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SYNTHESIS AND CNS ACTION OF 1-AZAFLUORENE DERIVATIVES

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UDC 615.214.21.012.1+615.214.21:015.4:612.82

In connection with the fact that tetrahydro-1-azafluorenes have been shown to be CNS stimulants [4], we believed it would be of interest to investigate the CNS effects of other derivatives of 1-azafluorene, including the aromatic derivatives.

In the present work we studied the neurotropic activity of 1-azafluorenone (I) [6] and its hydrochloride (II) 1-azafluorenol (III) [4], iodomethylates of 1-azafluorene and 1-azafluorenone (IV, V) [4, 5], 9-(4-nitrobenzylidene) (VI), 9-(4-bromobenzylidene)- (VII), and 9-(3,4-dimethoxybenzylidene)-1-azafluorenes (VIII) [3], tosylhydrazone (IX), and thiosemicarbazone of 1-azafluorenone (X), semicarbazones of 1- (XI), 3- (XII), and 4-azafluorenones (XIII) as well as 1-methyl-1H-indeno [2, 1-b]pyridine (XIV) [2]. Compounds IX-XIII were synthesized for the first time by reacting tosylhydrazone, thiosemicarbazide, and semicarbazide with the corresponding azafluorenones.

The neurotropic activity of compounds I-XIV was identified with the aid of the tests described in [1]. The results of the toxicity studies and several pharmacological effects of the azafluorene derivatives are presented in Table 1. In addition, a detailed study was made of the substances' action on spontaneous animal behavior.

An analysis of the obtained data showed that all of the investigated derivatives of 1-azafluorene have some kind of neurotropic activity. It was found that the compounds of the first group (I-V) act as stimulants. This brings the biological activity spectrum of sub-

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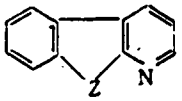
 0091-150X/87/2106-0408$12.50 © 1988 Plenum Publishing Corporation



I — XI

I: Z = >C=O; II: hydrochloride I; III: Z = >HCOH; IV: Z = >CH_2 iodomethylate V: iodomethylate I; VI: Z = >C=$CHC_6H_4NO_2$-*n*; VII: Z = >C=CHC_6H_4Br-*n*; VIII: Z = >C=$CHC_6H_3(OMe)_2$-*m*, *n*; IX: Z = >C=$NNHSO_2C_6H_4Me$-*n*; X: Z = >C=$NNHCSNH_2$; XI: Z = >C=$NNHCONH_2$.

stances I-V close to that of the earlier investigated partially hydrogenated derivatives of 1-azafluorene [4]. The iodomethylates IV and V are distinguished by their high level of toxicity.

The introduction of an arylidene fragment in position $C_{(9)}$ of 1-azafluorene significantly affects toxicity and the manifestation of psychotropic activity in compounds of the second group (VI-VIII). The 9-arylidene-1-azafluorenes VI-VIII are only slightly toxic (LD_{50} > 1000 mg/kg), and in contrast to the previous group of compounds, exhibit antidepressant activity. They have a combination of stimulant and sedative properties which can potentiate both the effects of hexenal and apomorphine simultaneously. The replacement of substituents in the aryl radical of the benzylidene fragment (substitution of a bromine or methoxy group by a nitro group) has little effect on their spectrum of biological activity.

With respect to chemical structure tosylhydrazone IX is related to the third group of compounds containing a =N-NHT group of position $C_{(9)}$. However, pharmacologically, it is closer to the group of arylidene derivatives that exhibit antidepressant activity.

The group of semicarbazones X-XIII was found to have a definite structure-biological action relationship. From a comparison of the activity of compounds X and XI, it can be seen that thiosemicarbazone X is less toxic and has a lower stimulating effect. The replacement of a sulfur atom by an oxygen atom not only increases toxicity but also changes the type of activity. Compound XI was found to have a sedative type psychotropic activity. A change in the nitrogen position in the azafluorene fragment of the semicarbazones (transition from 1- to 3-azafluorene) led to a loss of sedative action and the emergence of weak stimulating properties in compound XII. In the case of semicarbazone XIII, that change led to a complete disappearance of psychotropic activity.

Anhydrous alkalization of XIV, obtained by the action of alkaly on the salt IV, produced a weak sedative effect and moderate toxicity.

Thus, the results of our biological tests allowed to ascertain a relationship between neuropharmacological effects and structure in the series of the synthesized derivatives of azafluorene.

EXPERIMENTAL

IR spectra were recorded on a UR-20 (GDR) instrument in KBr pellets. Mass spectra were read on a MX-1303 instrument.

1-Azafluorenone tosylhydrazone (IX). A solution of 0.6 g (3 mmoles) of tosylhydrazide in 3 ml of ethanol was added to a solution of 0.5 (3 mmoles) of 1-azafluorenone in 15 ml of ethanol, and boiled for 20 min. After the mixture was cooled, the resultant precipitate was separated, washed with alcohol, and dried. Yield 0.6 g (62%) of tosylhydrazone in the form of bright yellow crystals, mp 148-150°C (from alcohol). IR spectrum, ν_{max}, cm^{-1}: 1625 (C=N), 1348, 1325, and 1170 (S=O). Found, %: C 65.2; H 4.4; N 11.9, M^+ 349 (mass spectrometrically). $C_{19}H_{15}N_3SO_2$. Calculated, %: C 65.3; H 4.3; N 12.0; M 349.

1-Azafluorene-9-one thiosemicarbazone (X). A warm solution of 1 g (5.5 mmoles) of 1-azafluorenone in 30 ml of ethanol was added to a solution of 1.1 g (12 mmoles) of thiosemicarbazide in a mixture of 6 ml of water and 4 ml of ethanol. Several drops of an alcohol HCl solution were added (to pH 4.0-5.0), and the mixture was agitated for 1 h at 55°C. The

TABLE 1. Several Neuropharmacological Effects and Acute Toxicity of 1-Azafluorene Derivatives

Compound	LD_{50}, mg/kg	Effect change, % of control			
		Hexenal (duration of sleep)	Apomorphine (stereotyping duration)	Arecoline (duration of hyperkinesis)	Corazole (duration of tremor)
I	250	−20	+11	+41	+30
II	200	−15	+7	+38	+17
III	350	+6	+18	+23	+120
IV	20	−40	+20	−23	+117
V	20	−35	+10	−15	+194
VI	>1000	+65	+25	−5	+17
VII	>>1000	+66	+35	−5	−7
VIII	>1000	+58	+15	+5	+166
IX	760	+62	+30	+20	+50
X	1000	−36	+16	+2	−54
XI	750	+67	−16	−30	+94
XII	350	−8	+4	−8	+30
XIII	400	+8	+4	−23	+74
XIV	75	+60	+1	+50	+16

Note. The predominant neuropharmacological effect in compounds I-V, X, and XII was stimulation, antidepression in compounds VI-VIII, sedation in compounds XI and XIV, and no effect in XIII.

precipitate was separated, washed with water, ethanol, and ether, and dried. Yield 1.2 g (86%) of thiosemicarbazone in the form of yellow crystals, mp 228-230°C (from ethyl acetate). Found, %: C 61.4; H 4.1; N 22.2; M^+ 254 (mass spectrometrically). $C_{13}H_{10}N_4S$. Calculated, %: C 61.4, H 3.9, N 22.1, M 254.

1-Azafluorene-9-one semicarbazone (XI). A 2-ml portion of water, 1 g (10 mmoles) of semicarbazide HCl, and 1.6 g of sodium acetate were added to a solution of 1 g (5.5 mmoles) of 1-azafluorenone in 15 ml of ethanol. The mixture was then heated for 15 min and agitated on a water bath, and then cooled. The resultant precipitate was separated and washed with water, and dried. Yield 1.1 g (85%) of semicarbazone in the form of pale yellow crystals, mp 220-221°C (from methanol). IR spectra, ν_{max}, cm^{-1}: 3100-3500 (broadened band, CONH and $CONH_2$), 1720 (C=O), 1625 (C=N). Found, %: C 65.3; H 4.3; N 23.1; M^+ 238 (mass spectrometrically). $C_{13}H_{10}N_4$. Calculated, %: C 65.6; H 4.2; N 23.5; M 238.

3-Azafluorene-9-one semicarbazone (XII) was obtained in the same way. Yield 90%, in the form of yellow crystals, mp 148-150°C (from an ethanol–water mixture). Found, %: C 65.4; H 4.4; N 23.3; M^+ 238 (mass spectrometrically). $C_{13}H_{10}N_4O$. Calculated, %: C 65.6, H 4.2, N 23.5, M 238.

4-Azafluorene-9-one semicarbazone (XIII) was obtained in the same way as semicarbazone XI. Yield 91%, yellow crystals, mp 243-244°C (from an ethanol–water mixture). Found, %: C 65.4) H 4.2) N 23.4) M^+ 238 (mass spectrometrically). $C_{13}H_{10}N_4O$. Calculated, %: C 65.6; H 4.2; N 23.5; M 238.

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SYNTHESIS OF 4-PIPERIDONE DERIVATIVES AND STUDY OF THEIR PHARMACOLOGICAL PROPERTIES

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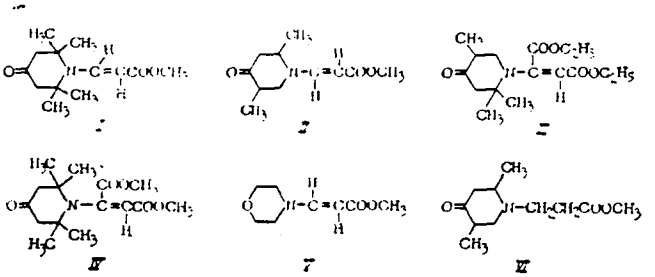
UDC 615.214.2:547.824].012.1

We synthesized a group of 4-piperidone derivatives (I-VI), and studied them with respect to certain pharmacological activity parameters.



EXPERIMENTAL CHEMICAL PART

The PMR spectra were run on a Bruker WM-400 spectrometer (^{1}H, 400 MHz, TMS), mass spectra on a M-80a Hitachi spectrometer (Japan) at a ionizing voltage of 12 and 70 eV, and IR spectra in $CHCl_3$ on a Specord 75 IR spectrophotometer in $CHCl_3$ in KBr cuvettes. The melting points were determined on a RNMX-05 apparatus. In the syntheses, absolute solvents and freshly prepared and freshly purified reagents were used.

Methyl Ester of trans-N-β-(2,2,6,6-Tetramethyl-4-oxo-1-piperidyl)acrylic Acid (I). A 1-g portion (12 mmoles) of methyl propiolate is added at 20°C to a solution of 1.7 g (11 mmoles) of 2,2,6,6-tetramethyl-4-oxopiperidine in 10 ml of MeOH. After 12 days, the crystals that separate are filtered, washed with CCl_4 (3 × 5 ml), and dried in vacuo. The yield of I is 1.03 g. Another 1.1 g of I are isolated from the mother liquor. The overall yield is 2.13 g of I (81%) of white needlelike crystals, mp 144-145°C. Found, %: C 65.47; H 8.80; N 5.64. $C_{13}H_{21}NO_3$. Calculated, %: C 65.22; H 8.86; N 5.85. M^+ m/z 239. IR spectrum (in CCl_4), ν, cm^{-1}: 1595 (C=C), 1690 and 1720 (C=O). PMR spectrum ($CDCl_3$), δ, ppm: 1.43 (Me), 2.60 (CH_2), 3.63 (MeO), 4.85 (H_α, $^3JH_\alpha H_\beta$ 14.0), 7.73 (H_β).

Methyl Ester of trans-N-β-(2e,5e-Dimethyl-4-oxo-1-piperidyl)-acrylic Acid (II). A solution of 1.66 g (13 mmoles) of 2.5-dimethyl-4-oxopiperidine in 5 ml of Et_2O is added at 20°C to a solution of 1.1 g (13 mmoles) of methyl propiolate in 10 ml of Et_2O. After 12 h, ether is evaporated, and the residue is distilled in vacuo. The yield of II is 1.7 g (80%), viscous liquid, bp 150-151°C (2 mm Hg). Found, %: N 6.72. $C_{11}H_{17}NO_3$. Calculated, %: N 6.63. IR spectrum (molecular layer), ν, cm^{-1}: 1605 (C=C), 1690 and 1715 (C=O). Mass spectrum at 70 eV, m/z (relative intensity in %) M^+ 211 (100), 196 (88.2), 180 (89.1), 168 (22.0), 152 (46.0), 141 (19.1), 140 (63.7), 112 (16.9), 110 (20.6), 82 (57.1). Mass spectrum at 12 eV: M^+ 211 (100), 196 (51.1), 180 (30.1), 168 (10.4), 152 (20.5), 141 (10.1), 140 (10.2), 112 (5.8) 84 (24.6). PMR spectrum ($CDCl_3$), δ, ppm: 1.14 (MeCN, $^3J_{MeCH}$ 7.08), 1.37 [MeCCO, $^3J_{MeCH}$ 6.59, 2.28 and 2.70 CH_2 (AB), $^2J_{H,H}$ 14.89, $^3JH_AHCMeCO$ 5.13 and $^3JH_BHCMe_{CO}$ 7.08, 2.60 ($HCMe_N$) 3.07 and 3.76 CH_2CO (AB), $^2J_{H,H}$ 13.67, $^3JH_AHCMe$ 8.79, 3.81 ($HCMe_{CO}$), 3.68 (MeO), 4.80 ($H_\alpha C=$, $^3J_{H,H}$ 13.18), 7.58 ($H_\beta C=$)].

Scientific-Research Institute for the Biological Testing of Chemical Compounds, Moscow District. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 21, No. 6, pp. 675-677, June, 1987. Original article submitted September 20, 1986

0091-150X/87/2106-0411$12.50 1988 Plenum Publishing Corporation