CARBOLINES

III.* 1-METHYL-4-TERT-BUTYL-β-CARBOLINE

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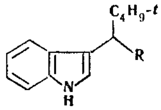
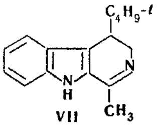
The reaction of tert-butyl(3-indolyl)carbinol with potassium cyanide yielded a nitrile which was reduced to β-tert-butyltryptamine. 1-Methyl-4-tert-butyl-β-carboline was prepared by cyclization of the acetyl derivative of this amine with subsequent dehydrogenation. An attempt to obtain this compound through 4-(3-indolyl)-5,5-dimethyl-2-hexanone was unsuccessful.

In the first communication of this series [2] we described a method for the synthesis of 4-substituted-β-carbolines by Beckmann rearrangement of β-(3-indolyl) ketone oximes. We have now attempted to use a similar method to obtain 1-methyl-4-tert-butyl-β-carboline (VIII).

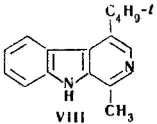
Carbinol I [3] was condensed with tert-butyl acetoacetate under the influence of a catalytic amount of sodium hydroxide in refluxing toluene to give keto ester II. When heated to 200°, II decomposed but did not decarboxylate and, consequently, could not be used for the subsequent synthesis. However, benzyl ester III, obtained like II from benzyl acetoacetate, smoothly underwent catalytic hydrogenolysis and decarboxylation to give ketone IV. Oxime IV gave only traces of the expected 3,4-dihydro-β-carboline (VII) on treatment with phosphorus pentachloride in nitrobenzene [2], which could not be isolated from the side products.



I - VI



VII



VIII

I $R=OH$, II $R=H_3C\cdot CO\cdot CH\cdot CO_2C(CH_3)_3$, III $R=H_3C\cdot CO\ CH\ CO_2CH_2C_6H_5$, IV $R=-CH_2COCH_3$, V $R=CN$, VI $R=CH_2NH_2$

We then decided to prepare VII by the Bischler–Napieralski reaction. For this, carbinol I was heated in glycol with excess potassium cyanide, and nitrile V was obtained. Tryptamine VI, previously reported as the picrate [4], was synthesized by the reduction of V with lithium aluminum hydride in ether. The acetyl derivative of amine VI was smoothly cyclized to 3,4-dihydro-β-carboline (VII) as a result of brief heating with phosphorus pentachloride in nitrobenzene. To complete the synthesis, VII was dehydrogenated by heating with palladium black in ethylene glycol.

It should be noted that the Bischler–Napieralski method in its classical execution [5] is of low suitability for the cyclization of β-substituted N-acyltryptamines. However, the use of the PCl_5–nitrobenzene combination makes it possible to accomplish the reaction in high yields.

EXPERIMENTAL

All of the melting points are uncorrected and were determined with a Koffler block. The IR spectra of mineral oil suspensions were obtained with a UR-10 spectrometer, while the UV spectra of alcohol solutions were obtained with an SF-4 spectrophotometer.

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*See [1] for communication II.

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tert-Butyl 2-Acetyl-3-(3-indolyl)-4,4-dimethyl Pentanoate (II). A total of 10 mg of powdered sodium hydroxide and 0.3 g (1.9 mmole) of tert-butyl acetoacetate were added to a solution of 0.2 g (0.99 mmole) of tert-butyl(3-indolyl)carbinol (I) in 2 ml of toluene, and the mixture was refluxed with water separation for 4.5 h. The resulting solution was diluted with ether, and the mixture was washed with dilute acid and water. The residue after removal of the solvents was chromatographed on activity III aluminum oxide. A chloroform–benzene mixture (1 : 1) eluted 0.22 g (68%) of crystals with mp 130-132° (from benzene, in a sealed capillary). Found %: C 73.8; H 8.6; N 4.0. $C_{21}H_{29}NO_3$. Calculated %: C 73.4; H 8.5; N 4.1. IR spectrum, cm^{-1}: 3430 (NH), 3390 (enol OH), 1720, 1725 ($COOC_4H_9$), 1710, 1690 (C=O).

Benzyl 2-Acetyl-3-(3-indolyl)-4,4-dimethyl Pentanoate (III). This was similarly obtained from I and benzyl acetoacetate. The reaction time was 8 h. The residue after removal of the solvent was crystallized from alcohol to give 74% of a product with mp 133-134°. Found %: C 76.3; H 7.3; N 3.6. $C_{24}H_{27}NO_3$. Calculated %: C 76.4; H 7.2; N 3.7.

4-(3-Indolyl)-5,5-dimethyl-2-hexanone (IV). A mixture of 2.9 g (7.7 mmole) of III and 1.67 g of platinum black (according to Brown [1]) in 29 ml of acetic acid was stirred for 27 h in a gentle stream of hydrogen. The catalyst was removed by filtration, and the solution was poured into water and extracted with ether. The extract was washed with water and sodium bicarbonate solution, dried with sodium sulfate, and the ether was evaporated. The residue was crystallized from alcohol to give 1.0 g (53%) of colorless crystals with mp 138-140°. Found %: C 79.1; H 8.4; N 5.9. $C_{16}H_{21}NO$. Calculated %: C 79.0; H 8.7; N 5.8. IR spectrum, cm^{-1}: 3420 (NH), 1715 (C=O).

2-(3-Indolyl)-3,3-dimethylbutyronitrile (V). A mixture of 3.6 g (17.7 mmole) of I, 2.67 g (41.1 mmole) of potassium cyanide, and 36 ml of anhydrous glycol was heated at 120° for 50 min, cooled, poured into water, and the mixture was extracted with ether. The extract was dried with sodium sulfate, the solvent was evaporated, and the residue was crystallized twice from isopropyl alcohol to give 1.7 g (45%) of V with mp 119-120° (from cyclohexane). Found %: C 79.4; H 7.4; N 13.3. $C_{14}H_{16}N_2$. Calculated %: C 79.2; H 7.6; N 13.2. IR spectrum, cm^{-1}: 3340 (NH), 2250 (CN).

2-(3-Indolyl)-3,3-dimethylbutylamine (VI). A solution of 4.1 g (0.02 mole) of V in 65 ml of ether was added carefully to a solution of 0.4 mole of lithium aluminum hydride (prepared from 3.8 g of lithium hydride and 31.8 g of aluminum bromide in 75 ml of ether), and the mixture was refluxed for 1.5 h. The excess aluminum hydride was decomposed with ethyl acetate, water and concentrated NaOH were added, and the mixture was extracted with ether. The ether extract yielded 3.4 g (81%) of VI with mp 175° (from benzene). Found %: C 77.8; H 9.3; N 13.2. $C_{14}H_{20}N_2$. Calculated %: C 77.7; H 9.3; N 13.0. IR spectrum, cm^{-1}: 3340 (indole NH), 3300 (NH_2).

1-Methyl-4-tert-butyl-3,4-dihydro-β-carboline (VII). Acetic anhydride [1 ml (10.6 mmole)] was added to 700 mg (3.2 mmole) of VI in 7 ml of pyridine, and the mixture was allowed to stand for 14 h at room temperature. The usual workup yielded 700 mg (84%) of crude N-acetyl derivative.

The amide obtained was dissolved in 7 ml of anhydrous nitrobenzene, and this solution was poured at 55° for 30 sec into a stirred suspension of 1.12 g (5.4 mmole) of PCl_5 in 7 ml of nitrobenzene, after which the mixture was stirred for another minute. The reaction mixture was rapidly cooled, and several pieces of ice were added to it. The mixture was dissolved in ether and extracted with dilute hydrochloric acid. The acidic solution was neutralized with ammonia and extracted with ether. An ether solution of hydrogen chloride was added to the dried ether extract, and the precipitated amorphous hydrochloride was dried in a vacuum desiccator to give 530 mg (70%) of chromatographically pure hydrochloride of VII. The picrate had mp 230-231° (from alcohol). Found %: C 56.2; H 4.8; N 14.9. $C_{16}H_{20}N_2 \cdot C_6H_3N_3O_7$. Calculated %: C 56.3; H 4.9; N 14.9. IR spectrum, cm^{-1}: 1380, 1550 (NO_2), 1630 (C=N), 3370 (NH).

1-Methyl-4-tert-butyl-β-carboline (VIII). A mixture of 2.3 g of the hydrochloride of VII, 23 ml of ethylene glycol, and 1.15 g of palladium black, prepared by the method in [1], was heated at 160° for 35 min. The cooled solution was filtered, diluted with water, made alkaline with potassium carbonate, and extracted with ether. Column chromatography [activity III Al_2O_3 and benzene–petroleum ether (3 : 2)] and crystallization from benzene yielded 1.12 g (49%) of VII with mp 196-197° (in a sealed capillary). The hydrochloride had mp 243-244° (from isopropyl alcohol). UV spectrum, λ_{max}, nm (log ε): 248 (3.52), 303 (3.15), 371 (2.73). The picrate had mp 264° (from alcohol). Found %: C 56.6; H 4.6; N 15.3. $C_{16}H_{18}N_2 \cdot C_6H_3N_3O_7$. Calculated %: C 56.5; H 4.5; N 15.0. IR spectrum, cm^{-1}: 1635 (C=N), 3350-3450 (NH).

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