THE CHEMISTRY OF INDOLE

XI. Synthesis of α-Carbolines and Pyrimido[1,2-*a*]indoles from 2-Aminoindoles*

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Khimiya Geterotsiklicheskikh Soedinenii, Vol. 6, No. 3, pp. 359–363, 1970

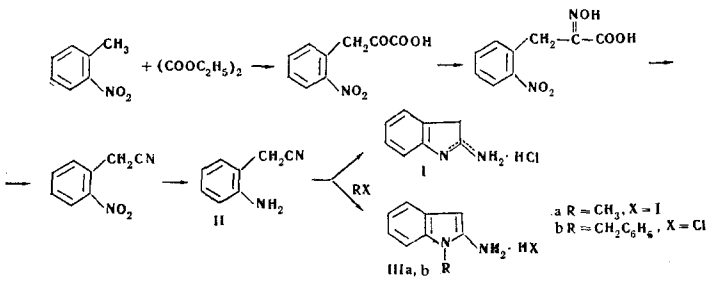
UDC 547.754'83

The reaction of 1-alkyl-2-aminoindoles with β-dicarbonyl compounds forms N-substituted α-carbolines, which is a new method for the synthesis of these difficulty accessible compounds. If the nitrogen atom is not alkylated, cyclization involving both nitrogen atoms takes place, leading to a previously unknown heterocycle, pyrimidino[1,2-*a*]indole.

Because they are difficult of access and oxidize readily, 2-aminoindoles have been investigated comparatively little. Based on a study of basicity, and UV, IR, and PMR spectra, it is thought that 2-aminoindole exists predominantly in the 3H-indole form [2,3]. The simplest alkylation and acylation reactions for 2-aminoindole take place in positions 1 and 3 or 1 and 2. Thus, not only the two nitrogen atoms but also position 3 of the indole nucleus are highly reactive in these compounds.

We have succeeded in showing that 2-aminoindole (I) condenses with acetylacetone at both nitrogen atoms with the formation of a pyrimidine ring. However, if the heteroatom of indole is shielded by an alkyl group, position 3 is attacked and an α-carboline structure is formed.

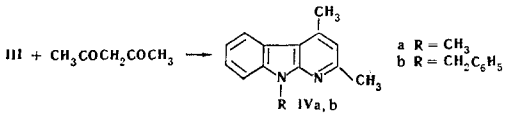
To synthesize 2-aminoindole and its derivatives, we condensed o-nitrotoluene with diethyl oxalate by the Reissert reaction and oximated, decarboxylated, and reduced the resulting o-nitrophenylpyruvic acid. The resulting aminonitrile II was cyclized into 2-aminoindole with sodium isopropoxide, or by the action of alkyl halides in ethanol (in the synthesis of the N-substituted compounds).



Heating the salts of 2-aminoindole I and III with acetylacetone in methanol or propanol with dry hydrogen chloride and toluene did not give the expected condensation products. But when the reaction was carried out in dry pyridine at 100° C, after only 2 hr the solutions no longer contained the initial 2-aminoindoles (chromatographic check in a thin layer of alumina). When the reaction mixture was poured into water we obtained substances (with yields of 80–100%) differing from the initial 2-aminoindoles. The compounds obtained from III were colorless and gave a strong blue fluorescence in UV light. 2-Aminoindole (I) formed a yellow substance possessing no fluorescence. According to elementary analysis, in all cases the reaction took place with the elimination of two molecules of water. The reaction products were stable to hydrolysis; they were recovered unchanged after being boiled in a mixture of acetic and concentrated hydrochloric acid (1 : 1) for 10 hr and also after being heated with polyphosphoric acid at 150° C for 5 min.

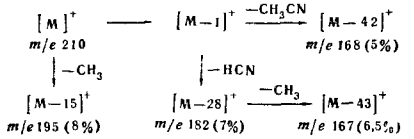
The IR spectra of all the compounds obtained had no stretching vibrations of a carbonyl group in the 1700–1720-cm^{-1} region. In accordance with this, we assumed that the compounds obtained from III had the structure of the α-carbolines IV.

*For part X, see [1].

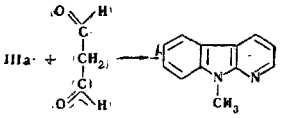


The absorption in the 1590- and 1592-cm^{-1} regions (for **IVa** and **b**, respectively) we ascribed to the C=N stretching vibrations. The UV spectra of compounds IV have absorption maxima at 265–268, 296 and 329 nm, which correspond to the data for α-carbolines [4]. The PMR spectrum of compound IV in trichloroacetonitrile characterizes this substance as an aromatic system with a multiplet in the region of δ 7.44–8.10. A singlet with δ 3.85 corresponds to three protons of a CH_3 group attached to a pyrrole nitrogen atom, and a singlet with δ 6.80 we ascribed to the β-proton of a pyridine nucleus. The chemical shifts for the methyl groups of the pyridine ring proved to be practically identical (δ 2.68).

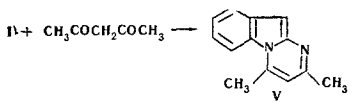
In the mass spectrum of compound **IVa**, the peak of the molecular ion M^+ with m/e 210 is the strongest and coincides with that calculated for $C_{14}H_{14}N_2$. In agreement with this, as is usually the case for N-alkylindoles [5] a peak with m/e 195, corresponding to the splitting off of a CH_3 group, has a considerable intensity. However, because of the presence of two other CH_3 groups attached to the pyridine nucleus, the main direction is the splitting off of a proton from the α-CH_3 group. The further fragmentation of the $(M - 1)^+$ ion leads to the splitting out of CH_3CN or HCN, and then of a CH_3 group.



Thus, the IR, UV, mass, and PMR spectra confirm the formation of α-carbolines. A definitive proof was the synthesis of the known [6] N-methyl-α-carboline from 2-amino-1-methylindole and malondialdehyde.



The reaction product V obtained by the condensation of unsubstituted 2-aminoindole (I) with acetylacetone differs from substance IV. Its UV spectrum (absorption maxima at 227, 266, 317, and 400 mμ) differs markedly from the spectra of compounds of the α-carboline series. In the 3200–3450-cm^{-1} region of the IR spectrum there are no absorption bands characteristic for stretching vibrations of the NH group of compounds of the indole series, which shows that both nitrogen atoms have taken part in the reaction and, moreover, there are no absorption bands of a carbonyl group in the 1700–1725-cm^{-1} region. The absorption band present at 1634 cm^{-1} must be ascribed to C=N stretching vibrations. In the mass spectrum of compound V, the peak of the molecular ion M^+ with m/e 196 is the strongest and coincides with that calculated for $C_{13}H_{12}N_2$. The most characteristic peak is that with m/e 181 (3.5%), corresponding to the detachment of a CH_3 group, but its intensity is nevertheless lower than in the spectrum of **IVa**. The splitting out of CH_3CN (peak with m/e 155, intensity 2.7%) takes place directly from the molecular ion without the previous splitting out of a proton, which corresponds to the pyrimidine structure V. Thus, the combination of spectral data and the very course of the synthesis allow us to assume that we have obtained a new heterocyclic system, 2,4-dimethylpyrimidino[1,2-*a*]indole (V).



We have attempted to obtain α-carbolines unsubstituted on the nitrogen of the pyrrole ring by treating N-acetyl- and N-ethoxycarbonyl-2-aminoindoles with acetylacetone. However, the reaction did not take place at room temperature and when the mixture was heated the acetyl (or ethoxycarbonyl) group was eliminated with the formation of compound V.

The debenzylation of substance **IVb** would not take place under the usual conditions (catalytic hydrogenation or the action of sodium in liquid ammonia).

EXPERIMENTAL

Oxime of o-nitrophenylpyruvic acid. At 15° C, 146 g (1 mole) of diethyl oxalate and 137 g (1 mole) of o-nitrotoluene were added dropwise to sodium ethoxide prepared from 23 g (1 g-at.) of sodium and 230 ml of absolute ethanol. The mixture was boiled for 25 min, 100 ml of water was added, and it was boiled for another hour. The ethanol and the unchanged o-nitrotoluene were distilled off with steam, and the residual solution was treated at 75–80° C with activated carbon and then filtered. The filtrate was cooled to 50° C, and 49 g (0.7 mole) of hydroxylamine hydrochloride in 75 ml of water was added. The excess acid was neutralized with 10% caustic soda solution, the solution was left overnight and then acidified with hydrochloric acid to Congo Red. The crystals that deposited were filtered off and washed with water. From the mother solution, sodium sulfate salted out another 6 g of product. The total yield was 127 g (57%) of a substance with mp 158–160° C [7].

o-Nitrobenzylcyanide. To 140 g (0.63 mole) of the oxime of o-nitrophenylpyruvic acid was added 1.4 *l* of water and 70 ml of acetic acid. The mixture was boiled for 1 hr 30 min and then cooled, the precipitate that deposited was filtered off, then washed with water and dried. After vacuum distillation, 66 g (56%) of o-nitrobenzylcyanide was obtained with mp 78–82° C [8]; R_f 0.67 [KSK silica gel, benzene–methanol (10 : 1)].

o-Aminobenzylcyanide. Without the temperature being allowed to rise, 157 ml of concentrated hydrochloric acid was slowly added to a suspension of 31 g (0.19 mole) of o-nitrobenzylcyanide, 390 ml of isopropanol, and 35 g (0.2 g-at.) of granulated tin cooled to 10° C. The mixture was kept at 30° C until a sample ceased to give the violet coloration of o-nitrobenzylcyanide with alkali. Then the solution was evaporated to a volume of 100 ml and cooled. The precipitate that deposited was filtered off (54 g) and dissolved in 600 ml of cold water. The solution was filtered and cooled to 5° C, and 85 ml of a 30% solution of caustic soda was added. The precipitate of the o-aminobenzylcyanide product was filtered off, washed with water, and extracted with boiling isopropanol (3 × 100 ml). The extract was filtered and evaporated to dryness in vacuo, giving 23 g (90%) of product with mp 70–72° C [8], R_f 0.38 [KSK silica gel, benzene–methanol (10 : 1)].

2-Aminoindole hydrochloride. A solution of 16 g (0.12 mole) of o-aminobenzylcyanide in 100 ml of isopropanol was added to the sodium isopropoxide obtained from 10 g (0.43 g-at.) of sodium and 200 ml of isopropanol. The mixture was boiled under reflux in a current of hydrogen for an hour and then diluted with 300 ml of water, and the alcohol was distilled off in vacuo. On cooling, the resulting solution deposited crystals of 2-aminoindole. The precipitate was filtered off and washed with a small amount of water and then dissolved in isopropanol, the solution was then neutralized with an ethanolic solution of hydrogen chloride. The residue from the evaporation of the reaction mixture to dryness was dissolved in a minimal amount of hot water, the solution was filtered, and hot acetone was added until turbidity appeared. On cooling, crystals of 2-aminoindole hydrochloride deposited. Yield 14.2 g (70%), mp 224–226° C [2].

2-Amino-1-methylindole hydriodide. A solution of 3 g (0.023 mole) of o-aminobenzylcyanide and 9.1 g (0.064 mole) of methyl iodide in 5 ml of absolute methanol was left to stand at room temperature for 3 days. The crystals that deposited were filtered off, washed with ether, and recrystallized from methanol. This gave 5.6 g (90%) of a substance with mp 262–263° C [9].

2-Amino-1-benzylindole hydrochloride. This was obtained in a manner similar to the preceding compound from 3.5 g (0.026 mole) of o-aminobenzylcyanide, 9.3 g (0.074 mole) of benzyl chloride, and 7 ml of absolute methanol. Yield 4.45 g (65%) of a substance with mp 256–259° C [8].

2-Amino-1-ethoxycarbonylindole hydrochloride. Similarly, 3 g (0.023 mole) of o-aminobenzylcyanide, 7 g (0.065 mole) of ethyl chloroacetate, and 7 ml of absolute methanol gave 3.7 g (76%) of a product with mp 255–258° C [9].

1,3,5-Trimethyl-α-carboline. A mixture of 1 g (4 mM) of 2-amino-1-methylindole hydriodide, 0.75 g (7.5 mM) of acetylacetone, and 8 ml of dry pyridine was heated under reflux in a current of inert gas for 2 hr 30 min. After cooling, the solution was poured into water, and the precipitate was filtered off and washed with water to give 0.75 g (almost quantitative yield) of a substance with mp 110–111° C (from dilute ethanol). IR spectrum (in methanol), λ_{max}, nm: 235, 265–268, 296, 329; log ε 4.63, 4.41, 4.41, 3.72. Found, %: C 79.90, 79.98; H 6.71, 6.91. Calculated for $C_{14}H_{14}N_2$, %: C 79.97; H 6.71.

1-Benzyl-3,5-dimethyl-α-carboline. In an analogous manner 1 g (4 mM) 2-amino-1-benzylindole hydrochloride, 0.5 g (5 mM) acetylacetone, and 10 ml dry pyridine gave 0.7 g (64%) of a substance, mp 120.5–121.5° C (in methanol).

UV spectrum (in methanol) λ_{max}, nm: 266, 295, 326; log ε 4.26, 4.26, 3.65. Found, %: C 83.26, 83.35; H 6.39, 6.46. Calculated for $C_{20}H_{18}N_2$, %: C 83.88; H 6.33. **Picrate**, mp 227–229° C (from ethanol).

1-Methyl-α-carboline. A mixture of 1 g (4 mM) of 2-amino-1-methylindole, 2 g (9 mM) of malondialdehyde [10], 0.7 ml of concentrated hydrochloric acid, and 3 ml of ethanol was left to stand at room temperature for 20 min. Then 15 ml of dry pyridine was added and it was left overnight in a sealed flask. After this it was filtered, the filtrate was evaporated to dryness in vacuo, water was added, and the mixture was extracted several times with ether. The extract was dried with sodium sulfate and evaporated to dryness. The residual yellow oil was purified by preparative chromatography on a plate of alumina in a benzene–methanol (10 : 1) system. This gave 0.3 g of a substance in the form of an oil which was converted into the picrate. The picrate was passed through a column of alumina in a benzene–methanol (10 : 1) system. The eluate was evaporated to dryness and, after recrystallization from hexane, 55 mg (8%) of 1-methyl-α-carboline with mp 53° C [6] was obtained. UV spectrum (in methanol), λ_{max}, nm: 265, 296, 335; log ε 4.16, 4.17, 3.52. **Picrate**, mp 225° C (from methanol) [6].

2,4-Dimethylpyrimidyl[1,2-*a*]indole (V). Acetylacetone, 0.75 g (7.5 mM), and 10 ml of dry pyridine were added to 1 g (6 mM) of 2-aminoindole hydrochloride, and the mixture was boiled in a current inert gas for 1 hr 30 min. After cooling, the solution was poured into water. The yellow crystals that deposited were filtered off, washed with water, and recrystallized from 50% aqueous methanol. This gave 1.17 g (88%) of a substance with mp 111.5–112.5° C; R_f 0.5 (Al_2O_3, benzene); UV spectrum (in methanol), λ_{max}, nm: 227, 266, 317, 400; log ε 4.14, 4.72, 3.66, 3.19. Found, %: C 79.31, 79.46; H 6.24, 6.28; N 14.37, 14.41. Calculated for $C_{13}H_{12}N_2$, %: C 79.56; H 6.16; N 14.28. **Picrate**, mp 227–229° C (from methanol). Found, %: C 54.01, 54.12; H 3.86, 3.79. Calculated for $C_{13}H_{12}N_2 \cdot C_6H_3N_3O_7$, %: C 53.65; H 3.55.

In analogous experiments, 50 mg (0.3 mM) of 1-acetyl-2-aminoindole [2] and 50 mg (0.5 mM) of acetylacetone in 2 ml of dry pyridine (2 hr 30 min at 60° C) gave 10 mg (12%) of the same substance V, mp 110–111° C. When the reaction was performed at room temperature, only the starting materials were recovered, and at higher temperatures (80 and 100° C) compound V was obtained with yields of 16 mg (19%) and 18 mg (22%), respectively.

On being boiled in a current of inert gas for 5 hr, 100 mg (0.4 mM) of 2-amino-1-ethoxycarbonylindole hydrochloride, 4 ml of pyridine, and 100 mg (1 mM) of acetylacetone yielded 50 mg (56%) of substance V with mp 110–111° C.

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1 April 1968

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