INDOLES

III. Synthesis of Indoles By the Fischer Method Under the Action of Alkylating Agents*

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Khimiya Geterotsiklicheskikh Soedinenii, Vol. 5, No. 1, pp. 94–96, 1969

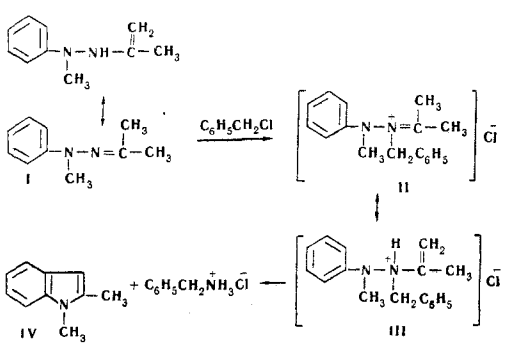
UDC 547.752.753.07

It has been found that arylhydrazones of carbonyl compounds smoothly undergo rearrangement into the corresponding indoles under the action of strong alkylating agents such as benzyl chloride, allyl bromide, and dimethyl sulfate in boiling methanol. The use of arylhydrazines substituted at the α-nitrogen atom leads to the formation of N-substituted indoles; However, where a hydrazine of the type of $ArNHNH_2$ is used, a mixture of the corresponding indole and of the indole substituted on the nitrogen atom by the radical of the alkylating compound is formed.

The condensing agents used in the Fischer indole synthesis are mainly compounds with an acidic nature—mineral [1, 2] and organic [3, 4] acids and metal chlorides [5, 6]. There are isolated items of information on the conversion of arylhydrazones into indoles under the action of organomagnesium compounds [7] and boron trifluoride [8]. Furthermore, cases have been described in which the formation of indoles from arylhydrazones takes place under the action of alkaline condensing agents [8] or in the absence of any catalysts whatever [9, 10]. There are two papers on the use as condensing agent of a cation-exchanger in a stationary system [11, 12].

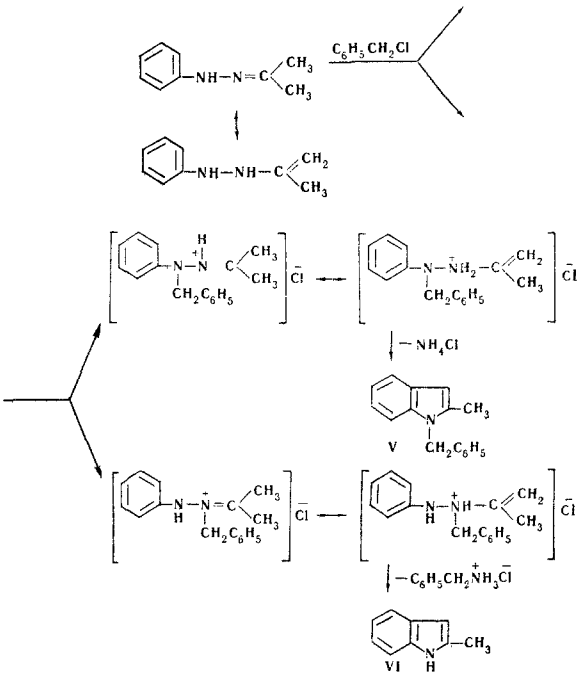
Developing our work on a new synthesis of tryptamines [13], we have found that arylhydrazones can be alkylated at the β-nitrogen atom with subsequent rearrangement into indoles.

We propose this as a preparative method for the synthesis of various indole systems. The most active alkylating agents—benzyl chloride, allyl bromide, and dimethyl sulfate—are used as condensing agents. When the reaction is carried out with hydrazones obtained from unsym-alkylphenylhydrazine, the β-nitrogen atom is alkylated. The quaternary ammonium salt (II) or the tautomeric vinylhydrazine hydrochloride (III) formed is rearranged in the manner of the Robinson-Suvorov reaction with the formation of the corresponding indole ring (IV) and the liberation of the corresponding amine.



* For part II, see [17].

When the reaction is carried out with arylhydrazones having the —NH—N= grouping, the two nitrogen atoms of the phenylhydrazone are alkylated to different extents, which leads to the formation of a mixture of N-substituted (V) and N-unsubstituted (VI) indoles.



The reaction takes place with similar success in the action of alkylating agents on both the pure arylhydrazone and on the unisolated arylhydrazone formed by boiling an arylhydrazine with a carbonyl compound in ethanol.

EXPERIMENTAL

N-Methyl-1, 2, 3, 4-tetrahydrocarbazole. A. A mixture of 2.44 g (0.02 mole) of α-methylphenylhydrazine and 1.96 g (0.02 mole) of cyclohexanone in 20 ml of ethanol was heated to the boil for 20 min. Then 2.53 g (0.02 mole) of benzyl chloride in 15 ml of aqueous ethanol (1 : 5) was added. The reaction mixture was boiled under reflux for 4 hr, after which the ethanol was distilled off and the residue was treated with a mixture of 40 ml of water and 35 ml of benzene. After drying, the benzene extract was distilled in vacuum to give 3.3 g (90%) of N-methyltetrahydrocarbazole with bp 156° C (5 mm), mp 50–52° C (from petroleum ether) [14]; R_f 0.75, dirty green spot*.

*Chromatography was carried out on rapid chromatographic paper of the Volodarskii mill impregnated with dimethylformamide in the benzene system. The revealing agent was a hydrochloric acid solution of p-dimethylaminobenzaldehyde in butanol. With each indole the reagent gives a characteristic coloration differing from the others.

B. N-Methyltetrahydrocarbazole was obtained similarly except that dimethyl sulfate was used instead of benzyl chloride as the condensing agent. After the reaction mixture had been boiled for 2 hours the yield was 70%.

1,3-Dimethylindole. This was obtained similarly from 0.01 mole of propionaldehyde, 0.01 mole of α-methylphenylhydrazine, and 0.01 mole of benzyl chloride. Yield 85%, bp 118–125° C (10 mm); R_f 0.85, lilac spot. **Picrate,** mp 144–145° C (from ether) [15].

N-Benzyl-1,2,3,4-tetrahydrocarbazole. This was obtained similarly from 0.01 mole of α-benzylphenylhydrazine, 0.01 mole of cyclohexanone, and 0.01 mole of benzyl chloride with a yield of 66%, bp 235–240° C (10 mm), mp 49–50° C (from petroleum ether); R_f 0.73, light blue spot. Found, %: C 87.21, 87.09; H 7.27, 7.20. Calculated for $C_{19}H_{19}H$, %: C 87.31; H 7.32 [19].

N-Benzyl-2-methylindole. This was obtained similarly from 0.01 mole of α-benzylphenylhydrazine, 0.01 mole of acetone, and 0.01 mole of benzyl chloride. Yield 77%, viscous oil with bp 206–210° C (18 mm). Found, %: C 87.02, 86.91; H 7.05, 6.97; N 6.23, 6.18. Calculated for $C_{16}H_{15}N$ %: C 86.83, H 6.83; N 6.33 [18].

1,2-Dimethyltryptophol. This was obtained similarly from 0.02 mole of α-methylphenylhydrazine, 0.02 mole of acetopropyl alcohol and 0.02 mole of benzyl chloride. The reaction mixture was boiled for 6 hr. Yield 60%, bp 186–190° C (6 mm), 210° C (19 mm); R_f 0.74, red-violet spot. Found, %: N 7.34, 7.28. Calculated for $C_{12}H_{15}NO$, %: N 7.44.

N-Benzyl-2,3-dimethylindole. This was obtained similarly from 0.01 mole of α-benzylphenylhydrazine, 0.01 of methyl ethyl ketone, and 0.01 mole of allyl bromide. Yield 62%, bp 200–205° C (10 mm), bp 60–61° C (from petroleum ether); R_f 0.72, dark blue spot. Found, %: N 6.12, 6.03. Calculated for $C_{17}H_{17}N$, %: 5.91.

2,3-Dimethylindole and N-benzyl-2,3-dimethylindole. A mixture of 0.1 mole of phenylhydrazine and 0.1 mole of methyl ethyl ketone was boiled under reflux in 250 ml of ethanol for an hour. Then 0.1 mole of benzyl chloride and 25 ml of water were added, and the reaction mixture was boiled for another 8 hr. After the solvent had been distilled off, the residue was dissolved in a mixture of 150 ml of benzene and 100 ml of water, and the benzene layer was washed with water (3 × 50 ml). After the benzene extract had been dried, the benzene was driven off and the residue was distilled in vacuum to give 2.59 g (25%) of 2,3-dimethylindole with bp 165–170° C (13 mm), mp 105–107° C (from aqueous methanol); R_f 0.55, gray-blue spot; **picrate,** mp 155–156° C (from ether) [5]; and 15.3 g (65%) of N-benzyl-2,3-dimethylindole with bp 210–214° C (from petroleum ether), melting without depression in admixture with authentic N-benzyl-2,3-dimethylindole with bp 210–214° C (12 mm), mp 60–61° C (from petroleum ether), melting without depression in admixture with authentic N-benzyl-2,3-dimethylindole; R_f 0.72, dark blue spot.

1,2,3,4-Tetrahydrocarbazole and N-benzyl-1,2,3,4-tetrahydrocarbazole. Similarly, phenylhydrazine, cyclohexanone, and benzyl chloride gave 5.8 g (34%) of 1,2,3,4-tetrahydrocarbazole with mp 115–117° C (from petroleum either) [5], R_f 0.65, light green spot; **picrate,** mp 131–133° C (from ethanol); and 12.45 g (48%) of N-benzyl-1,2,3,4-tetrahydrocarbazole with bp 236–250° C (12 mm), mp 49–50° C (from petroleum ether), melting without depression in admixture with authentic N-benzyltetrahydrocarbazole.

3-Ethyl-2-propylindole and N-benzyl-3-ethyl-2-propylindole. Similarly, phenylhydrazine, dipropyl ketone, and benzyl chloride yielded 5.12 g (27%) of 3-ethyl-2-propylindole with bp 185–190° C (10 mm), mp 129–130° C (from petroleum ether) [16], R_f 0.66, blue-green spot; and 12.4 g (45%) of N-benzyl-3-ethyl-2-propylindole with bp 215–220° C (10 mm), R_f 0.70, blue-lilac spot. Found, %: N 5.14, 5.12. Calculated for $C_{20}H_{23}N$, %: N 5.05.

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3 November 1966

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