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XXXVII.* THE REACTION OF 2-AMINOINDOLE WITH β-DIKETONES

R. S. Sagitullin, T. V. Mel'nikova,
A. N. Kost, V. F. Snegirev, and E. N. Frenkel'

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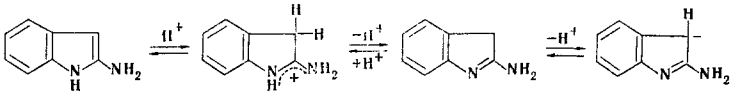
In the reaction of 2-aminoindoles with β-diketones, depending on the basicity of the medium, cyclization may take place with the participation of position 1 or 3 and the formation of the corresponding α-carbolines, pyrimidoindoles, or mixtures of them.

In the reaction of 1-alkyl-2-aminoindoles with β-diketones, the carbon atom in position 3 takes place in the condensation, which leads to the formation of 9-alkyl-α-carbolines. In the case of 2-aminoindole (I) unsubstituted on the pyrrole nitrogen atom, condensation with acetylacetone gave 2,4-dimethylpyrimido-[1,2-*a*]indole (II) [2, 3].

In view of the ease of oxidation of 2-aminoindole, it was used in the reaction in the form of a salt and the reaction was performed in pyridine, the basicity of which (pK_a 5.2) is much lower than the basicity of (I) (pK_a 8.15). This means that in pyridine solution the equilibrium is shifted in the direction of the protonated form B; nevertheless the reaction may also take place with the participation of form C. The production of (II) can be explained in this case by the intermediate acid-catalyzed formation of an azomethine and the partial deactivation of the β position of the indole.



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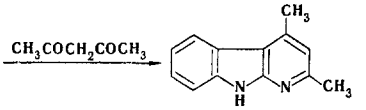
It is known that the condensation of α-aminopyrazoles with acetylacetone can take place with the formation of a pyrimidine structure (in the presence of an acid) or of a pyridine structure (in the presence of a base) [4]. It might be assumed that in our case, when the reaction was performed in a strongly basic medium, (I) would form the anion D and condense with acetylacetone through the β-carbon atom. A carbanion stabilized by conjugation with a double carbon–nitrogen bond can activate the carbon atom of an oxo group or add to the enolyzed form of a diketone in the manner of a Michael reaction.



III

In actual fact, the condensation of (I) with acetylacetone in isopropanol in the presence of an excess of triethylamine or alcoholic alkali formed only 2,4-dimethyl-α-carboline (III), identical with an authentic sample [5], which has the bright blue fluorescence in UV light that is characteristic for α-carbolines, in contrast to the nonfluorescing (II) [3]. The PMR spectrum (in trifluoroacetic acid) has the singlets of two methyl groups in the 2.66- and 2.81-ppm regions. The signal of the proton in position 3 of the indole ring is absent, and a broadened signal at 11.73 ppm (in dimethyl sulfoxide) corresponds to the NH group of indole.

*For Communication (XXXVI), see [1].

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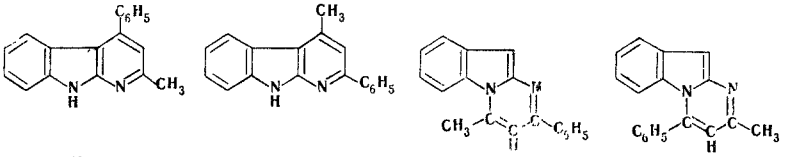
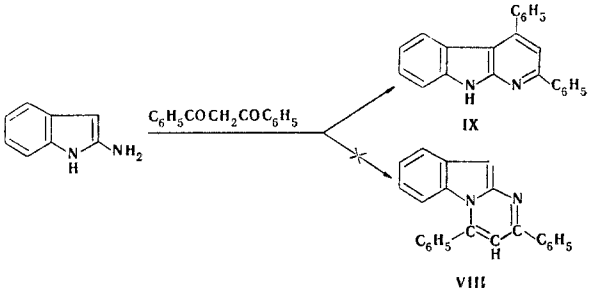


IV V VI VII

The reaction of (I) with β-diketones of unsymmetrical structure, such as benzoylacetone, can, in the general case, give four isomers (IV-VII). When the reaction was carried out in isopropanol in the presence of an excess of triethylamine, a mixture of the isomeric α-carbolines (IV) and (V) in a ratio of 1:1 (according to GLC) was produced, and this mixture could be separated by chromatography on alumina. The reaction of (I) with benzoylacetone in pyridine formed a mixture of all four isomers (IV-VII), but the main component (70%) proved to be one of the pyrimidoindoles (VI or VII). Chromatography on alumina also yielded 15.7% of (IV), 9.3% of (V), and 5% of the isomeric pyrimidoindole (VII or VI). The PMR spectrum (in dimethyl sulfoxide) of the major product had no signal of the proton of an NH group but had two singlets in the 6.37- and 6.67-ppm region corresponding to the protons of pyrimidine and pyrrole rings. There was a multiplet of aromatic protons in the 7.3-8.0-ppm region. The mass spectra of (VI) and (VII) have the peaks of the molecular ions with m/e values corresponding to the calculated figure (258). The other peaks are of low intensity and difficult to interpret. The UV spectrum of the major isomer has three absorption bands: λ_{max} 266 (strongest), 320, and 432 nm. The spectrum obtained is similar to that of 2,4-dimethylpyrimido-[1,2-*a*]indole [6], the bathochromic shift of the long-wave band probably being caused by the influence of the phenyl group conjugated with the pyrimidine ring (Fig. 1), and differed sharply from the spectrum of an α-carboline such as (IV).

Thus, the available information is in favor of a pyrimidine structure (VI or VII). It is difficult to determine the structure of substances (VI) and (VII) more accurately with the information available. On the one hand, such condensations generally take place in such a way that the aliphatic keto group reacts with the amino group [4]. On the other hand, in this case steric factors must come into play, i.e., the interaction of the phenyl ring (or the methyl group) with position 7 of the indole nucleus. The mechanism of condensation also remains open.



IX VIII

It has been reported previously [3] that the condensation of 2-aminoindole with dibenzoylmethane gives a compound to which the structure of 2,4-diphenylpyrimido[1,2-*a*]indole (VIII) was ascribed. Unlike other pyrimidoindoles, it possesses fluorescence. It has been found that the cyclization took place at the carbon atom and 2,4-diphenyl-α-carboline was formed, this being identical with the substance (IX) obtained by condensing 2-aminoindole with benzylideneacetophenone.

The UV spectrum of compound (IX) is characteristic for α-carbolines, having three absorption maxima, at 217, 253, and 321 nm. The PMR spectrum (in dimethyl sulfoxide) has the broadened signal of the proton of the NH group in the 12.6-ppm region, the signal of an indole proton in position 3 is absent, and an aromatic multiplet in the 7.6-9.0-ppm region corresponds to the 15 aromatic protons. The performance of the reaction in pyridine also gives (IX) but in far lower yield (25%). The formation of (VIII) was not observed, possibly because of steric hindrance.

Compounds (IV, V, and IX) were identical with samples of authentic structure according to melting points, chromatographic mobilities, and IR spectra. A separate paper has been devoted to the question of determining their structure.

EXPERIMENTAL

The UV spectra were taken on a Cary-15 instrument in methanol, the PMR spectra on a Varian T-60 instrument, and the mass spectra on an MKh-1303 mass spectrometer.

2,4-Dimethyl-α-carboline (III). A mixture of 0.084 g (0.5 mmole) of 2-aminoindole hydrochloride and 0.5 g (5 mmoles) of acetylacetone was boiled in 2 ml (2 mmoles) of a 1 N ethanolic solution of caustic potash for 15 min in a current of nitrogen. After cooling, the precipitate that had deposited was filtered off and washed with ethanol. This gave 0.08 g (81%) of 2,4-dimethyl-α-carboline (III) in the form of colorless crystals with mp 222-224°C (from benzene) [5]. UV spectrum: λ_{max} 218, 239, 261, 296, 322 nm (log ε 4.45, 4.26, 4.02, 4.13, 3.60).

Similarly, 0.084 g (0.5 mmole) of the hydrochloride of (I), 0.2 g (2 mmoles) of acetylacetone in 1.5 ml of isopropanol, and 0.14 ml of triethylamine gave 0.06 g (61%) of (III), with mp 221-222°C.

Reaction of 2-Aminoindole with Benzoylacetone. a) A mixture of 0.17 g (1 mmole) of the hydrochloride of (I), 0.17 g (1 mmole) of benzoylacetone, 2 ml of isopropanol, and 0.28 ml (2 mmoles) of triethylamine was boiled for 2 h in a current of nitrogen, and after cooling the mixture of isomeric α-carbolines that precipitated was filtered off. Yield 0.22 g (85%). After preparative separation on a plate coated with alumina (activity grade II) in the benzene–ethyl acetate (3:1) system, 0.07 g of 4-methyl-2-phenyl-α-carboline (V) with mp 190-192°C and 0.09 g of 2-methyl-4-phenyl-α-carboline (IV) with mp 230-231°C (from benzene) were obtained. UV spectrum of (IV): λ_{max} 220, 251, 305 nm (log ε 4.75, 4.38, 4.19). UV spectrum of (V): λ_{max} 218, 250, 312 nm (log ε 4.54, 4.60, 4.58). The composition of the mixture of (IV) and (V) was determined on a "Tswett-5" chromatograph (column 1 m long and 4 mm in internal diameter filled with 5% of SE-30 on Chromosorb W, 100/120 mesh). At a rate of flow of nitrogen of 60 ml/min and a temperature of 250°C, the retention time of (IV) was 4 min 10 sec and of (V) 7 min 40 sec.

b) A mixture of 0.24 g (1.21 mmole) of the hydrochloride of (I) and 0.32 g (1.97 mmole) of benzoylacetone in 6 ml of pyridine was boiled for 2 h 30 min in a current of nitrogen. The cooled reaction mixture was poured into water, and the precipitate that deposited was filtered off and dried in vacuum. This gave 0.33 g (81.5%) of a mixture of (IV-VII), which was separated on a plate coated with alumina in the benzene–ethyl acetate (50:1) system. The following compounds were isolated: 0.029 g of (IV) (proportion in the mixture 15.7%), mp 230-231°C (from benzene) (according to the literature [7], mp 229-229.5°C); 0.17 g (9.3%) of (V), mp 190-192°C (from benzene); and 0.127 g (70%) of 2(4)-methyl-4(2)-phenylpyrimido[1,2-*a*]-indole (VII or VI), orange crystals, mp 119-120°C (from dilute methanol) not fluorescing in UV light; UV spectrum: λ_{max} 266, 320, 432 nm (log ε 4.65, 3.70, 3.20). Found, %: C 83.2; H 5.5. $C_{18}H_{14}N_2$. Calculated, %: C 83.7; H 5.4. In addition, 0.01 g (5%) of 4(2)-methyl-2(4)-phenylpyrimido[1,2-*a*]indole (IV or VII) was isolated in the form of orange crystals with mp 150-154°C not fluorescing in UV light. Molecular weight 258 (mass spectrally).

2,4-Diphenyl-α-carboline (IX). A mixture of 0.084 g (0.5 mmole) of the hydrochloride of (I), 0.16 g (0.7 mmole) of dibenzoylmethane, 1.5 ml of isopropanol, and 0.14 ml (1 mmole) of triethylamine was boiled in a current of nitrogen for 2 h. Then it was cooled, and the precipitate was filtered off and washed with ethanol. This gave 0.13 g (81%) of (IX), mp 222-224°C; fluorescing in UV light. UV spectrum: λ_{max} 2.17, 253, 321 nm (log ε 4.67, 4.65, 4.53). PMR spectrum (in dimethyl sulfoxide): singlet 12.6 ppm (NH); multiplet of aromatic protons 7.6-9.0 ppm (15 H). When the reaction was performed in pyridine, the yield was 25%.

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