SYNTHESIS AND BIOLOGICAL ACTIVITY OF DERIVATIVES OF 3-OXO-8,9-DIPHENYL-1,2,3,4-TETRAHYDRO-1,5-DIAZEPINO[1,2,3,-ef]INDOLE

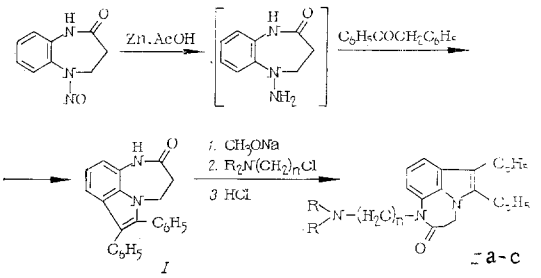
A. N. Grinev, E. V. Lomanova,
G. N. Pershin, and O. V. Okinshevich

UDC 615.281:547.751].012.1.07

In connection with the high biological activity of benzodiazepine derivatives [1] we have effected the synthesis and have studied the antimicrobial activity of new derivatives of 1,2,3,4-tetrahydro-1,5-diazepino[1,2,3-ef]indole.

The 3-oxo-8,9-diphenyl-1,2,3,4-tetrahydro-1,5-diazepino[1,2,3-ef]indole (I) was synthesized by the method of Fischer. The starting material, 1-amino-2,3,4,5-tetrahydrobenzo-1,5-diazepin-4-one, was obtained by reduction of the nitroso derivative [2] with zinc in acetic acid and was condensed without isolation with desoxybenzoin. p-Toluenesulfonic acid was used as catalyst.

N-Dialkylaminoalkyl derivatives of diazepino[1,2,3-ef]indole (IIa-c) were obtained by alkylating the sodium derivative of compound (I) with dialkylaminoalkyl chlorides.



IIa: R = C_7H_5, n = 2 IIb: R = CH_3, n = 3 IIc: R = C_2H_5, n = 3

The structures of the obtained compounds were confirmed by IR and UV spectra. Bands were observed in the IR spectrum of compound (I) for the stretching vibrations of a carbonyl group in the region of 1670 cm^{-1}. Bands for the absorption of an amide NH group were observed at 3060 and 3200 cm^{-1} which disappeared from the spectra of the N-substituted derivatives (IIa-c). In the IR spectra of compounds (IIa-c) the bands for the stretching vibrations of the carbonyl group were shifted to 1650 cm^{-1}. The UV spectra of the diazepinoindole derivatives were characterized by the presence of three absorption maxima at 215, 235, and 315 nm (log ε 4.51, 4.39, and 4.11).

EXPERIMENTAL CHEMISTRY

The IR spectra of the obtained compounds were taken in Nujol on a UR-20 spectrometer (East Germany) and UV spectra on Hitachi EPS-3T and Perkin-Elmer 575 instruments in dioxane.

3-Oxo-8,9-diphenyl-1,2,3,4-tetrahydro-1,5-diazepino[1,2,3-ef]indole (I). Zinc dust (32.5 g: 0.5 mole) was added in small portions at a temperature not exceeding 25°C with stirring to a suspension of 1-nitroso-4-oxo-2,3,4,5-tetrahydrobenzo-1,5-diazepine (19.1 g: 0.1 mole) in glacial acetic acid (250 ml) with ice cooling. The solid, consisting of unreacted zinc and zinc acetate, was filtered off and washed on the filter with acetic acid (50 ml). Desoxybenzoin (9.6 g: 0.05 mole) and p-toluenesulfonic acid (8.6 g: 0.05 mole) were added to the combined filtrate (solution of 1-amino-4-oxo-2,3,4,5-tetrahydrobenzo-1,5-diazepine in acetic acid). The reaction solution obtained in this way was heated with stirring on a boiling water bath for 2 h, then cooled with ice, poured into water (500 ml), the solid was filtered off, and washed with water. Yield of (I) was 9 g (54.5%), mp 310-311°C (from dioxane). Found, %: C 81.52; H 5.29, N 8.27. $C_{23}H_{28}N_2O$. Calculated, %: C 81.63, H 5.36, N 8.28.

S. Ordzhonikidze All-Union Scientific-Research Institute for Pharmaceutical Chemistry, Moscow. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 18, No. 4, pp. 454-456, April, 1984. Original article submitted April 12, 1983.

 0091-150X/84/1804-0272$08.50

TABLE 1. Antimicrobial Activity of Compounds (I, IIa-c) (minimum suppressing dose, μg/ml)

Microorganisms	Compound			
	I	IIa	IIb	IIc
Staphylococcus aureus 209-P	>240	3,9	3,9	3,9
Streptococcus haemolyticus 295	>250	3,9	3,9	15,6
Corinebacterium cliph. gravis PW	>250	15,6	3,9	15,6
Bac. anthracoides 1312	>250	3,9	7,8	125
Mycobacterium tuberculosis	>500	1	62,5	62,5
Microsporum lanosum	>500	62,5	15,6	250
Trichophyton gypseum	>500	15,6	62,5	250
Achorion Schonleini	>500	15,6	31,2	250
Actynomyces albus	>500	500	7,8	125
Candida albicans	>500	62,5	62,5	500

3-Oxo-4-diethylaminoethyl-8,9-diphenyl-1,2,3,4-tetrahydro-1,5-diazepino[1,2,3-ef]indole Hydrochloride (IIa). A solution (11.3 ml) of sodium methylate, obtained from sodium (92 g) and methanol (920 ml), was poured into a solution of (I) (6.76 g: 0.02 mole) in dry dimethylformide (100 ml). The reaction mixture was evaporated in vacuum to half the initial volume and cooled. A solution of diethylaminoethyl chloride (5.4 ml: 0.04 mole) was added to the obtained solution of sodium derivative and the reaction mixture was boiled for 3 h, then poured into ice water. The precipitated oil was extracted with ether (100 ml). The extract was passed through a column of aluminum oxide to purify it from resin. The ether layer was evaporated to small volume *in vacuo*, cooled, and acidified with an ether solution of HCl to pH 4.0. The precipitate was filtered off. The yield of (IIa) was 4.8 g (51%), mp 220-222°C (from a mixture of acetone–alcohol). Found, %: C 73.30; H 6.80; N 8.89; Cl 7.25. $C_{29}H_{32}N_3 \cdot OCl$. Calculated, %: C 73.48; H 6.80; N 8.86; Cl 7.48.

3-Oxo-4-dimethylaminopropyl-8,9-diphenyl-1,2,3,4-tetrahydro-1,5-diazepino[1,2,3-ef]indole hydrochloride (IIb) was obtained in a similar manner to compound (IIa). For the experiment (I) (6.76 g: 0.02 mole), dry dimethylformamide (100 ml), sodium methylate solution (8.64 ml), and dimethylaminopropyl chloride (4.86 g: 0.04 ml) were taken. Yield of (IIb) was 6 g (64%), mp 212-214°C (with decomposition, from a mixture of acetone–alcohol). Found, %: C 71.30; H 6.70; N 9.04; Cl 7.55. $C_{28}H_{30}N_3OCl$. Calculated, %: C 71.70; H 6.66; N 8.96; Cl 7.56.

8,9-Diphenyl-3-oxo-4-diethylaminopropyl-1,2,3,4-tetrahydro-1,5-diazepino[1,2,3-ef]indole Hydrochloride Hydrate (IIc). This was obtained similarly to compound (IIa). Compound (I) (3.38 g: 0.01 mole), dry dimethylformamide (50 ml), sodium methylate solution (4.32 ml), and diethylaminopropyl chloride (2.99 g: 0.02 mole) were taken for the experiment. The yield of (IIc) was 2.5 g (50%) mp 190-192°C (with decomposition, from an alcohol–acetone mixture). Found, %: C 72.30; H 7.02; N 8.74; Cl 7.22. $C_{30}H_{34}N_3OCl \cdot {}^1/_2H_2O$. Calculated, %: C 72.49; H 7.09; N 8.45; Cl 7.13.

EXPERIMENTAL BIOLOGY

The antimicrobial activity of the synthesized compounds was studied with twofold serial dilutions in liquid nutrient medium [3] in relation to four forms of gram-positive, five forms of gram-negative bacteria, an acid stable mycobacterium tuberculosis of strain H37RV, and five forms of pathogenic molds. Compound (I) proved to be practically inactive and did not suppress the growth of microorganisms at a concentration of 250-500 μg/ml. The remaining compounds possessed marked antimicrobial properties. As is evident from Table 1 compounds (IIa, b) were characterized by the greatest activity in relation to gram-positive bacteria and the pathogenic molds. Compound (IIa) possessed the greatest antitubercular activity, the minimum tuberculostatic concentration of which proved to be 1 μg/ml in Sauton's medium protein loading.

The studied substances were practically devoid of activity in relation to gram-negative bacteria (*Escherichia coli*, *Salmonella typhosa*, *Proteus vulgaris*, *Bacillus pyocyaneus*), their minimum suppressing concentration in experiments with these microorganisms exceeded 250 μg/ml.

Compound (IIa) was tested in an experimental skin microspore model in guinea pigs as a 1% oil emulsion which was applied once daily for three weeks. The compound proved to have no irritant action on the skin but its therapeutic effect was insignificant (the index of effectiveness in comparison with a control group of untreated animals was 6%).

LITERATURE CITED

1. A. V. Bogatskii, S. A. Andronati, and N. Ya. Golovenko, Tranquillzers (1,4-Benzodiazepines and Related Structures) [in Russian], Kiev (1980).
2. W. Ried and G. Ürlass, Chem. Ber., 86, 1101 (1953).
3. G. N. Pershin (ed.), Methods of Experimental Chemotherapy [in Russian], 2nd edn., Moscow (1971).

EFFECT OF THE STRUCTURE OF SOME CHEMICAL COMPOUNDS ON ANTIALCOHOL ACTIVITY

M. M. Borisov, V. V. Avidon, and T. P. Mufazalova

UDC 615.246.9.03:616.89-008.441.13-085/.015.11

One of the urgent tasks of modern pharmacology and the chemistry of medicinals is the creation of effective pharmacological preparations for the prophylaxis and treatment of alcoholism. The purposeful search for antialcohol preparations currently calls for correlation of the available data on the chemistry and pharmacology of both preparations being used clinically and compounds that have only been investigated experimentally. The methods of modern theoretical chemistry make it possible to uncover a set of structural features that provide a certain profile of the pharmacological effect. This approach is valuable not only for planning the synthesis but also for the purposeful selection of preparations. The aim of the present communication was to find some new approaches to the search for potential antialcohol preparations.

Preparations that affect alcohol addiction experimentally belong to various classes of chemical of chemical compounds. It has been observed that antialcohol substances are encountered with highest frequency in two series of compounds, viz., indole and phenylethylamine derivatives. These classes of compounds also include neuromediators of the central nervous system: dopamine, noradrenaline, and serotonin.

Despite the fact that the literature contains information regarding the effect of a number of representatives of these classes of compounds on alcohol addiction experimentally, the relatively small number of such compounds did not make it possible to establish a relationship between the chemical structure and the antialcohol activity.

In recent years chemists and pharmacologists have been conducting a great deal of research dealing with the synthesis of and the experimental search for new original compounds that are capable of having an effect on various stages in the development of alcoholism. With these ends in mind, we have made a study of new compounds synthesized in various institutions in our country and delivered to the Scientific-Research Institute for BIKhS for the investigation of their antialcohol activity. The effect of a number of compounds on alcohol addiction in rats and mice was investigated in the laboratory of psychopharmacology by the methods that we described in [1]. Approximately 30 compounds among those tested for this form of activity were derivatives of indole and phenylethylamine and were also similar to them in structure. The fundamental experimental data for 29 compounds, as well as the literature data (for 23 compounds), made it possible to undertake an analysis of the relationship between the chemical structure of a compound and its antialcohol activity.

The data were processed with a computer by means of the packet of TOPOLOG programs in the IOS of the Academy of Sciences of the Latvian SSR; the adequacy of the methods used was taken into account. Representatives of two classes of chemical compounds, viz., phenylethylamine and indole derivatives (see Table 1), were primarily selected for analysis.

In the course of the analysis we uncovered structural fragments that can be divided into three groups: 1) fragments that are encountered only in the case of compounds that suppress alcohol addiction; 2) structural fragments that are encountered only in inactive compounds; 3) fragments that are encountered in both active and inactive compounds. We also discovered

---

Scientific-Research Institute for BIKhS, Moscow Region. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 18, No. 4, pp. 457-461, May, 1984. Original article submitted June 16, 1982.

 0091-150X/84/1804-0274$08.50