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SYNTHESIS AND PHARMACOLOGICAL ACTIVITY OF 1,4-DIAZEPINO[3,2,1-hi]-INDOLES

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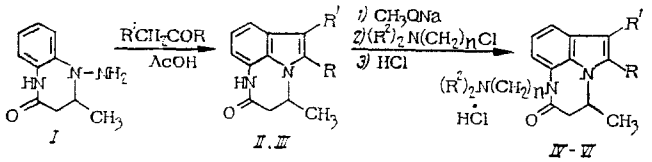
UDC 615.281:547.751].012.1

As a consequence of the interest evoked by condensed heterocyclic systems containing the benzodiazepine fragment as pharmacologically active compounds, we synthesized the previously unknown derivatives of tetrahydro-1-methyl-3-oxo-1,4-diazepino-[3,2,1-hi]indole (II-VI):



I, II, III, IV-VI

I: $R = CH_3$, $R^1 = C_6H_5$; III: $R + R^1 = (CH_2)_4$; IV: $R = CH_3$, $R^1 = C_6H_5$, $R^2 = CH_3$, $n = 3$; V: $R = CH_3$, $R^1 = C_6H_5$, $R^2 = C_2H_5$, $n = 2$; VI: $R = CH_3$, $R^1 = C_6H_5$, $R^2 = C_2H_5$, $n = 3$.

1,4-Diazepino[3,2,1-hi]indoles II and III were synthesized by the Fischer method. The starting compound 1-amino-2-methyl-4-oxo-2,3,4,5-tetrahydro(1,5)benzodiazepine, obtained according to the scheme previously described in [3], was condensed with methyl benzyl ketone. p-Toluenesulfonic acid was used as catalyst.

Alkylation of the N-sodium derivative of compound II with dialkylaminoalkyl chlorides gave N-dialkylaminoalkyl derivatives of diazepino-[3,2,1-hi]indole IV-VI.

The structure of the synthesized compounds was confirmed by their IR and UV spectra. In the IR spectrum of compounds II and III bands of the stretching vibrations of the lactam carbonyl group are observed at 1680-1665 cm^{-1}. The absorption bands in the 3200-3160 cm^{-1}

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Translated from Khimiko-farmatsevtichekii Zhurnal, Vol. 23, No. 2, pp. 155-156, February, 1989. Original article submitted November 18, 1987.

0091-150X/89/2302-0113$12.50

region correspond to the stretching vibrations of the NH group. In the IR spectra of compounds IV-VI, a decrease in the absorption frequency of the carbonyl group to 1670-1650 cm^{-1} and the absence of absorption bands characteristic for the NH group is observed. The UV spectra of the diazepino-[3,2,1-hi]indole derivatives are characterized by the presence of three absorption maxima at 215, 247, 310 nm.

The investigation was carried out under the direction of Professor A. N. Grinev.

EXPERIMENTAL CHEMICAL

The IR spectra were run on a "Perkin-Elmer 599" spectrophotometer in mineral oil, the UV spectra on "Perkin-Elmer 575" spectrophotometer in alcohol and dioxane. The melting points of the compounds were determined on a "Boëtius" microheating apparatus.

1,9-Dimethyl-8-phenyl-3-oxy-(1,4)-1,2,3,4-tetrahydrodiazepino-[3,2,1-hi]indole (II). A 5.26 g portion (0.039 mole) of methyl benzyl ketone is added to 7.5 g (0.039 mole) of 1-amino-2-methyl 4-oxo-2,3,4,5-tetrahydro-1,5-benzodiazepine. The mixture is stirred at room temperature for 15 min. Then, 100 ml of acetic acid and 6.7 g (0.039 mole) of p-toluenesulfonic acid are added. The reaction mixture is stirred at 70-75°C for 3 h, then cooled and poured onto ice. White crystals precipitate. The precipitate is filtered, washed with water, and dried. Yield of compound II, 4.6 g (42%), mp 256-258°C (from methanol). $C_{19}H_{18}N_2O$.

1-Methyl-3-oxo-8,9-trimethylene-(1,4)-1,2,3,4-tetrahydrodiazepino[3,2,1-hi]indole (III) is obtained in a similar way as compound II. The quantities used for the synthesis were 7.5 g (0.039 mole) of 1-amino-2-methyl-4-oxo-2,3,4,5-tetrahydro-1,5-benzodiazepine, 3.87 g (0.039 mole) of cyclohexanone, 6.7 g (0.039 mole) of p-toluenesulfonic acid and 100 ml of acetic acid. Yield of compound III, 3.2 g (32.3%), mp 290-292°C (from a methanol–dioxane mixture). $C_{16}H_{18}N_2O$.

1,9-Dimethyl-8-phenyl-3-oxo-4-dimethylaminopropyl(1,4)-1,2,3,4-tetrahydrodiazepino[3,2,1-hi]indole Hydrochloride (IV). A 4.32 ml portion (0.01 mole) of a sodium methylate solution, obtained from 46 g of sodium and 460 ml of methanol, is added to a solution of 2.89 g (0.01 mole) of II in 50 ml of dry dimethylformamide. The reaction mixture is heated at 70°C for 1 h, and then methanol is distilled off in vacuo. To the residue, 2.43 g (0.02 mole) of dimethylaminopropyl chloride are added, and the reaction mixture is boiled for 3 h, and then cooled, and poured into water. The oil that separates is extracted with ether. The ether extract is dried over magnesium sulfate and evaporated in vacuo to a volume of 15-20 ml, and the material is deposited on a column (diameter 15 mm, length 150 mm) with aluminum oxide. The elution is carried out with ether. The eluate is evaporated in vacuo to a volume of 50-70 ml. To the remaining ether solution of base IV, an ether solution of hydrogen chloride is added to pH 4.0, the precipitated white crystals are filtered, washed with ether, and dried. Yield of compound IV, 0.9 g (22%), mp 141-143°C (from an acetone–alcohol mixture) $C_{24}H_{29}N_3O \cdot HCl$.

1,9-Dimethyl-8-phenyl-3-oxo-4-diethylaminoethyl(1,4)-1,2,3,4-tetrahydrodiazepino[3,2,1-hi]-indole Hydrochloride (V) is obtained in a similar way as compound IV. For the synthesis, 2.89 g (0.01 mole) of II, 50 ml of dry dimethylformamide, 4.32 g of sodium methylate solution, and 2.7 g (0.02 mole) of diethylaminoethylchloride are used. Yield of compound V, 2.5 g (53%), mp 221-223°C (from an acetone–alcohol mixture) $C_{25}H_{31}N_3O \cdot HCl$.

1,9-Dimethyl-8-phenyl-3-oxo-4-diethylaminopropyl(1,4)-1,2,3,4-tetrahydrodiazepino[3,2,1-hi]-indole Hydrochloride (VI) is obtained in a similar way as compound IV. For the synthesis, 2.89 g (0.01 mole) of II, 50 ml of dry dimethylformamide, 4.32 g of sodium methylate solution, and 2.99 g (0.02 mole) of diethylaminopropyl chloride are used. Yield of compound VI, 1.3 g (29%), mp 198-200°C (from an acetone–alcohol mixture) $C_{26}H_{33}N_3O \cdot HCl$.

EXPERIMENTAL PHARMACOLOGICAL

In view of the structural similarity of the synthesized derivatives IV-VI to the antidepressant azepindole [1], the compounds were studied with respect to the antidepressant activity indexes (effect on the hypothermal action of reserpine and ptosis, effect on the hypothermal action of l-DOPA), on the phenamine effect, and the soporific action of hexenal in mice by intravenous administration (60 mg/kg). The compounds were also studied with respect to the anxiolytic activity indexes in mice [2] and anorexigenic activity indexes [4] in mice and rats. In experiments on narcotized cats, the effect of the compounds on the arterial pressure, respiration and the third eyelid tonus was studied.

All the compounds studied are slightly toxic. The LD_{50} for compounds IV, V, VI is 567, 417 and 570 mg/kg, respectively, after oral administration.

The investigation showed that compounds IV-VI do not have the effect characteristic for compounds with antidepressant activity. In doses of 10-80 mg/kg, they either did not influence the depressant effect of reserpine (hypothermia and ptosis) or somewhat intensified it. All the compounds studied in doses of 40-80 mg/kg had no influence the phenamine effects, nor did they change the hyperthermal action of l-DOPA. Compounds IV and VI somewhat intensified the soporific effect of hexenal in mice when administered intraveneously (60 mg/kg). Thus, in the control group the duration of the soporific action was 14.8 (14.0-16.0) min, whereas during a preliminary introduction of compounds IV, V, it was 21.0 (10-32.0) min.

Comparative studies showed that compounds IV-VI have a weak anorexigenic activity in mice and rats when administered subcutaneously or orally.

The examination of anxiolytic properties of the compounds in experiments on mice shows that in this respect, the compounds are considerably inferior to diazepam.

In experiments on narcotized cats, compounds IV, I, and VI in doses of 1-10 and 20 mg/kg caused a short-term (3-5 min) hypotensive reaction (40-60 mm Hg), and did not change the third eyelid tonus.

Thus, with respect to the antidepressant, anorexigenic and anxiolytic activities that were studied, the synthesized compounds were found to be slightly active.

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SYNTHESIS AND ANTIINFLAMMATORY ACTIVITY OF 5-PHENACYLIDENE-2-IMINO-4-OXAZOLIDONES

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UDC 615.276:547.787.1].012.1

Compounds containing a 2-imino-4-oxazolidone ring exhibit antispasmolytic [12], psychostimulant [11], and other types of biological action [10].

We have synthesized and pharmacologically examined compounds of this series containing a phenacylidene substituent in position 5 of the oxazolidene ring. These compounds were synthesized by recycling 5-aryl-2,3-dihydrofuran-2,3-diones (I) upon reacting with cyanamides [1]. The reaction proceeds readily with a non-substituted cyanamide as well as with monoalkyl- and monoarylcyanamides with the formation of 5-phenacylidene-2-imino-4-oxazolidones (IIa-j). Recycling of the furan ring is not possible if there is a steric tert-butyl group in the mono-substituted cyanamide. The reaction proceeds only if the furandiones I undergo thermolysis [2] in which case the aroylketenes generated in the first stage of the process enter the $[4\pi+2\pi]$-cycloaddition reaction with the formation of 6-aryl-2-tert-butylamino-1,3-oxazine-4-ones (IVa-d).

The yields and mp of the synthesized compounds are given in Table 1.

The IR-spectra of compounds IIc-j have peaks due to vibrations of the N–H groups (3250-3300 cm^{-1}), C=O in position 4 (1725-1735 cm^{-1}), the C=N bond (1678-1681 cm^{-1}) in the phenacylidene substituent (1621-1635 cm^{-1}). Compounds IIa, b have carbonyl signals at position

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Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 23, No. 2, pp. 157-160, February, 1989. Original article submitted November 24, 1987.

0091-150X/89/2302-0115$12.50