AZAINDOLE DERIVATIVES

XLVI.* SYNTHESIS AND PHARMACOLOGICAL STUDY OF 1-PHENYL-3-HYDROXYMETHYL-4-METHYL-7-AZAINDOLE AND ITS O-ACYL DERIVATIVES

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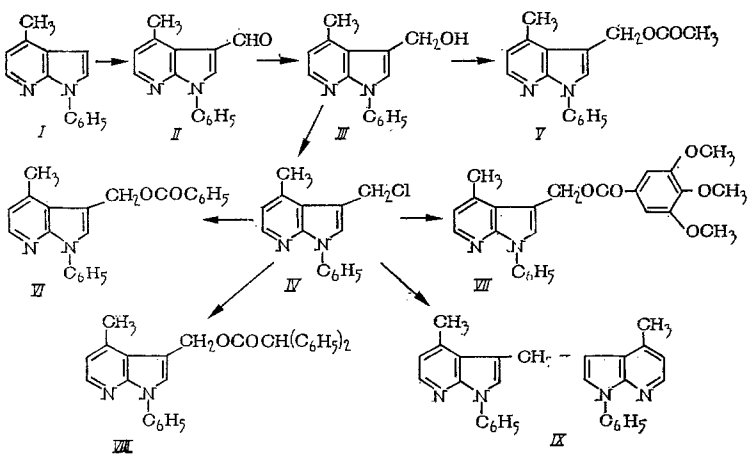
Despite the interest in 7-azaindole derivatives as aza analogs of biologically active indole compounds, literature data on the pharmacological properties of this class of materials are limited. The depressing effect of the unsubstituted 7-azaindole on the central nervous system [2], its effect as a tryptophan inhibitor [3], incorporation of 7-azatryptophan in protein and ribonucleic metabolism [4, 5], reserpine-like activity of 12-azadeserpidine [6], vasodilating effect of 1-(imidazolylalkyl)-7-azaindoles [7], and the α-adrenoblocking effect of 7-azaindolyl-3-acetamidoxime [8], a hypotensive agent [9], have been described. From data of a series of patents, a sedative, antiphlogistic, and stimulating effect characterizes 7-azaindolylalkylamidines, -guanidines, and -amidoximes [10]; a sedative, hypotensive, and anticonvulsion effect characterizes 7-azaindolylalkylpiperazines [11]; an antiphlogistic and analgesic effect characterizes 1-acyl-7-azaindolyl-3-acetic acids [12]; and an antidepressive effect characterizes certain N-alkyl-7-azaindoles [13]. Data are absent in the literature on the pharmacological activity of alcohols of the 7-azaindole series and their O-acyl derivatives.

During a systematic study of 7-azaindole derivatives we developed a convenient method of introducing into position 3 of these compounds the hydroxymethyl group by the Vilsmeier reaction with subsequent reduction of the formed 3-formyl-7-azaindoles with sodium borohydride [14]. Total yields of 3-hydroxymethyl derivatives amount to 75-80%. 1-Phenyl-3-hydroxymethyl-4-methyl-7-azaindole (III), which was transformed into the corresponding O-acyl derivatives (V-VIII), was obtained by the indicated scheme.



* For Communication XLV see [1].

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Acetylation of (III) was achieved by boiling with acetic anhydride and led to 1-phenyl-3-acetoxymethyl-4-methyl-7-azaindole (V) in a yield of 94%. To obtain other O-acyl derivatives (III) was transformed into 1-phenyl-3-chloromethyl-4-methyl-7-azaindole (IV), which was subjected to interaction with sodium salts of the corresponding acids in an anhydrous dimethylformamide medium at 80°. Yields of (VI-VIII) amount to 54-73%. It should be noted that the use of more than three equivalents of sodium salts is necessary for the normal occurrence of reactions in these cases. Upon using a smaller excess a side process of formation of bis(1-phenyl-4-methyl-7-azaindole-3)-methane (IX) is noted, while already at a ratio of (IV) hydrochloride to sodium benzoate of 1 : 1.3 (IX) is the main reaction product, isolated in a yield of 64%. Formation of (IX), together with O-acyl derivatives, also occurs upon reaction of (III) with acid chlorides of the corresponding acids in chloroform or pyridine. We observed earlier an analogous process of molecule symmetrization, but with formation of the simple ether, upon reaction of (IV) with potassium cyanide in an 80% alcohol medium [15]. The synthesized compounds (III), (V-VIII) are weak bases, and their salts (hydrochlorides, phosphates, citrates, sulfates) are partially hydrolyzed upon solution in water with liberation of the free bases. Therefore, for the pharmacological study aqueous solutions of hydrochloride salts were prepared directly before examinations.

The executed investigations showed that (III) in various forms of experimental animals (rats, rabbits, dogs) upon introduction internally and parenterally produces a state, reminiscent of narcosis: animals lie without moving, the ocular slit is constricted, breathing slows down, reflex sensitivity is decreased, reaction to corazol and strychnine is weakened. The initial effective dose of preparation upon intraveneous introduction amounted to 50-75 mg/kg and the lethal dose was 250 mg/kg. Effect develops rapidly and is of brief character. Transfer of stimulation from the nerve to the transverse striated muscles and also passing of stimulation along the vegetative branch of the nervous system are retained. Introduction of O-acyl groups deprives the compounds of pharmacological activity: (V) and (VI) did not produce changes in the behavior and general state of the animals upon injection into the abdominal cavity of white mice in doses of 200-1000 mg/kg. These compounds also did not possess antispasmodic activity.

EXPERIMENTAL

1-Phenyl-3-hydroxymethyl-4-methyl-7-azaindole (III). To 15 ml of distilled dimethylformamide was added at 10° in drops 5 ml of phosphorus oxychloride, and then at room temperature a solution of 10.4 g of 1-phenyl-4-methyl-7-azaindole (I) in 15 ml of dimethylformamide. After maintaining the reaction mixture for 45 min at 35°C it was poured into 100 g of ice and treated with a solution of 9.6 g of sodium hydroxide in 40 ml of water. The obtained suspension was heated to boiling, cooled, and extracted with benzene. After distillation of benzene the 1-phenyl-3-formyl-4-methyl-7-azaindole (II) was washed with 5 ml of a 1 : 1 mixture of diethyl ether and petroleum ether, 100 ml of methanol was added, and then at room temperature with stirring for 20 min 3 g of sodium borohydride was added. After maintaining for 30 min at room temperature with stirring the methanol was distilled in vacuum, 60 ml of water was added to the residue, and (III) was extracted with chloroform. The chloroform extract was dried with potassium carbonate and evaporated in vacuum. We obtained 9 g (76.3%) of (III), mp 124-125° [14].

1-Phenyl-3-acetoxymethyl-4-methyl-7-azaindole (V). A solution of 0.55 g of (III) in 5 ml of acetic anhydride was boiled for 3 h and evaporated in vacuum. We obtained 0.6 g (94%) of (V). Colorless crystals, mp 94-95° (from petroleum ether). The material is highly soluble in the usual organic solvents and poorly soluble in water. Found %: C 72.97; H 5.42; N 10.07. $C_{17}H_{16}N_2O_2$. Calculated %: C 72.75; H 5.73; N 10.00.

Hydrochloride is colorless crystals, mp 117-118°. The material is soluble in alcohol and acetone and is hydrolyzed in water. Found %: C 64.09; H 5.48; Cl 11.01; N 8.95. $C_{17}H_{16}N_2O_2HCl$. Calculated %: C 64.40; H 5.36; Cl 11.20; N 8.84.

1-Phenyl-3-benzoyloxymethyl-4-methyl-7-azaindole (VI). To 0.5 g of the hydrochloride of (IV) [14] was added 0.8 g of sodium benzoate and 3 ml of anhydrous dimethylformamide. The reaction mass was heated for 3 h at 80°, after which it was evaporated in vacuum, 10 ml of water was added, and the mixture was extracted with chloroform. The chloroform solution, dried with potassium carbonate, was evaporated in vacuum. We obtained 0.4 g (73%) of (VI), colorless crystals, mp 135-136° (from alcohol). The material is highly soluble in acetone, benzene, and chloroform, and poorly soluble in ether, alcohol, and water. Found %: C 76.84; H 5.31; N 8.34. $C_{22}H_{18}N_2O_2$. Calculated %: C 77.12; H 5.26; N 8.17.

Analogously, from 0.55 g of (IV) hydrochloride and 1.32 g of sodium diphenylacetate was obtained 0.45 g (55%) of 1-phenyl-3-diphenylacetoxymethyl-4-methyl-7-azaindole (VIII), mp 63-64° (from a 1:1 mixture of petroleum ether and alcohol). Found %: C 77.64; H 6.07; N 6.01. $C_{29}H_{24}N_2O_2 \cdot H_2O$. Calculated %: C 77.32; H 5.77; N 6.22. From 0.5 g of (IV) hydrochloride and 1.32 g of sodium 3,4,5-trimethoxybenzoate was obtained 0.4 g (54%) of 1-phenyl-3-(3,4,5-trimethoxybenzoyloxymethyl)-4-methyl-7-azaindole (VII), mp 111-112° (from alcohol). Found %: C 69.29; H 5.63; N 6.74. $C_{25}H_{24}N_2O_5$. Calculated %: C 69.18; H 5.77; N 6.45.

Bis(1-phenyl-4-methyl-7-azaindolyl-3)-methane (IX). A solution of 0.65 g of (IV) hydrochloride and 0.4 g of sodium benzoate in 7 ml of anhydrous dimethylformamide was heated for 3 h at 80°. The solvent was distilled in vacuum, 10 ml of water was added, and the mixture was extracted with benzene. The benzene solution was dried with potassium carbonate and evaporated in vacuum. We obtained 0.3 g (64%) of (IX), colorless crystals, mp 187-188°. The material is highly soluble in alcohol, acetone, chloroform, and benzene, and is poorly soluble in ether and water. Found %: C 80.73; H 5.73; N 13.55. $C_{29}H_{24}N_4$. Calculated %: C 81.10; H 5.60; N 13.20.

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