3-METHYL-8-ALKYLBENZO[g]ISOQUINOLINES

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1,2,5-Trimethyl-4-(p-alkylbenzyl)piperideines were converted to 2,5-dimethyl-4-(p-alkylbenzyl)pyridines and 3-methyl-8-alkylbenzo[g]isoquinolines.

Benzoisoquinolines – three-ringed, condensed, nitrogen-containing systems – are a group of compounds which have not yet received sufficient study. Physiologically active compounds are found among their derivatives. Investigations of the synthesis of dyes based on them are promising. There are still no papers devoted to a study of the electrical properties of benzoisoquinoline systems. However, perhaps the most important value of these compounds consists in the fact that they can serve as fragments of systems which are close to alkaloids. For example, several opium alkaloids contain the 1-benzylbenzo[g]isoquinoline structure.

The condensation of $N-[\beta-(2-naphthyl)ethyl]amides or the condensation of <math>2-(2'-aminoethyl)naphtha$ lene with formaldehyde [1-5], the intramolecular cyclization of 4-benzylpyridine-3-carboxylic acid [6], or the dehydrocyclization of 4-(o-xylyl)pyridine [7] is usually employed to synthesize benzo[g]isoquinolines.

In our laboratory for the first time 4-benzylpyridines containing a methyl group in the 3-position of the pyridine ring have been used for the synthesis of substituted benzo[g]isoquinolines. These substituted natural systems are converted to benzo[g]isoquinolines by catalytic dehydrocyclization [8]. However, the synthesis of the 4-benzyl-substituted pyridines themselves is based on the accessible 4-piperidones [9].

Continuing our research in this direction we have turned to a study of the transformations which 1,2,5-trimethyl-4-(p-methyl- (I) [ethyl (II), isopropyl (III)] benzyl)piperideines undergo on a K-16 dehydrating catalyst at 460-470°C. Piperideines are converted only to the corresponding substituted pyridines on this catalyst at 400-410°. The latter undergo dehydrocyclization on the same catalyst at 500° to form benzo-[g]isoquinolines [8].

We expected that the reaction under the experimental conditions that we selected can proceed both to form pyridine bases and to form substituted benzo[g]isoquinolines.

The starting piperideines (I-III) obtained by dehydration of the corresponding tertiary γ -piperidols [10] are not pure substances. The gas-liquid chromatographic data indicate that they are a mixture of at least three isomers which apparently differ with respect to the position of the double bond (probably with endo and exo orientations).

Catalytic conversion of I yielded 82% of 2,5-dimethyl-4-(p-methylbenzyl)pyridine (IV) and 4.6% of 3,8dimethylbenzo[g]isoquinoline (VII). Compound II yielded 65% of 2,5-dimethyl-4-(p-ethylbenzyl)pyridine (V) and 2.2% of 3-methyl-8-ethylbenzo[g]isoquinoline (VIII). Similarly, 48.5% of 2,5-dimethyl-4-(p-isopropylbenzyl)pyridine (VI) and 3.75% of 3-methyl-8-isopropylbenzo[g]isoquinoline (IX) were obtained from III.

Benzo[g]isoquinolines VII-IX are high-melting yellow crystalline substances which are slightly soluble in acetone, alcohol, and petroleum ether. They form picrates, and some of them also form perchlorates.

The UV spectra of benzo[g]isoquinolines VII-IX (λ_{max} 233, 256-257, 312, 326, 343, 362-365, 385, and 405 nm) are in quite good agreement with the UV spectra of unsubstituted benzo[g]isoquinoline (λ_{max} 230, 250, 311, 328, 345, 353, 372, and 392 nm) [11, 12].

Patrice Lumumba University, Moscow. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 3, pp. 373-375, March, 1971. Original article submitted September 23, 1968.

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The liberated substituted pyridine bases (IV-VI) were oxidized by means of potassium permanganate to trib**a**sic keto acids -4-p-carboxybenzoyl)pyridine-2,5-dicarboxylic acid, which was isolated as its trimethyl ester, and 2,5-dicarbomethoxy-4-(p-carbomethoxybenzoyl) pyridine (X).



These transformations of pyridine bases IV-VI were accomplished to determine the position of the alkyl substituent in the benzyl radical.

The IR spectrum of X in the region of the valence vibrations of the carbonyl groups has a band at 1690 cm⁻¹ due to the valence vibrations of the C = O bond of the diaryl ketone. (Thus, in the IR spectrum of 2,5-dimethyl-4-benzoylpyridine there is a band at 1675 cm⁻¹; the shift of this band for X to the higher-frequency region is possible as a consequence of the relative shift of electrons from the carbonyl group to the carboxyl groups.) In addition, the IR spectrum of X contains a band at 1725 cm⁻¹, which should be ascribed to the valence vibrations of the C = O bonds of the ester groupings. (Thus, the IR spectrum of 2,5-dicarbethoxy-4-phenylpyridine contains a similar band at 1732 cm⁻¹.)

The band at 1750 cm^{-1} , also in the IR spectrum of X, has not yet been assigned.

EXPERIMENTAL

The catalytic conversions (dehydrogenation, N-demethylation, and dehydrocyclization) of piperideines I, II, and III were carried out in a quartz flow system on a K-16 catalyst (275 ml) at 460-470°. Before the experiment, the catalyst was maintained at 560-580° for 3 h in a gentle air stream.

<u>3.8-Dimethylbenzo[g]isoquinoline (VII)</u>. A solution of 51.4 g (0.224 mole) of piperideine I in 50 ml of anhydrous benzene was passed at a constant flow rate for 4 h through a contact tube. A total of 13.5 liters of gas (23°, 745 mm) was collected. At the end of the experiment 200 ml of benzene was passed through the contact tube at the same temperature. The catalyzate was dried with fused potassium hydroxide. The benzene was removed by distillation, and 100 ml of petroleum ether (bp 80-90°) was added to the residue. The resulting precipitate was recrystallized from petroleum ether to give 2.1 g (0.01 mole) of VII as flaky, yellow-green crystals with mp 252-254°. Found %: C 86.8; H 6.5; N 6.9. $C_{15}H_{13}N$. Calculated %: C 86.9; H 6.3; N 6.8. The picrate was obtained as yellow crystals with mp 244-246° (decomp., from alcohol-acetone).

<u>Perchlorate of VII</u>. A total of 1 ml of 30% perchloric acid was added to a suspension of 0.05 g (0.24 mmole) of VII in 2 ml of acetone. Compound VII dissolved rapidly, and the solution took on an orange color. The solution was evaporated, and the residue was treated with 0.3 ml of acetone and 3 ml of ether to give 0.04 g (0.13 mmole) of the perchlorate of base VII as orange crystals with mp 199-201° (from acetone – ether). Found %: N 4.5. $C_{15}H_{13}N \cdot HClO_4$. Calculated %: N 4.6.

The solution remaining after separation of VII was distilled to remove petroleum ether and fractionated to give 38.5 g (0.183 mole) of IV with bp 114-120° (0.5 mm) and mp 46-47° (from acetone) [10].

<u>3-Methyl-8-ethylbenzo[g]isoquinoline (VIII)</u>. This was similarly obtained from 52.5 g (0.212 mole) of II in 50 ml of benzene. The reaction time was 4 h. A total of 10.5 liters of gas (23°, 745 mm) was collected. The reaction yielded 1.05 g (0.00475 mole) of VIII and 31.1 g (0.138 mole) of V with bp 125-131° (0.5 mm)

[10]. Compound VIII was obtained as yellow-green crystals with mp 197-199° (from petroleum ether). Found %: C 86.8; H 6.8; N 6.4. $C_{16}H_{15}N$. Calculated %: C 86.9; H 6.8; N 6.3. The picrate was obtained as yellow crystals with mp 212.5-214° (from alcohol). Found %: N 11.9. $C_{16}H_{15}N \cdot C_{6}H_{2}(NO_{2})_{3}OH$. Calculated %: N 12.4. The perchlorate was obtained as orange crystals with mp 186-187° (decomp., from acetone – ether). Found %: N 4.7. $C_{16}H_{15}N \cdot HClO_{4}$. Calculated %: N 4.4.

<u>3-Methyl-8-isopropylbenzolg]isoquinoline (IX)</u>. A mixture of 13.1 g (0.051 mole) of III and 30 ml of benzene was used for the reaction. The experimental time was 3 h. A total of 4.0 liters of gas (23°, 745 mm) was collected, and 0.45 g (0.0019 mole) of IX and 5.96 g (0.025 mole) of VI with bp 130-141° (0.5 mm) [10] were isolated. Compound IX was obtained as greenish crystals with mp 166-167° (from petroleum ether). Found %: C 86.8; H 7.6; N 5.7. $C_{17}H_{17}N$. Calculated %: C 86.8; H 7.2; N 5.9. The picrate was obtained as orange crystals with mp 185-187° (decomp., from alcohol). Found %: N 11.8. $C_{17}H_{17}N \cdot C_{6}H_{2} \cdot (NO_{2})_{3}OH$. Calculated %: N 11.9.

2,5-Dicarbomethoxy-4-(p-carbomethoxybenzoyl)pyridine (X). A. Potassium permanganate [135 g (0.855 mole)] was added gradually with vigorous stirring at 100° to 20.5 g (0.097 mole) of IV and 500 ml of water. The manganese dioxide was removed from the hot solution by filtration and heated twice with a dilute aqueous solution of potassium hydroxide (150 ml). The filtrate and aqueous alkali extract were evaporated to 150 ml, and 18% hydrochloric acid was added to pH 2. The resulting precipitate (25 g) was washed with water and dried at 100° (15 mm). Concentrated sulfuric acid (40 ml) was added with cooling to a suspension of this precipitate in 200 ml of anhydrous methanol. The mixture was refluxed for 15 h, evaporated in vacuo to 150 ml, and poured into a mixture of 300 ml of cold water and 200 ml of ether. The mixture was stirred vigorously, and the resulting precipitate was dried and recrystallized from acetone to give 8.49 g (0.237 mole) of X. An additional 1.3 g (0.0036 mole) of X was isolated from the ether layer. The total yield of colorless crystals with mp 153-155° (from acetone) was 28%. Found %: C 60.6; H 4.4; N 3.8. $C_{18}H_{15}NO_7$. Calculated %: C 60.5; H 4.2; N 3.9.

B. A mixture of 1.86 g (8.3 mmole) of V, 100 ml of water, and 14 g (89 mmole) of potassium permanganate was used for the oxidation. The oxidation and subsequent workup were carried out similarly to give 0.89 g (2.5 mmole) of X with mp 152-155°.

C. A mixture of 2.05 g (8.6 mmole) of VI, 120 ml of water, and 13 g (82 mmole) of potassium permanganate was taken for the oxidation. The oxidation and all of the subsequent steps were carried out similarly to give 0.77 g (2.15 mmole) of X with mp 151-154°. Base X does not form a picrate under the usual conditions.

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