AZAINDOLE DERIVATIVES

XXXVII.* NORMAL AND ANOMALOUS COURSE OF REACTIONS IN THE SYNTHESIS OF 12-AZA-β-CARBOLINES

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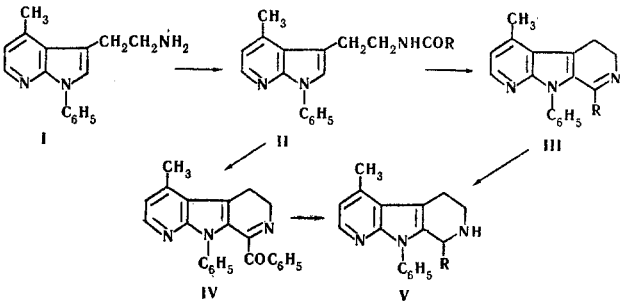
The synthesis of substituted 3,4,5,6-tetrahydro-12-aza-β-carbolines on the basis of the corresponding 7-azatryptamines was realized using the Bischler–Napieralski and Pictet–Spengler reactions. The effect of the character of the acylating residue in the synthesis of 12-aza-β-carboline derivatives via the Bischler–Napieralski reaction was studied. It was established that if the N-acylating group is a phenylacetic-acid residue, oxidation by air oxygen occurs along with cyclodehydration, and the corresponding ketone, 3-benzoyl-5,6-dihydro-12-aza-β-carboline, is formed instead of the normal product, the 3-benzyl-5,6-dihydro-12-aza-β-carboline derivative.

We previously described [2] the synthesis of a new tricyclic system, 12-aza-β-carboline, in examples of the Bischler–Napierlaski cyclization of 1-phenyl-4-methyl-3-(β-acetamidoalkyl)-7-azaindoles.

In developing these investigations it was of interest to study how the character of the N-acylating residue in the corresponding 7-azatryptamines affects the reaction of these compounds with phosphorus oxychloride. N-Acyl-1-phenyl-4-methyl-7-azatryptamines (II), which, in addition to the previously studied acetyl group [2], have formyl (IIa), benzoyl (IIb), 3,4,5-trimethoxybenzoyl (IIc), and phenylacetyl (IId) residues, were used as the starting compounds for the indicated reactions.



1-Phenyl-4-methyl-7-azatryptamine (I) [3] was refluxed with formic acid in order to obtain N-formyl derivative IIa. The remaining 7-azatryptamides (IIb-d) were synthesized by Schotten–Baumann acylation of I with the appropriate acyl chlorides and were obtained in yields from 83 to 91%.

The cyclodehydration of the 7-azatryptamides of aromatic acids (IIb and c) proceeded smoothly under the influence of phosphorus oxychloride in refluxing benzene or without solvent and gave the normal reaction products – 5,6-dihydro-12-aza-β-carbolines (IIIb and c).

*See [1] for Communication XXXVI.

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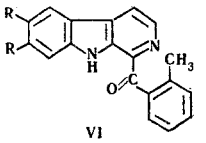
In contrast to its closest homolog, the 7-azatryptamide of acetic acid [2], the Bischler–Napierlaski cyclization of the 7-azatryptamide of formic acid (IIa) is accompanied by pronounced resinification, even under mild conditions (at room temperature), and it was not possible to obtain the corresponding 12-aza-β-carboline. There are references in the literature [4] regarding similar difficulties arising in the case of other heterylethylamines on attempts to cyclodehydrate their N-formyl derivatives. In this connection, a compound of the 12-aza-β-carboline series which is unsubstituted in the 3-position was obtained on the basis of the Pictet–Spengler reaction rather than via the Bischler–Napieralski reaction. Reaction of I with formaldehyde in the presence of dilute hydrochloric acid made it possible to synthesize 1-phenyl-9-methyl-3,4,5,6-tetrahydro-12-aza-β-carboline (Va) in 55% yield.

Close to quantitative yields of 3,4,5,6-tetrahydro-12-aza-β-carbolines Vb and Vc were obtained by treatment of the corresponding 5,6-dihydro derivatives (IIIb, c) with sodium borohydride under mild conditions.

The cyclodehydration of the 7-azatryptamide of phenylacetic acid (IId) proceeded in an unusual manner. The normal reaction product in this case should have been 1-phenyl-3-benzyl-9-methyl-5,6-dihydro-12-aza-β-carboline (IIId). However, instead of IIId we isolated 46% of an oxygen-containing substance, the IR spectrum* of which did not have absorption in the 3100-4000 cm^{-1} region but had an intense carbonyl band at 1685 cm^{-1}, along with bands characteristic for the C=C and C=N bonds (1592 and 1608 cm^{-1}). The carbonyl band can be assigned to the ketone group conjugated with the phenyl and dihydroazacarboline rings. The position of the carbonyl group agrees satisfactorily with the PMR-spectroscopic data. In addition to the singlet from the CH_3 group attached to C_9 (2.72 ppm), the high-frequency region of the PMR spectrum† of the compound contains only two triplets (3.21 and 4.20 ppm; J 1.7 Hz), which should be assigned to the A_2B_2 system for C_5 and C_6 of the 5,6-dihydro-12-aza-β-carboline ring. No signals which characterize the CH_2 group of the benzyl residue attached to the C_3 substituted 5,6-dihydro-12-aza-β-carboline are present in the spectrum. In addition, the compound is smoothly converted to 80% yields of 1-phenyl-3-benzyl-9-methyl-3,4,5,6-tetrahydro-12-aza-β-carboline (Vd) by reduction under mild conditions with sodium borohydride. All of the above makes it possible to assert that the product of the anomalous cyclization of IId is a ketone – 1-phenyl-3-benzoyl-5,6-dihydro-12-aza-β-carboline (IV).

A similar anomalous product of the Bischler–Napieralski reaction was previously observed [5] during the cyclization of the tryptamide of o-tolylacetic acid under the influence of phosphorus pentoxide. In this case, if the process was carried out in the presence of air oxygen, one also isolated a carbonyl-containing compound, to which the VI (R = H) structure was assigned on the basis of a comparison of it with yobirone.



VI

Huebner and co-workers [6] later described the same type of oxidative reaction during the cyclodehydration of the 5,6-dimethoxytryptamide of o-tolylacetic acid with phosphorus pentoxide, and the VI ($R = OCH_3$) structure, in analogy with the yobirones, was assigned to the product, which has an intense absorption band at 1667 cm^{-1} in its IR spectrum. One cannot exclude the fact that in both cases the authors could have been dealing, as in the cyclization of IId, with the corresponding 5,6-dihydro derivatives (whose definitive structure could be established with the PMR spectra) rather than with the completely dehydrogenated compounds of the carbonyl series.

EXPERIMENTAL

N-Formyl-1-phenyl-4-methyl-7-azatryptamine (IIa). 1-Phenyl-4-methyl-7-azatryptamine (I) [2 g (0.008 mole)] was refluxed for 2 h with 4 ml (0.11 mole) of formic acid. After evaporation of the reaction

*The IR spectrum in mineral oil was obtained with a UR-10 spectrometer.

†The PMR spectrum was obtained with a JNM-4H-100 spectrometer (100 MHz), the solvent was deuterochloroform, and the internal standard was tetramethylsilane. We are obliged to thank S. L. Portnovaya, E. M. Pereslen', and Yu. I. Pomerantsov for their assistance in carrying out the spectral investigations.

mass in vacuo, the residue (2.2 g) was recrystallized from ethyl acetate to give 1.4 g (63%) of IIa with mp 120-121° in the form of colorless crystals that were quite soluble in benzene, alcohols, and chloroform, slightly soluble in ether and ethyl acetate, and insoluble in heptane and water. Found %: C 79.92; H 6.00; N 15.27. $C_{17}H_{17}N_3O$. Calculated %: C 73.09; H 6.13; N 15.04.

N-(α-Phenylacetyl)-1-phenyl-4-methyl-7-azatryptamine (IId). Aqueous 20% sodium hydroxide [38 ml (0.23 mole)] was added to a solution of 2.26 g (0.009 mole) of I in 50 ml of benzene, and 3.48 g (0.023 mole) of phenylacetyl chloride in 25 ml of benzene was added dropwise to it with stirring. After stirring for 3 h at room temperature, the benzene layer was separated, and the aqueous layer was additionally extracted with benzene. The combined benzene extracts were dried with potassium carbonate and evaporated in vacuo to give 3.04 g (92%) of IId in the form of colorless crystals with mp 114-115° (from ethyl acetate). The compound is quite soluble in chloroform, slightly soluble in ether, acetone, and ethyl acetate, and insoluble in heptane and water. Found %: C 78.27; H 6.02; N 11.15. $C_{24}H_{23}N_3O$. Calculated %: C 78.02; H 6.28; N 11.37.

N-(3',4',5'-Trimethoxybenzoyl)-1-phenyl-4-methyl-7-azatryptamine (IIc). This was similarly obtained from 6.1 g (0.024 mole) of I and 12 g (0.052 mole) of 3,4,5-trimethoxybenzoyl chloride. Compound IIc (8.6 g), which was slightly soluble in benzene, was filtered after carrying out the reaction. An additional 1.22 g of IIc, to give an overall yield of 91% of colorless crystals with mp 157-158°, was obtained after evaporation of the benzene solution. The product was quite soluble in chloroform, slightly soluble in benzene, methyl acetate, and acetone, and insoluble in ether, petroleum ether, and water. Found %: C 70.27; H 6.26; N 9.65. $C_{26}H_{27}N_3O_4$. Calculated %: C 70.09; H 6.11; N 9.43.

N-Benzoyl-1-phenyl-4-methyl-7-azatryptamine (IIb). This was obtained the same way as IId. Compound IIb was dissolved in 60 ml of acetone, filtered with charcoal, and acidified with alcoholic hydrogen chloride to give 1.72 g (83%) of IIb monohydrate hydrochloride in the form of colorless crystals with mp 151-153°. The compound was soluble in alcohol, slightly soluble in benzene, acetone, and chloroform, and insoluble in ether. Found %: C 67.01; H 6.05; N 10.41; Cl 8.67; H_2O 4.40. $C_{23}H_{21}N_3O \cdot HCl \cdot H_2O$. Calculated %: C 67.38; H 5.90; N 10.25; Cl 8.65; H_2O 4.55.

1,3-Diphenyl-9-methyl-5,6-dihydro-12-aza-β-carboline (IIIb). A mixture of 1.2 g (0.003 mole) of IIb, 2.5 ml (0.027 mole) of phosphorus oxychloride, and 50 ml of anhydrous benzene was refluxed for 5 h. After treatment of the reaction mixture with 50 ml of ice water, it was made alkaline, the benzene layer was separated, and the water layer was additionally extracted with benzene. The combined benzene extracts were dried with magnesium sulfate and evaporated in vacuo to give 0.9 g (79%) of IIIb in the form of colorless crystals with mp 152-154° (from alcohol). The compound was quite soluble in benzene and chloroform and slightly soluble in alcohol and acetone. Found %: C 81.91; H 5.57; N 12.45. $C_{23}H_{19}N_3$. Calculated %: C 81.86; H 5.68; N 12.45. The hydrochloride was obtained in the form of yellow crystals with mp 242-243° (from absolute alcohol) and was soluble in water and hot alcohol and insoluble in ether, acetone, and benzene. Found %: N 11.00; Cl 9.79. $C_{23}H_{19}N_3 \cdot HCl$. Calculated %: N 11.24; Cl 9.48.

1-Phenyl-3-(3',4',5'-trimethoxyphenyl)-9-methyl-5,6-dihydro-12-aza-β-carboline (IIIc). Compound IIc [8.6 g (0.019 mole)] was refluxed for 2.5 h with 22 ml (0.24 mole) of phosphorus oxychloride. Ice water (150 ml) was added to the resulting yellow precipitate, the mixture was made alkaline, and IIIc was extracted with benzene. Evaporation of the benzene solution yielded 7.3 g (89%) of IIIc in the form of colorless crystals with mp 180-182° (from acetone). The compound was quite soluble in benzene and chloroform, slightly soluble in ether and acetone, and insoluble in water. Found %: C 72.66; H 5.88; N 9.86. $C_{26}H_{25}N_3O_3$. Calculated %: C 73.04; H 5.89; N 9.83. The hydrochloride was obtained in the form of yellow crystals with mp 230-232° (decomp., from absolute alcohol) that were quite soluble in water, slightly soluble in alcohol, and insoluble in ether, ethyl acetate, and acetone. Found %: N 9.34; Cl 7.45. $C_{26}N_{25}N_3O_3 \cdot HCl$. Calculated %: N 9.06; Cl 7.64.

1-Phenyl-3-benzoyl-9-methyl-5,6-dihydro-12-aza-β-carboline (IV). Compound IId [2 g (0.0054 mole)] was refluxed for 2 h with 4 ml (0.044 mole) of phosphorus oxychloride in 30 ml of anhydrous benzene. The reaction mass was cooled, poured over ice, and the mixture was made alkaline with ammonium hydroxide. The benzene solution was separated, dried with potassium carbonate, and evaporated in vacuo. The residue was recrystallized from acetone to give 0.9 g (46%) of IV with mp 185-186° in the form of yellow crystals that were soluble in chloroform and benzene and slightly soluble in ether, alcohol, acetone, and water. Found %: C 78.76, 79.04; H 5.22, 5.16; N 11.61, 11.43. $C_{24}H_{19}NO$. Calculated %: C 78.87; H 5.24; N 11.50.

1-Phenyl-9-methyl-3,4,5,6-tetrahydro-12-aza-β-carboline (Va). Aqueous (38%) formalin [3.4 ml (0.12 mole)] was added to a solution of 3.4 g (0.014 mole) of I in 213 ml of dilute (1:125) sulfuric acid heated to 70°. After 15 min at 70° the mixture was cooled and made alkaline with 50% potassium carbonate solution. The base which separated was extracted with ether. The ether solution was dried with magnesium sulfate and evaporated in vacuo. The residue (3.04 g) was refluxed for 1 h with 1240 ml of dilute (1:125) sulfuric acid, made alkaline with 50% potassium carbonate, and extracted with chloroform. The residue after removal of the chloroform was recrystallized from benzene to give 1.94 g (55%) of Va with mp 204-206° in the form of colorless crystals that were quite soluble in chloroform, slightly soluble in alcohol and benzene, and insoluble in petroleum ether and water. Found %: C 77.34; H 6.54; N 15.61. $C_{17}H_{17}N_3$. Calculated %: C 77.53; H 6.51; N 15.96. The dihydrochloride was obtained in the form of colorless crystals with mp 277-278° (from isopropyl alcohol) that were quite soluble in water and slightly soluble in alcohol, chloroform, benzene, ethylacetate, acetone, and ether. Found %: N 12.33; Cl 20.70. $C_{17}H_{17}N_3 \cdot 2HCl$. Calculated %: N 12.50; Cl 21.09.

1,3-Diphenyl-9-methyl-3,4,5,6-tetrahydro-12-aza-β-carboline (Vb). Sodium borohydride [1.08 g (0.031 mole)] was added in the course of 30 min to a solution of 2.16 g (0.0064 mole) of IIIb in 300 ml of methanol; the temperature of the reaction mass was held at 25-30°. After 2 h, the methanol was removed, 50 ml of water was added to the residue, and Vb was extracted with benzene. The solution was dried with potassium carbonate, evaporated, and the residue was dissolved in acetone. The solution was filtered with carbon, and the hydrochloride was isolated by the addition of alcoholic hydrogen chloride to give 2.3 g (96%) of colorless crystals with mp 267-268°. The crystals were quite soluble in water and methanol and insoluble in ether and acetone. Found %: C 73.58; H 5.69; N 10.98; Cl 9.56. $C_{23}H_{21}N_3 \cdot HCl$. Calculated %: C 73.49; H 5.90; N 11.18; Cl 9.43.

1-Phenyl-3-(3',4',5'-trimethoxyphenyl)-9-methyl-3,4,5,6-tetrahydro-12-aza-β-carboline (Vc). This was obtained in the same way as Vb by reduction of 0.84 g (0.0019 mole) of IIIc with 0.2 g (0.0057 mole) of sodium borohydride in methanol. The hydrochloride of Vb [0.9 g (98%)] was obtained in the form of colorless crystals with mp 208-210° (from absolute alcohol). The crystals were soluble in water and insoluble in ether, acetone, ethyl acetate, and benzene. For analysis, the sample was dried in vacuo for 4 h at 160°. Found %: C 66.95; H 5.99; N 8.94; Cl 7.54. $C_{26}H_{27}N_3O_3 \cdot HCl$. Calculated %: C 67.01; H 6.06; N 9.02; Cl 7.61.

Reduction of 1-Phenyl-3-benzoyl-9-methyl-5,6-dihydro-12-aza-β-carboline (IV). Sodium borohydride [2.5 g (0.072 mole)] was added at 25-30° to 1.94 g (0.0053 mole) of IV in 300 ml of methanol. After 2 h at room temperature the methanol was removed, 50 ml of water was added to the residue, and Vd was extracted with chloroform and converted to the hydrochloride. 1-Phenyl-3-benzyl-9-methyl-3,4,5,6-tetrahydro-12-aza-β-carboline dihydrate dihydrochloride [1.96 g (80%)] was obtained in the form of colorless crystals with mp 216-218°. The crystals were quite soluble in hot chloroform and alcohol and slightly soluble in acetone and ethyl acetate. Found %: C 62.68; H 6.09; N 9.43; Cl 15.63. $C_{24}H_{23}N_3 \cdot 2HCl \cdot 2H_2O$. Calculated %: C 62.33; H 6.32; N 9.09; Cl 15.34.

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