, H-10), 8.26 (1H, s, H-5), 7.93 (1H, s, H-4), 8.03 ppm (2H, q, $J_{6,7} = J_{9,8} = 9$ Hz, $J_{6,8} = J_{9,7} = 2$ Hz H-6 and H-9). UV spectrum (in alcohol), λ_{max} (log ε): 208 (4.48), 248 (4.65), 282 (4.86), 331 (3.08), 348 (3.50), 366 (3.70), 400 (3.56), 415 nm (3.43). Found: C 90.4; H 4.9; N 4.4%; M^+ 331. $C_{25}H_{17}N$. Calculated: C 90.6; H 5.1; N 4.2%; M 331. At the end of the chromatography, 1.03 g (21%) of orange crystals of benzoazafluoranthene VI, with mp 154.5-155.5°C (from heptane) and R_f 0.56, were isolated. PMR spectrum (in $CDCl_3$), δ: 7.77 (1H, s, H-5), 7.61 ppm (1H, s, H-10) [2]. UV spectrum (in alcohol), λ_{max} (log ε): 215 (4.66), 246 (4.58), 260 (4.66), 345 (3.68), 364 (3.62), 450 nm (3.78). Found: C 90.9; H 4.7; N 4.2%; M^+ 329. $C_{25}H_{15}N$. Calculated: C 91.2; H 4.6; N 4.3%; M 239. The picrate of VI had mp 215-217°C (from alcohol). Found: N 10.0%. $C_{25}H_{15}N \cdot C_6H_3N_3O_7$. Calculated: N 10.0%.

Dehydrocyclization of 1,3-Diphenyl-2-azabenzo[g]isoquinoline. The experiment was carried out with the same apparatus with 5 g (0.015 mole) of V in 30 ml of benzene. The temperature in the catalyst zone was 550-560°C, and the reaction time was 1.5 h. Chromatography of the residue (3.5 g) from the catalyzate yielded initially 2.43 g of starting V (mp 151-152°C) and then 0.8 g (16%) of benzoazafluoranthene VI (mp 154-155°C and R_f 0.56).

1,3-Diphenyl-2-azaanthraquinone (VII). Water (2 ml) was added to a solution of 0.5 g (1.5 mmole) of benzoisoquinoline V in 40 ml of glacial acetic acid, after which 0.5 g (1.6 mmole) of potassium dichromate was added in portions, and the mixture was refluxed for 1 h. It was then cooled and poured into water, and the aqueous mixture was worked up to give 0.5 g (90%) of yellow crystals of azaanthraquinone VII with mp 247-248°C (from benzene) and R_f 0.05. IR spectrum: 1675 cm^{-1} (CO). Found: C 83.0; H 4.0; N 3.7%; M^+ 361. $C_{25}H_{15}NO_2$. Calculated: C 83.1; H 4.2; N 3.9%; M 361.

12b-Hydroxy-5-oxo-7-phenyl-8-aza-5,12b-dihydrobenzo[a]fluoranthene (VIII) and 5-Oxo-7-phenyl-8-aza-5,12b-dihydrobenzo[a]fluoranthene (IX). Water (20 ml) was added to a solution of 1.15 g (3.49 mmole) of benzoazafluoranthene VI in 200 ml of glacial acetic acid, after which 2.1 g (6.9 mmole) of finely ground potassium dichromate was added in portions in the course of 30 min. The mixture was heated for 5 h at 55-65°C, after which it was poured into 150 ml of a saturated solution of sodium chloride. The precipitate (1 g) was washed repeatedly with water, and the mother liquor was neutralized with ammonium hydroxide. The liberated base was extracted with ether, and the ether extract was worked up to give 0.25 g of crystals, which were combined with the previously isolated precipitate and chromatographed (elution with heptane). A total of 0.52 g of starting VI (mp 154-155°C and R_f 0.56) and 0.01 g of

yellow-green crystals of IX that decomposed at 275-277°C without melting and had R_f 0.42 were isolated successively. IR spectrum: 1688 cm^{-1} (C=O). Found: M^+ 345. Calculated: M 345. Subsequent elution with ether gave 0.41 g (59%) of oxidized product VIII as yellow-green crystals with mp 244-245°C (from ether) and R_f 0.51 (ether). IR spectrum: 1680 (C) and 3248 cm^{-1} (OH). Found: C 83.8; H 4.9; N 3.7%; M^+ 361. $C_{25}H_{13}NO_2$. Calculated: C 83.6; H 4.9; N 3.9%; M 361.

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CHEMISTRY OF HETEROCYCLIC N-OXIDES AND RELATED COMPOUNDS. 10.* REACTION OF PYRIDINE N-OXIDE WITH 4-METHYL- AND 4-PHENYL-SUBSTITUTED HANTZSCH ESTERS

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The corresponding dehydrogenation products were obtained in the reaction of diethyl 1,4-dihydro-2,4,6-collidine-3,5-dicarboxylates and diethyl 1,4-dihydro-4-phenyl-2,6-lutidine-3,5-dicarboxylate with pyridine N-oxide. The reaction with dihydrocollidine is accompanied by simultaneous demethylation in the 4 position and methylation of the pyridine ring.

In [1-5] we established that the N-oxides of pyridine bases, which have high dehydrogenating activity, can be used for the dehydrogenation of dihydro derivatives of pyridine, naphthalene, anthracene, and completely saturated heterocycles — piperidine and the alkaloid anabasine. Of the investigated compounds, the dehydrogenation of diethyl 1,4-dihydro-2,6-lutidine-3,5-dicarboxylate (the Hantzsch ester) takes place especially readily. In a continuation of our research it seemed of interest to study the dehydrogenation of 4-substituted Hantzsch esters by heteroaromatic N-oxides.

In the present communication we present the results of a study of the dehydrogenation of diethyl 1,4-dihydro-2,4,6-collidine-3,5-dicarboxylate and diethyl 1,4-dihydro-4-phenyl-2,6-lutidine-3,5-dicarboxylate with pyridine N-oxide.

In addition to the expected dehydrogenation, which leads to the formation of diethyl 2,4,6-collidine-3,5-dicarboxylate (III) and pyridine, the reaction of diethyl 1,4-dihydro-2,4,6-collidine-3,5-dicarboxylate (I) with pyridine N-oxide (II) also involves the simultaneous demethylation of the starting ester in the 4 position to give considerable amounts of diethyl 2,6-lutidine-3,5-dicarboxylate (IV), as well as the simultaneous methylation of pyridine to give 2- and 4-picolines. Acetaldehyde, ethanol, and propyl, isobutyl, and isoamyl alcohols are formed in very small amounts as side products, probably as a result of hydrolysis, oxidation, and alkylation.

Ester IV is most likely formed as a result of radical demethylation of starting dihydrocollidine I. This is confirmed by the formation of C_3-C_5 alcohols and particularly 2- and 4-picolines, which may be obtained as a result of radical alkylation, and by the fact that demethylation does not occur [6] in the ionic dehydrogenation of dihydrocollidine I by the

*See [1] for Communication 9.

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