7-AZAINDOLE DERIVATIVES
XVIII. Synthesis of 12-Aza-β-carbonyl Derivatives*
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The Bischler-Napiralski reaction is used to synthesize 1-phenyl-3, 9-dimethyl-5, 6-dihydro-12-aza-β-carboline, and its 5-methyl and 5-ethyl derivatives, from 1-phenyl-4-methyl-8-aminoalkyl-7-azaindoles. 5, 6-Dihydro-12-aza-β-carbolines prepared by sodium borohydride reduction are converted into 1-phenyl-3, 9-dimethyl-3, 4, 5, 6-tetrahydro-12-aza-β-carboline and its 5-methyl and 5-ethyl derivatives. 1-Phenyl-9-methyl-12-azaharman is synthesized by palladium dehydrogenation of 1-phenyl-3, 9-dimethyl-5, 6-dihydro-12-aza-β-carboline.

Derivatives of the 12-aza-β-carboline system are inadequately described in the literature. Only one patent [2] has been published containing an exposition of the conversion, by the classical Woodward [3] method, of 7-azatryptamine into 12-azadeserpidine (I), where a component element of the azayohimbane system is 12-aza-β-carboline.

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\begin{align*}
&\text{I} \quad \text{II} \quad \text{III} \\
&\text{IV} \quad \text{V} \quad \text{VI}
\end{align*}
\]

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\begin{align*}
\text{Ia} & \quad R=H; \quad \text{IIa} \quad R=H; \quad \text{IIc} \quad R=C_2H_5; \quad \text{IIIa} \quad R=H; \quad \text{IIIb} \quad R=CH_3; \quad \text{IIIc} \quad R=C_2H_5; \\
\text{IVa} & \quad R=H; \quad \text{IVb} \quad R=CH_3; \quad \text{IVc} \quad R=C_2H_5; \quad \text{Va} \quad R=H; \quad \text{Vb} \quad R=CH_3; \quad \text{Vc} \quad R=C_2H_5.
\end{align*}
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Developing previous research on 7-azaindole derivatives, we have synthesized 1-phenyl-3, 9-dimethyl-12-aza-β-carboline (1-phenyl-9-methyl-12-azaharman) (VI), its di- and tetrahydro derivatives, as well as similarly substituted

*For Part XVII see [1].
12-aza-β-carbolines with methyl and ethyl groups at position 5 (IV, V). These syntheses were based on the Bischler-
Napiralski reaction.

1-Phenyl-4-methyl-7-azatryptamine (IIa), 1-phenyl-3-(β-aminopropyl)-4-methyl-7-azaindole (IIb), and 1-
phenyl-3-(β-aminobutyl)-4-methyl-7-azaindole (IIc), prepared by the previously described method [4], were acetylated
with acetic anhydride. Reaction took place at room temperature, and gave 73-78% yields. The N-acetyl derivatives
thus synthesized crystallized well from benzene, and their melting points rose regularly on passing from the lowest homo-
log to the highest. The IR spectra of these compounds had the absorption bands at 1656-1680 and 3288-3322 cm⁻¹ char-
acteristic of acetylated primary amines.

Cyclodehydration of the acetyl derivatives IIIa-c was effected
by 2 hours boiling with phosphorus oxychloride, and derivatives of 5,
6-dihydro-12-aza-β-carboline (IVA-c) were obtained in 62-66%
yield.

The C=N double bond in ring C of the dihydroazacarbolines
IVA-c was smoothly reduced by sodium borohydride in methanol at
room temperature, to give 74-75% yields of derivatives of 3, 4, 5,
6-tetrahydro-12-aza-β-carboline (VA-c). Apparently reduction was
stereospecific, and with compounds Vb and Vc formation of only
one stereoisomer was observed.

Both di- and tetrahydro-12-aza-β-carbolines readily add
water of crystallization, and the majority of the compounds syn-
thesized by us were obtained as crystal hydrates.

The UV spectra of 5, 6-dihydro-12-aza-β-carbolines differ
substantially from those of the corresponding 3, 4, 5, 6-tetrahydro
derivatives (see figure), and can be used to determine the com-
pounds' degree of unsaturation.

Boiling 1-phenyl-3, 9-dimethyl-5, 6-dihydro-12-aza-β-
carboline (IVA) with palladium in xylene gives a 93% yield of 1-
phenyl-9-methyl-12-azaharman (VI).

Experimental

N-Acetyl-1-phenyl-4-methyl-7-azatryptamine (IIIa). 5 ml Ac₂O was added to 1.8 g (7.2 mmole) azatrypt-
amine IIa [4], and the reaction mixture warmed, when it darkened slightly. The mixture was then left overnight at
room temperature, after which it was evaporated under reduced pressure. The residue was recrystallized from benzene,
yield 1.58 g (78.8%) IIIa, colorless crystals mp 184-185 °C, bp 285 °C (0.9 mm). The compound was readily soluble in
CHCl₃, Me₂CO, and alcohols, sparingly soluble in benzene, AcOEt, and ether, insoluble in water, petrol ether, and
heptane. IR spectrum:* 1668, 3820 cm⁻¹ (-NHCOCH₃). Found: C 78.88, 74.88; H 6.69, 6.85; N 14.12, 18.90%. Calculated for
C₁₈H₁₉N₃O: C 78.72, H 6.48, N 13.84%.

N-Acetyl-1-phenyl-3-(β-aminopropyl)-4-methyl-7-azaindole (IIIb). This was similarly prepared from 1.28 g
(4.8 mmole) 1-phenyl-3-(β-aminopropyl)-4-methyl-7-azaindole (IIb) [4], and 2 ml Ac₂O, yield of IIIb, 1.15 g
(77.7%) mp 145-148.8 °C (ex benzene), bp 248-246 °C (1 mm). The compound was readily soluble in CHCl₃, Me₂CO,
and alcohols, sparingly soluble in benzene, ether, AcOEt, insoluble in water and petrol ether. IR spectrum: 1686,
3828 cm⁻¹ (NHCOCH₃). Found: C 74.33, 74.27; H 6.85, 6.87; N 13.30, 13.90%. Calculated for C₂₀H₂₁N₃O: C 74.27, H 6.84,
N 13.68%.

N-Acetyl-1-phenyl-3-(β-aminobutyl)-4-methyl-7-azaindole (IIIc). This was synthesized under the same condi-
tions as those used for IIIa, from 1.57 g (5.6 mmole) 1-phenyl-3-(β-aminobutyl)-4-methyl-7-azaindole (IIc) [4] and
3 ml Ac₂O. Yield of IIIc, 1.32 g (72.9%), mp 152-153 °C (ex benzene). The compound was readily soluble in alcohols,
CHCl₃, and Me₂CO, sparingly soluble in benzene, ether, AcOEt, insoluble in water and petrol ether. IR spectrum: 1680,
3288 cm⁻¹ (NHCOC₂H₅). Found: C 74, 77; H 6.84, 7.13; N 12.91%. Calculated for C₂₂H₂₅N₃O: C 74, 77; H 7.16; N 13.08%.

N-Acetyl-1-phenyl-3-(β-aminopropyl)-4-methyl-7-azaindole (IIIb). This was similarly prepared from 1.28 g
(4.8 mmole) 1-phenyl-3-(β-aminopropyl)-4-methyl-7-azaindole (IIb) [4], and 2 ml Ac₂O, yield of IIIb, 1.15 g
(77.7%) mp 145-145.5 °C (ex benzene), bp 245-246 °C (1 mm). The compound was readily soluble in CHCl₃, Me₂CO,
and alcohols, sparingly soluble in benzene, ether, AcOEt, insoluble in water and petrol ether. IR spectrum: 1686,
3288 cm⁻¹ (NHCOC₂H₅). Found: C 74, 77; H 6.84, 7.13; N 12.91%. Calculated for C₂₂H₂₅N₃O: C 74, 77; H 7.16; N 13.08%.

1-Phenyl-3, 9-dimethyl-5, 6-dihydro-12-aza-β-carboline (IVA). A mixture of 2.3 g (8.1 mmole) N-acetyl-
azatryptamine IIIa and 10 ml POCl₃ was refluxed for 2 hr, the reaction products poured on to ice, made alkaline with
aqueous ammonia, and extracted with benzene. The benzene extract was dried over K₂CO₃, and evaporated under

* All IR spectra were determined in vaseline, using a UR-10 spectrophotometer, and the UV spectra were de-
termined in ethanol with a SF-4 spectrophotometer.