CHEMISTRY OF INDOLE

XX.* REACTION OF 2-AMINOINDOLES WITH α , β -UNSATURATED KETONES

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 α , β -Unsaturated ketones form pyrimido[1,2-a]indoles with 2-aminoindole, while 1-alkyl-2aminoindoles under these conditions are converted to the corresponding α -carbolines. The structures of the compounds obtained were confirmed by alternative synthesis.

UDC 547.752'83: 543.422.4

We have previously shown that 2-aminoindoles react with β -diketones to form pyrimido[1,2-a]indoles; if, however, the indole is alkylated in the 1 position, the carbon atom in the 3 position participates in the condensation and results in the formation of 9-alkyl- α -carbolines [2-4]. It turned out that α , β -unsaturated ketones also react with 1-alkyl-2-aminoindoles to form α -carbolines. Thus, when 1-methyl-2-aminoindole (I) methiodide is refluxed with benzalacetophenone in isopropyl alcohol in the presence of an equivalent amount of alkali, a chromatogram of the reaction mixture after 20 min indicates the absence of the starting aminoindole (I) and the formation of II (mp 123-124°C) in 82% yield. II gives a pronounced blue fluorescence on irradiation with UV light. The PMR spectrum of the compound in trifluoroacetic acid characterizes it as a completely aromatic structure with an aromatic proton multiplet at ~ 7.50 ppm and a CH₃ singlet at 3.98 ppm. The IR spectrum does not contain absorption in the regions corresponding to absorption of the NH and CO groups. II was identical to 2,4-diphenyl-9-methyl- α -carboline obtained by the reaction of I with dibenzoylmethane.

Thus the condensation of I with an α , β -unsaturated ketone is accompanied, as is usually the case in this sort of reaction, by autooxidation with the formation of an aromatized structure.



Neither dihydro structure III nor its isomer with a different position of the double bond could be isolated. The high yields of II exclude the possibility that the process takes place via a disproportionation step.

Similarly, 2-aminoindole, which is unsubstituted in the 1 position, forms 2,4-diphenylpyrimido[1,2-a]indole (IV) by condensation with both dibenzoylmethane and benzalacetophenone with yields close to quantitative in both cases.

*See [1] for communication XIX.

M. V. Lomonosov Moscow State University. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 1, pp. 61-64, January, 1971. Original article submitted September 29, 1969.

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The reaction of 1-methyl-2-aminoindole with benzalacetone gave a substance which also has all of the properties of α -carbolines but differs in melting point and chromatographically from the compound obtained from benzoylacetone. In each case one might expect the formation of isomers V or VI, which differ in the position of the substituents in the pyridine ring.



Chromatography of the reaction mixture on aluminum oxide indicated that only one of the isomers is obtained in both cases; this indicates the definite trend of these processes. The mass spectra of both compounds contain an intense molecular ion peak (M^+) with m/e 272, but, in view of the high aromaticity of these structures, the remaining peaks are of low intensity and are difficult to interpret; this makes it difficult to arrive at unambiguous conclusions. However, the position of the CH₃ group in the second sample was proved by oxidation with selenium dioxide to the corresponding acid, which readily forms a characteristically colored chelate compound with divalent iron ions. The first sample does not give this sort of reaction.

Thus the amino group of 1-methyl-2-aminoindole reacts with the more readily enolized acetyl group of benzoylacetone to give isomer VI. A similar trend in the condensation of unsymmetrical β -diketones with aniline has already been noted (see, for example, [5]).



In the case of benzalacetone the amino group also nucleophilically attacks the carbon-carbon double bond to give isomer V.



Consequently, despite the fact that the reaction occurs in alkaline media in both cases (in contrast to the classical conditions for the Doebner-Miller and Conrad-Limpach syntheses), the decisive factor is apparently the reaction of the NH₂ group rather than the reaction with the β position of the indole ring.

We have previously noted [6] that 2-aminoindoles condense with malonic ester to form 2-oxo-4-hydroxy- α -carbolines but that this reaction does not occur when even one of the hydrogen atoms of the CH₂ group of malonic ester is replaced by an alkyl group. In the case of β -diketones the reaction proceeds under milder conditions, and substitution of the hydrogen atom in the CH₂ group between the carbonyl groups does not substantially restrict the reaction. In fact, aminoindole I or 1-benzyl-2-aminoindole react with methylacetylacetone to give satisfactory yields of the corresponding 9-substituted 2,3,4-trimethyl- α -carbolines (VII). Nevertheless, the previously selected conditions [3, 4] (carrying out the process in pyridine) do not always make it possible to obtain good yields, particularly in the case of dibenzoylmethane and benzoylacetone. The corresponding α -carbolines and pyrimidoindoles could be obtained only when the process was carried out in isopropyl alcohol or dimethylformamide with the introduction of sesquimolar amounts of triethylamine. Thus the condensation preferably occurs in an undoubtedly alkaline media and requires polar solvents (which is apparently associated with the high polarity of the intermediate state).

EXPERIMENTAL

Chromatography in a thin layer of aluminum oxide in benzene-heptane (1:2), chloroform-cyclohexane (1:2), and carbon tetrachloride systems with subsequent development with iodine was used to determine the end of the reaction and to estimate the purity of the compounds obtained. The UV spectra in methanol were obtained with a Cary spectrometer.

<u>9-Methyl-2,4-diphenyl- α -carboline (II).</u> A) A mixture of 0.27 g (1 mmole) of 1-methyl-2-aminoindole (I) hydriodide, 0.45 g (2 mmole) of dibenzoylmethane, and 0.21 ml (0.15 mmole) of triethylamine in 4 ml of isopropyl alcohol was refluxed for 1.5 h. The reaction mixture was cooled and poured into water, and the resulting precipitate was filtered and washed with water to give 0.24 g (72%) of II with mp 123-124° (from methanol). Found %: C 86.47, 86.66; H 5.30, 5.45. C₂₄H₁₈N₂. Calc. %: C 86.19; H 5.44.

B) A mixture of 0.5 g (1.82 mmole) of I hydriodide, 0.42 g (2 mmole) of benzalacetophenone, and 0.38 ml (2.6 mmole) of triethylamine in 6 ml of isopropylalcohol was refluxed for 3 h. The reaction mixture was cooled, poured into water, and extracted with benzene. The extract was dried with calcined calcium chloride and evaporated in vacuo. The residue was recrystallized from methanol with activated charcoal to give 0.59 g (95.5%) of II with mp 122-124° (from methanol). A sample of this compound did not depress the melting point of II described above.

The yield of II was 82% when the reaction was carried out in alcoholic alkali.

 $\frac{2,4-\text{Diphenylpyrimido}[1,2-a]\text{indole (IV).} A) \text{ IV } [0.3 \text{ g } (94\%)] \text{ was similarly obtained via method (A)} from <math>\overline{0.17 \text{ g } (1 \text{ mmole}) \text{ of } 2-\text{aminoindole hydrochloride, } 0.4 \text{ g } (1.9 \text{ mmole}) \text{ of dibenzoylmethane, and } 0.21 \text{ ml}} (1.5 \text{ mmole}) \text{ of triethylamine in 3 ml of isopropyl alcohol and had mp } 222-224^{\circ} (from methanol). Found \%: C 86.15, 86.21; H 5.20, 5.04. C_{23}H_{16}N_2. Calc. \%: C 86.21; H 5.04. UV spectrum, <math>\lambda_{\text{max}}$ (nm) (log #): 218 (4.51), 255 (4.51), 324 (4.36).

B) IV [0.31 g (97%)] with mp 222-224° (from methanol) was obtained from 0.17 g (1 mmole) of 2aminoindole hydrochloride and 0.22 g (1.04 mmole) of benzalacetophenone by refluxing for 3 h in isopropyl alcohol. The product did not depress the melting point of the sample described above.

2,3,4-Trimethyl-9-benzyl- α -carboline (VII, $R = CH_2C_6H_5$). A mixture of 0.26 g (1 mmole) of 1-benzyl-2-aminoindole hydrochloride, 0.25 g (2.19 mmole) of methylacetylacetone, and 0.21 ml (1.5 mmole) of triethylamine in 4 ml of isopropyl alcohol was refluxed for 3 h. The mixture was cooled, and the resulting crystals were filtered and washed with water and isopropyl alcohol and recrystallized first from isopropyl alcohol and then from petroleum ether to give 0.1 g (33%) of VII ($R = CH_2C_6H_5$) with mp 217-219°. Found %: C 83.63, 83.74; H 6.92, 6.99. $C_{21}H_{20}N_2$. Calc. %: 83.95; H 6.72.

<u>2-Methyl-4-phenyl-9-benzyl- α -carboline</u>. This compound [0.25 g (72%)] with mp 118-120° (from isopropyl alcohol, petroleum ether) was obtained from 0.26 g (1 mmole) of 1-benzyl-2-aminoindole hydrochloride, 0.32 g (2 mmole) of benzoylacetone, and 0.21 ml (1.5 mmole) of triethylamine by refluxing for 3 h. Found %: C 85.79, 85.93; H 5.96, 6.09. $C_{25}H_{20}N_2$. Calc. %: C 86.16; H 5.80.

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