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7-AZAINDOLE DERIVATIVES

XVIII. Synthesis of 12-Aza-β-carbonyl Derivatives*

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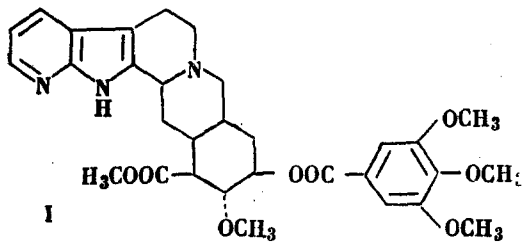
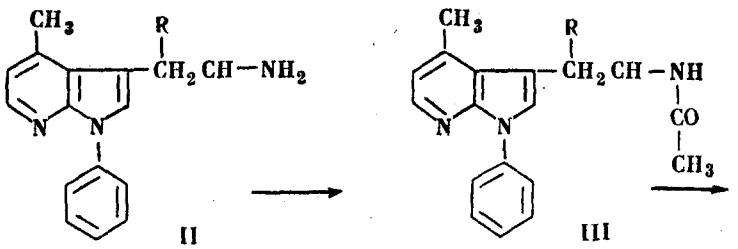
The Bischler-Napiralski reaction is used to synthesize 1-phenyl-3, 9-dimethyl-5, 6-dihydro-12-aza-β-carboline, and its 5-methyl and 5-ethyl derivatives, from 1-phenyl-4-methyl-3-aminoalkyl-7-azaindoles. 5, 6-Dihydro-12-aza-β-carbolines prepared by sodium borohydride reduction are converted into 1-phenyl-3, 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.

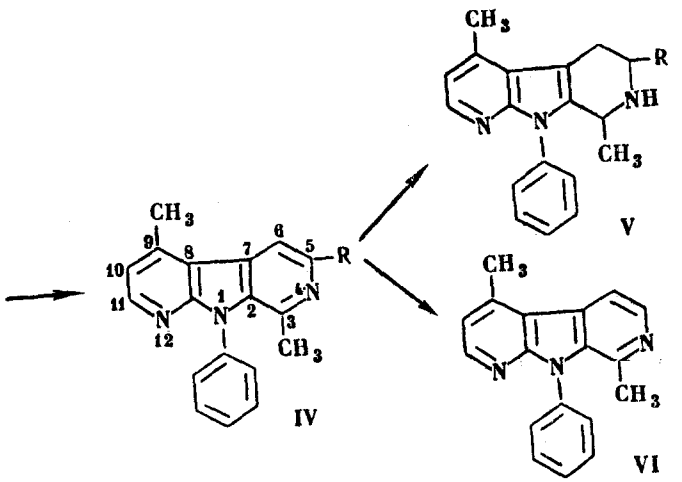
Derivatives of the 12-aza-β-carboline system are inadequately described in the literature. Only one patent [2] has been published containing an exposition of the conversion, by the classical Woodward [3] method, of 7-azatryptamine into 12-azadeserpidine (I), where a component element of the azayohimbane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



I



II III



IV V VI

IIa R=H; IIb R=CH_3; IIc R=C_2H_5; IIIa R=H; IIIb R=CH_3; IIIc R=C_2H_5;
IVa R=H; IVb R=CH_3; IVc R=C_2H_5; Va R=H; Vb R=CH_3; Vc R=C_2H_5.

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 actylated 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 homolog to the highest. The IR spectra of these compounds had the absorption bands at 1656-1680 and 3288-3322 cm^{-1} characteristic of acetylated primary amines.

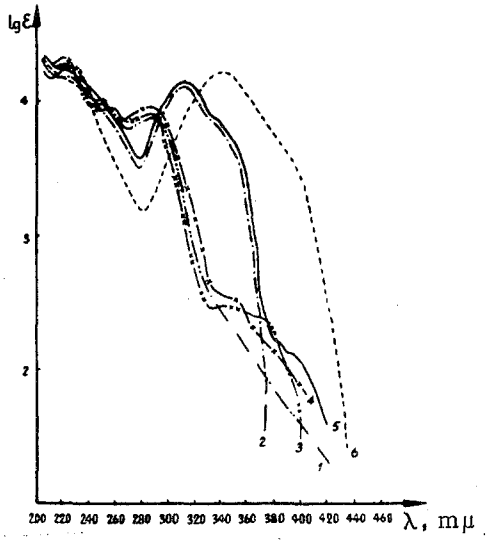
Cyclodehydration of the acetyl derivatives IIIa-c was effected by 2 hours boiling with phosphorus oxychloride, and derivatives of 5, 6-dihydro-12-aza-β-carboline (IVa-c) were obtained in 62-66% yield.

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 synthesized 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 compounds' 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).



UV spectra: 1) dihydrochloride Va; 2) IVb; 3) dihydrochloride of Vb; 4) hydrochloride of Vc; 5) IVc; 6) dihydrochloride of IVa.

Experimental

N-Acetyl-1-phenyl-4-methyl-7-azatryptamine (IIIa). 5 ml Ac_2O was added to 1.8 g (7.2 mmole) azatryptamine 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 1.55 g (73.8%) IIIa, colorless crystals mp 134-135°, bp 235° (0.9 mm). The compound was readily soluble in $CHCl_3$, Me_2CO, and alcohols, sparingly soluble in benzene, AcOEt, and ether, insoluble in water, petrol ether, and heptane. IR spectrum:* 1663, 3320 cm^{-1} (−$NHCOCH_3$). Found: C 73.88; H 6.69; N 14.12%. Calculated for $C_{18}H_{19}N_3O$: C 73.72; H 6.48; N 14.33%.

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 Ac_2O, yield of IIIb, 1.15 g (77.7%) mp 145-145.5° (ex benzene), bp 245-246° (1 mm). The compound was readily soluble in $CHCl_3$, Me_2CO, and alcohols, sparingly soluble in benzene, ether, AcOEt, insoluble in water and petrol ether. IR spectrum: 1656, 3288 cm^{-1} ($NHCOCH_3$). Found: C 74.33, 74.46; H 6.85, 6.67; N 13.90%. Calculated for $C_{19}H_{21}N_3O$: 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 conditions 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 Ac_2O. Yield of IIIc, 1.32 g (72.9%), mp 152-153° (ex benzene). The compound was readily soluble in alcohols, $CHCl_3$, and Me_2CO, sparingly soluble in benzene and ether, IR spectrum: 1680, 3322 cm^{-1} ($NHCOCH_3$). Found: C 74.61; H 7.13; N 12.91%. Calculated for $C_{20}H_{23}N_3O$: 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-acetylazatryptamine IIIa and 10 ml $POCl_3$ 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 K_2CO_3, and evaporated under

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

reduced pressure, to give a residue (2.02 g) which was dissolved in acetone, after which ethanolic HCl was added till the reaction was acid to congo red. The precipitate of IVa formed was recrystallized from 15 ml ethanol, to give 1.75 g (62%) VIII dihydrochloride hemihydrate. Pale yellow crystals mp 215-216°. The compound was readily soluble in water, sparingly soluble in alcohols, insoluble in ether, Me_2CO, AcOEt, benzene, and $CHCl_3$. For UV spectrum see figure. Found: C 60.68, 60.84; H 5.80, 5.74; Cl 19.94; N 11.56%. Calculated for $C_{18}H_{17}N_3 \cdot 2HCl \cdot 1/2\,H_2O$: C 60.51; H 5.60; Cl 19.88; N 11.76%.

Base: pale yellow crystals mp 151-152° (ex heptane-ether 1:1). The compound was readily soluble in Me_2CO, benzene, and alcohols, sparingly soluble in ether, insoluble in water, petrol ether, and heptane. Found: C 76.16; H 6.51; N 14.86%. Calculated for $C_{18}H_{17}N_3 \cdot 1/2\,H_2O$: C 76.05; H 6.34; N 14.79%.

1-Phenyl-3, 5, 9-trimethyl-5, 6-dihydro-12-aza-β-carboline (IVb). This was prepared using the same conditions as in the preceding experiment, and starting from 0.68 g (2.2 mmole) IIIc and 3 ml $POCl_3$. After distilling off the benzene, the base crystallized. The compound was recrystallized from petrol ether, yield of IVb, 0.42 g (63.7%), mp 120-121°. It was readily soluble in ordinary organic solvents, sparingly soluble in petrol ether, insoluble in water. The UV spectrum is given in the Figure. Found: C 76.61, 76.80; H 6.87, 6.92; N 14.18, 14.23; H_2O 3.06%. Calculated for $C_{19}H_{19}N_3 \cdot H_2O$: C 76.51; H 6.71; N 14.09; H_2O 3.02%.

1-Phenyl-3, 9-dimethyl-5-ethyl-5, 6-dihydro-12-aza-β-carboline (IVc). 0.37 g (1.2 mmole) IIIc and 1 ml $POCl_3$ were reacted as in experiment where IVa was prepared. After distilling off the benzene, the base crystallized (0.34 g). The compound was recrystallized from petrol ether, yield of IVc, 0.23 g (66%). Colorless crystals, mp 113-114°. Readily soluble in ether, benzene, alcohols, $CHCl_3$, sparingly soluble in petrol ether, insoluble in water. The UV spectrum is given in the figure. Found: C 78.89; H 6.79; N 13.58%. Calculated for $C_{20}H_{21}N_3$: C 79.21; H 6.93; N 13.86%.

1-Phenyl-3, 9-dimethyl-3, 4, 5, 6-tetrahydro-12-aza-β-carboline (Va). 0.2 g (5.3 mmole) $NaBH_4$ was added in portions, over 5 min, to a solution of 0.8 g (2.8 mmole) IVa in 10 ml MeOH, the reaction mixture stirred for 30 min, then evaporated under reduced pressure. 10 ml water was added to the residue, and the mixture extracted with ether, the ether extract dried over K_2CO_3, and the hydrochloride of Va isolated, mass 0.7 g (75%), colorless crystals. The compound frothed at 110°, lost water, and decomposed at 252°; it was readily soluble in water and alcohols, insoluble in ether, Me_2CO, EtOAc, benzene, $CHCl_3$, dioxane, and tetrahydrofuran. The UV spectrum is given in the figure. Found: C 58.75; H 6.29; Cl 19.01; N 11.24%. Calculated for $C_{18}H_{19}N_3 \cdot 2HCl \cdot H_2O$: C 58.70; H 6.25; Cl 19.29; N 11.41%.

1-Phenyl-3, 5, 9-trimethyl-3, 4, 5, 6-tetrahydro-12-aza-β-carboline (Vb). This was prepared in the way described above, by reducing 0.16 g (0.54 mmole) IVb with 0.16 g (4.2 mmole) $NaBH_4$ in 2 ml MeOH. Yield of the Vb dihydrochloride hemihydrate, 0.15 g (75%). Colorless crystals, which slowly lost water at about 110°, and decomposed at 306-307°; readily soluble in water, less soluble in alcohols, insoluble in ether, acetone, AcOEt, benzene, $CHCl_3$, and dioxane. For the UV spectrum, see the figure. Found: C 60.71; H 6.42; Cl 19.00; N 11.31%. Calculated for $C_{19}H_{21}N_3 \cdot 2HCl \cdot 1/2\,H_2O$: C 61.12; H 6.43; Cl 19.03; N 11.26%.

1-Phenyl-3, 9-dimethyl-5-ethyl-3, 4, 5, 6-tetrahydro-12-aza-β-carboline (Vc). This was prepared similarly to Va, by reducing 0.17 g (0.56 mmole) IVc with 0.17 g (4.6 mmole) $NaBH_4$ in 5 ml MeOH. Yield of Vc hydrochloride, 0.14 g (74%). The compound was dried in a vacuum-drying pistol (100°, 5 mm, 24 hr). Colorless crystals, mp 311-312° (decomp), readily soluble in water, sparingly soluble in alcohols, insoluble in ether, Me_2CO, benzene, $CHCl_3$, and dioxane. For UV spectrum see figure. Found: C 70.34, 70.53; H 7.09, 7.24; Cl 10.03; N 12.46, 12.64%. Calculated for $C_{20}H_{23}N_3 \cdot HCl$: C 70.28; H 7.03; Cl 10.39; N 12.30%.

1-Phenyl-9-methyl-12-azaharman (VI). 0.45 g (1.6 mmole) IV in 10 ml dry xylene was refluxed with 0.1 g palladium black for 2 hr. The palladium was filtered off, and the xylene filtrate evaporated under reduced pressure. The residue was extracted with ether, yield 0.33 g (73%) VI, pale yellow crystals mp 239° (decomp). (At 100-110° the compound lost water of crystallization). It was readily soluble in benzene, Me_2CO, alcohols, and $CHCl_3$, sparingly soluble in ether, insoluble in water. Found: C 71.68; H 5.60; N 14.04%. Calculated for $C_{18}H_{15}N_3 \cdot 1.5H_2O$: C 72.00; H 6.00; N 14.00%.

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