INVESTIGATION OF LACTAMS

XX. SYNTHESIS AND PHARMACOLOGICAL ACTIVITY OF AZEPINO[3,4-b]INDOLE DERIVATIVES

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The recently developed methods of synthesizing substituted 1H,2,3,4-tetrahydroazepino[3,4-b]indoles [1-3] from caprolactam have opened broad perspectives for preparing condensed indole derivatives of biological interest [4]. In particular, it became of interest to synthesize the indole analogs of such biologically active compounds as Corazol (α,β-pentamethylenetetrazole) [5], Omethylcaprolactim [6], and also a series of 1,2- and 10-substituted azepino[3,4b]indoles for pharmacological investigation.

Unsubstituted and 7-methoxysubstituted 1-oxo-1H,2,3,4,5-tetrahydroazepino[3,4-b]indoles (I and II) were chosen as the starting substances for the synthesis of these compounds.

When I was treated with phosphorus oxychloride in the presence of diethylaniline, the adduct, to which structure III was assigned on the basis of its chemical properties, elemental analysis, and IR spectrum, was obtained in a way similar to the corresponding reaction of 1-oxo-1,2,3,4-tetrahydro-β-carboline [7]; this structure agrees with the modern concepts [8] concerning the structure of the adducts of acid amides, among them lactams, with phosphorus oxychloride. An absorption band at 1110 cm^{-1}, which corresponds to the C – O– P bond [10], is presented in the IR spectrum of III along with an absorption band at 1620 cm^{-1} (the C = N bond) [9] and at 3170 cm^{-1} (the NH group).

When adduct III is treated with alcohols, the 1-alkoxy-3H,4,5-dihydroazepino[3,4-b]indoles (IV-V) were obtained. Adduct (VI) was similarly obtained from II by treating it with phosphorus oxychloride; 1,1-dimethoxy-3H,4,5-dihydroazepino[3,4-b]indole (VII) was synthesized by the methanolysis of (VI). In contrast to 1-methoxy-3,4-dihydro-β-carboline [7] and the simplest lactim ether, O-methylcaprolactim (VIII), the lactim-ether group in its indole analog IV is considerably less reactive. In particular, IV does not react with primary or secondary amines, and only when it was reacted with such a strong nucleophilic reagent as hydrazine hydrate was 1-hydrazino-3H,4,5-dihydroazepino[3, 4-b]indole (IX) obtained, from whose cyclization with nitrous acid was synthesized the indole analog of Corazol, tetrazolo (5,1-a)-azepino[3,4-b]-indole (X). However, IV partially retains the properties inherent to lactim ethers. In particular, the reaction of IV with dimethylsulfate is accompanied by an intermolecular rearrangement forming 1-oxo-2-methyl-1H,2,3,4,5-tetrahydroazepino[3,4-b]indole (XI) similarly to VIII [11]. An isomeric XI, 10-methyl-1-oxo-1H,2,3,4,5-tetrahydroazepino[3, 4-b]indole (XII), was synthesized by a method similar to the one by which 9-methyl-1-oxo-1,2,3,4-tetrahydro-β-carboline [12] was obtained, i.e., by methylating I with dimethylsulfate in an alkaline medium.

It should be emphasized that the syntheses of XI and XII are examples of the selective alkylation of I which opens a course both to 10- and 2-substituted azepino[3,4-b]indoles, and which in turn can be the starting compounds for preparing new azepino[3,4-b]indole derivatives. Compound XII is one of them; 1-ethoxy-10-methyl-3H,4,5-dihydroazepino[3,4-b]indole (XIII) was obtained by ethylating it with triethyloxonium fluoroborate:

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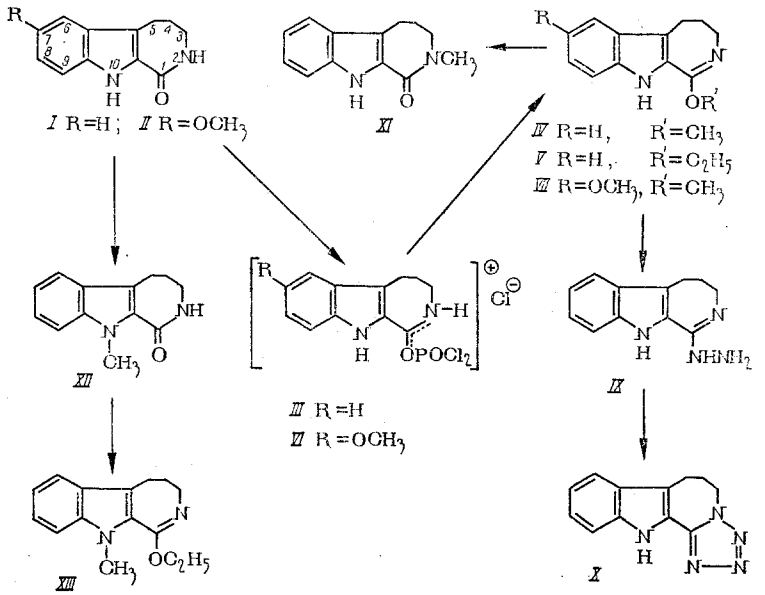
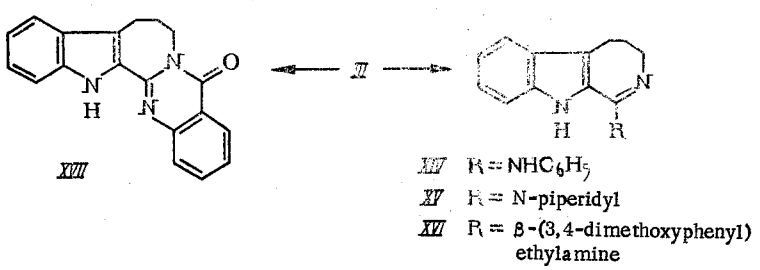


In connection with the fact that attempts to condense IV with various aliphatic and aromatic amines, which were undertaken for the purposes of preparing N-substituted 1-amino-3H,4,5-dihydroazepino[3,4-b]-indole (types XIV-XVI), did not yield positive results, the reaction of III with aniline, piperidine, and homoveratrylamine was studied. This reaction proceeded smoothly, and XIV-XVI were synthesized in high yields. Further, when III was condensed with anthranilic acid, its analog, homorutecarpine (XVII), was obtained similarly to the synthesis of the alkaloid rutecarpine [13].



The closeness of the azepino[3,4-b]indoles we synthesized, in their chemical structure, to β-carboline derivatives served as the basis for investigating the effect of these preparations on the central nervous system.

As a result of this investigation, it was established that their tranquilizing effect on the central nervous system, which is accompanied by muscle relaxation and hypothermia, is the main effect of their action on the central nervous system. Compounds IV, V, and XIII proved to be the most active in this regard. In addition, these preparations cause a state of catalepsy in rats and mice, and have a soporific effect when the dosages are further increased (to 200 to 400 mg/kg).

It is interesting to note that when a second methoxyl group is introduced into position seven of compound IV, i.e., during its transformation into compound VII, these phenomena (catalepsy and the soporific effect) are not observed. The compounds we synthesized have little pharmacological effect on the other indicators (the effect on smooth muscle, the cardio-vascular system, and respiration).

EXPERIMENTAL

The Adduct of 1-Oxo-1H,2,3,4,5-tetrahydroazepino[3,4-b]indole with Phosphorus Oxychloride (III). A mixture of 13.4 g of I, 150 ml of phosphorus oxychloride, and 1 ml of diethylaniline was heated with stirring at 80°C for 10 to 15 min. Compound I completely dissolved during the heating process. The reaction mixture was cooled in an ice bath; the precipitate was filtered off, washed with ether, and dried. Compound III, 21.7 g (91.6%) was obtained, mp 150 to 153°C. ν_{NH} 3170 cm^{-1}, $\nu_{C=N}$ 1620 cm^{-1}, and ν_{POC} 1110 cm^{-1}. Found %:

C 40.20; H 3.56; Cl 29.34; N 8.06; and P 9.30. $C_{12}H_{12}Cl_3N_2O_2P$. Calculated %: C 40.73; H 3.39; Cl 30.12; N 7.92; and P 8.76.

1-Methoxy-3H,4,5-dihydroazepino[3,4-b]indole (IV). To 200 ml of methanol was added in portions over a 10 min period 22 g of III with agitation while cooling with ice; the mixture was agitated for 15 to 20 min while cooling and for 15 min at room temperature. The reaction mixture was heated to the boil, boiled for 5 min, and evaporated to dryness in vacuo. The remainder was dissolved in 75 ml of cold water, 50 ml of chloroform was added to the solution, and the mixture was made alkaline with 10% ammonia to pH 8.0 while cooling with ice. The organic layer was separated out, the aqueous layer was extracted with (2 × 50 ml) chloroform, the extract was dried with sodium sulfate and evaporated in vaccuo. The residue was triturated with ether, a small amount of I was filtered off, the filtrate was evaporated, the residue was triturated with 20 ml of petroleum ether and filtered. The remainder was washed with (3 × 5 ml) petroleum ether and dried. Compound IV, 12.05 g (90%), was obtained, mp 100 to 101°C. The substance was highly soluble in a majority of organic solvents and in dilute acids, and insoluble in water and bases. It was crystallized from n-heptane in order to analyze it; mp 100 to 102°C. $\nu_{C=N}$ 1660 cm^{-1}. Found %: C 72.77; H 6.60; and N 13.28. $C_{13}H_{14}N_2O$. Calculated %: C 72.89; C 6.54; and N 13.08.

The hydrochloride of IV melted at 225 to 227°C, and the bitartrate of IV melted at 122 to 124°C.

1-Ethoxy-3H,4,5-dihydroazepino[3,4-b]indole (V) was similarly synthesized, yield 79.5%, mp 117 to 118°C (from n-hexane). Found %: C 73.02; H 6.61; and N 12.15. $C_{14}H_{16}N_2O$. Calculated %: C73.68; H 7.01; and N 12.28.

1,7-Dimethoxy-3H,4,5-dihydroazepino[3,4-b]indole (VII) was synthesized similarly from II through the intermediate VI, mp 142 to 143°C (from ether). Found %: C68.85; H 6.77; and N 11.75. $C_{14}H_{16}N_2O_2$. Calculated %: C 68.85; H 6.51; and N 11.47.

The hydrochloride of VII melted at 182 to 183°C.

1-Hydrazino-3H,4,5-dihydroazepino[3,4-b]indole (IX). To a solution of 1 ml of 85% hydrazine hydrate in 5 ml of alcohol at 20°C was added dropwise with stirring a solution of 1.5 g of IV in 8 ml of alcohol; the mixture was stirred for 2 h and allowed to sit overnight. It was cooled with ice; the precipitate was filtered off, washed with ether, and dried. Compound IX, 1.05 g (70%), was obtained, mp 173 to 175°C. The substance was crystallized from benzene, then from alcohol, for its analysis; needles, mp 177 to 178°C. Found %: C 66.89, 67.17; H 6.80, 7.24; and N 26.20. $C_{12}H_{14}N_4$. Calculated %: C 67.29; H 6.54; and N 26.16.

The hydrochloride of IX consisted of pale yellow crystals, mp 235 to 238°C (from methanol).

Tetrazolo-[5,1-a]azepino]3,4-b]indole (X). To a solution of 2.6 g of IX in 15 ml of 50% acetic acid at -5°C was added dropwise with agitation over a 5 min period a solution of 1.5 g of sodium nitrite in 4 ml of water. The mixture was stirred 1.5 h, the precipitate filtered off, washed with water, and dried. Compound X, 1.85 g (69%), was obtained, mp 290°C. The substance was difficultly soluble in the majority of organic solvents and in dilute acids and bases; it was crystallized from ethyl cellosolve for its analysis; plates, mp 292 to 294°C. Found %: C 63.90; H 4.85; and N 30.62. $C_{12}H_{11}N_5$. Calculated %: C 64.00; H 4.88; and N 31.20.

1-Oxo-2-methyl-1H,2,3,4,5-tetrahydroazepino[3,4-b]indole (XI). To a solution of 4 g of IV in 50 ml of dry benzene was added 2 ml of dimethylsulfate; the mixture was boiled for 10 h. A precipitate formed from the reaction mixture during heating; it was filtered off, washed with ether, and dried. Three grams (75%) of XI was obtained, mp 225 to 228°C (decomp.). The substance was highly soluble in chloroform, more difficultly in alcohol, difficultly soluble in ether and ethyl acetate, and insoluble in dilute acids and bases; it was crystallized from acetone (1:70) for its analysis; needles, mp 240 to 242°C. ν_{NH} 3290 cm^{-1}, ν_{CO} 1610 cm^{-1}. Found %: C 73.04; H 6.51; and N 13.69. $C_{13}H_{14}N_2O$. Calculated %: C 72.89; H 6.54; and N 13.08.

1-Oxo-10-methyl-1H,2,3,4,5-tetrahydroazepino[3,4-b]indole (XII). A suspension of 3 g of I in 12 ml of acetone and 8 ml of 25% sodium hydroxide was heated to the boil and 4.8 ml of dimethyl sulfate was added dropwise over a period of 40 min. The suspension was heated another 30 min; the solids then went into solution.

The reaction mixture was evaporated in vacuo to a volume of 15 to 20 ml, diluted with 20 ml of water, and extracted with chloroform. The extract was dried with sodium sulfate and evaporated to dryness in vacuo, the residue triturated with ether, filtered, washed with ether, and dried. Compound XII, 2.05 g (63.8%),

was obtained, mp 121 to 123°C. The substance was crystallized from water, then from benzene, for the analysis; prisms, mp 126 to 128°C. ν NH 3080, 3220, and 3290 cm^{-1}, ν_{CO} 1660 cm^{-1}. Found %: C 73.00; H 6.67; and N 12.90. $C_{13}H_{14}N_2O$. Calculated %: C 72.89; H 6.54; and N 13.08.

1-Ethoxy-10-methyl-3H,4,5-dihydroazepino[3,4-b]indole (XIII). To triethyloxonium fluoroborate (prepared from 10 g of boron trifluoride etherate in 20 ml of absolute ether and 5 g of epichlorohydrin) in 7 ml of chloroform at 10°C was added with stirring a solution of 7.1 g of XII in 25 ml of chloroform, and stirring was continued for approximately 12 hours. The fluoroborate complex of XIII precipitated out during the reaction; it was filtered off, washed with chloroform, and dried. The weight of the complex came to 2.6 g, mp 210 to 212°C. To a suspension of 4 g of the complex in 15 ml of chloroform at 0°C was added dropwise 8 ml of a 25% aqueous solution of potassium carbonate to a pH of approximately 8.0. After letting it stand (~15 min), the organic layer was separated out, the aqueous layer was extracted with (3 × 20 ml) chloroform, and the extract was dried with sodium sulfate. After drying it, it was evaporated, and the residue was triturated with petroleum ether; 2 g of XIII was obtained, mp 98 to 100°C. The substance was soluble in a majority of organic solvents and in dilute acids, and difficultly soluble in water and dilute bases. It was crystallized from n-hexane (1:80) for its analysis; needles, mp 121 to 122°C. $\nu_{C=N}$ 1660 cm^{-1}. Found %: C 73.87; H 7.12; and N 11.95. $C_{15}H_{18}N_2O$. Calculated %: C 74.38; H 7.43; and N 11.57.

The hydrochloride of XIII melted at 214 to 216°C.

1-Anilino-3H,4,5-dihydroazepino[3,4-b]indole (XIV). To a solution of 4.6 g of III in 40 ml of dry dimethylformamide was added dropwise 10 ml of aniline over a 10 min period; the temperature of the reaction mixture was held at 10 to 15°C by cooling it with ice water. The mixture was boiled for 4 h, evaporated in vacuo, the residue washed with ether, then triturated with water, filtered, and dried. Compound XIV, 2.9 g (81%), was obtained, mp 162 to 164°C.

The substance was soluble in chloroform, more difficultly in other organic solvents, insoluble in water and in dilute bases and acids. Compound XIV was crystallized from benzene (1:70) for its analysis; prisms, mp 164 to 165°C. Found %: C 78.50; H 6.30; and N 15.71. $C_{18}H_{17}N_3$. Calculated %: C 78.54; H 6.18; and N 15.27.

1-(N-Piperidino)-3H,4,5-dihydroazepino[3,4-b]indole Hydrochloride (XV). To a solution of 4.4 g of III in 40 ml of dimethylformamide at 15°C was added dropwise over a 10-min period 10 ml of piperidine; the mixture was boiled for 4 h, and 2.75 g of hydrochloride (XV) was isolated. The substance was crystalized from water (1:20) for its analysis; prisms, mp 155 to 157°C. Found %: C 63.56; H 7.86 Cl 10.94; and N 13.04. $C_{17}H_{21}N_3 \cdot HCl \cdot H_2O$. Calculated %: C 63.45; H 7.46; Cl 11.04; and N 13.06.

1-[β-(3,4-Dimethoxyphenyl)ethylamino]-3H,4,5-dihydroazepino [3,4-b]indole hydrochloride (XVI) was synthesized similarly; yield 86%, mp 221 to 223°C (from methanol). Found %: C 65.97; H 6.45; Cl 8.91; and N 10.82. $C_{22}H_{25}N_3O_2 \cdot HCl$. Calculated %: C 66.08; H 6.25; Cl 8.88; and N 10.57.

Homorutecarpine (XVII). To a solution of 4.5 g of III in 20 ml of dimethylformamide was added dropwise a solution of 10 g of anthranilic acid in 20 ml of dimethylformamide; the mixture was boiled for 4 h, evaporated to dryness in vacuo, the residue triturated with an aqueous sodium hydroxide solution (pH ~ 8.0), filtered, and dried. Compound XVII, 3.7 g (96%), was obtained. The substance was difficultly soluble in a majority of organic solvents, in water, and in dilute acids and bases; it was crystallized from ethyl cellosolve for its analysis; needles, mp 222 to 224°C. Found %: C 75.83; H 4.90; and N 13.87. $C_{19}H_{15}N_3O$. Calculated %: C 75.74; h 4.98; and N 13.95.

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