SEARCH FOR NEW DRUGS

SYNTHESIS AND NEUROTHROPIC PROPERTIES OF 1-(2,6-DICHLOROPHENYL)-3-AMINO(ALKOXY)METHYLENEINDOLIN-2-ONE

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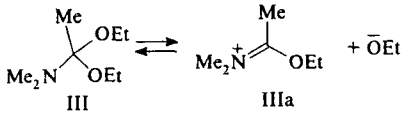
The presence of an active methylene unit in position 3 of the oxindole molecule provides for the ability of condensation of various reagents at this site. Previously we have demonstrated that dimethylformamide diethylacetal smoothly reacts with 1-(2,6-dichlorophenyl)indolin-2-one (Ia) and its derivatives with the formation of the corresponding enamines, the latter being the initial reagents for the synthesis of transamination products and condensed indoles [1 – 3]. In this work we have used a series of lactim esters, including O-methylvalerolactims (II, $n = 1$), O-methylcaptolactims (II, $n = 2$), orthoformic ester, and N,N-dimetylacetamide (III), as condensing agents.

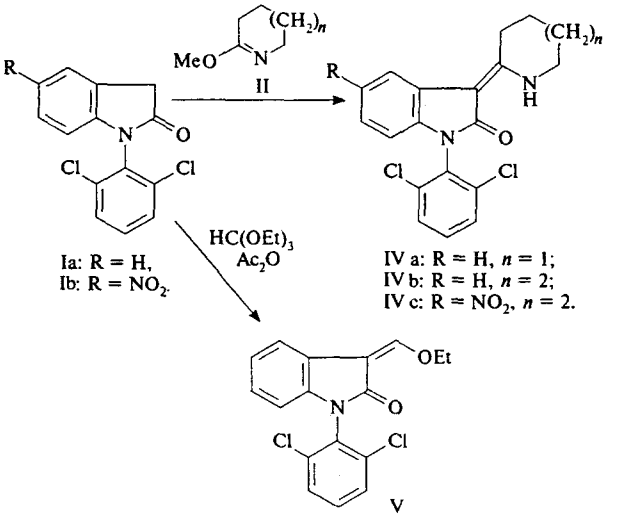
It was found that, in accordance with the commonly accepted notions [4], the amidacetals are much more reactive than the lactim esters and orthoesters. Indeed, the condensation process with amidacetals proceeds readily even at room temperature, while the interaction with lactim esters II requires boiling in the absence of solvent, and the reaction with orthoformic ester is possible on boiling in the presence of acetic anhydride. This order of reactivity is quite understandable since the behavior of amidacetals in the case under consideration is characterized by equilibrium involving ambidentate cations and alkoxy anions:



III IIIa

Here, the anion acts as an acceptor of the 3-H proton of the indolinone cycle and the IIIa cation serves an electrophilic agent. The weakly basic lactim esters II are much less effective in splitting protons at position 3 of the indolinone cycle. In the orthoester – acetic anhydride system, the equilibrium $CH(OEt_3) + Ac_2O \leftrightarrows \overset{+}{C}H(OEt)_2 + AcOEt + \overline{O}Ac$ is shifted noticeably toward the left part.

Heating indolinone Ia or its 5-nitro derivative (Ib) with lactim esters II leads to azacycloalkylidene derivatives (IVa – IVc), and the reaction of Ia with orthoformic ester – to ethoxymethyleneindolinone (V).



The interaction of indolinone Ia with acetal III exhibits certain special features [5, 6]. In contrast to the condensation with DMF acetal [1, 2], this reaction may proceed by different pathways. The process conducted in a nonpolar solvent (benzene) yields a mixture of ethoxy- (VI) and dimethylamino (VII) ethylidene derivatives, whereas only compound

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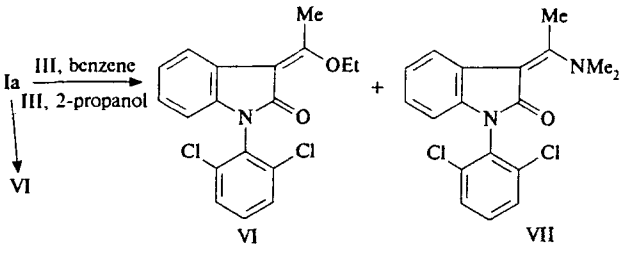
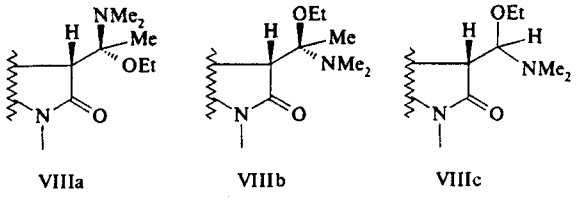
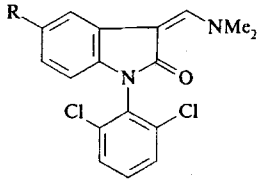
VI can be isolated upon the reaction in a polar solvent (2-propanol):



In principle, the formation of dimethylaminoethylideneindolinone VII must be more advantageous than the yield of ethoxyethylideneindolinone VI because the OEt group serves as a better leaving group as compared to Me_2N. The fact that compound VI yet appears can be explained by considerable spatial hindrances related to intermediates (VIIIa, VIIIb).

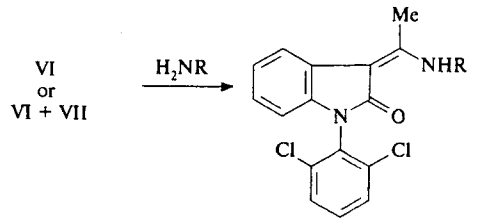


The S-*trans* mutual arrangement of the H-C^3 proton and EtO group in VIIIa favors the cleavage of alcohol with the formation of compound VII, while in VIIIb (with the S-*trans* arrangement of the H-C^3 proton and NMe_2 group) the elimination of dimethylamine leads to ethoxyethylidene derivative VI. Note that in a much less spatially constrained intermediate VIIIc, formed in the reactions of Ia and Ib with DMF acetal, the free rotation about the exocyclic C–C bond provides the ability of forming exclusively dimethylaminomethylene derivatives (IXa, IXb) [1, 2]:



IXa: R = H,
IXb: R = NO_2.

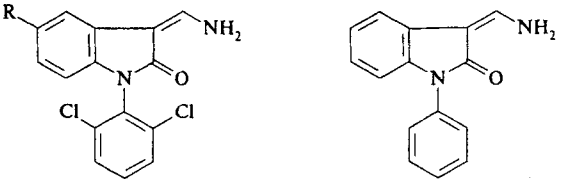
Both ethoxy (VI) and dimethylamino (VII) ethylideneindolinone derivatives readily interact with amines to form the corresponding enamines (Xa, Xb).



Xa: R = H,
Xb: R = CH_2Ph.

The proposed structures of indolinone VII and its derivatives Xa and Xb were confirmed by ^1H NMR data (see the experimental part below), A comparison of the spectrum of compound VII to that of the indolinone IXa reported previously [1] shows evidence of the same situation concerning the double C=C bond: both spectra contain lines corresponding to the *E*- and *Z*-isomers. At the same time, there is a certain difference between the spectra of compounds VII and IXa: the ethylidene derivative VII gives three signals due to methyl groups of the $N(CH_3)_2$ substituent. Retarder rotation about the ordinary C–N bond, manifested in the latter spectrum, reflects a conjugation of the dimethylamino group to the enamine double bond, which is greater in ethylidene derivatives than in methylene derivatives (a similar phenomenon was reported in [7, 8]). This interpretation is also confirmed by a considerable shift of the IR absorption band of the amide carbonyl toward lower frequencies in the spectrum of compound VII ($\nu_{max} = 1635\ cm^{-1}$) compared to compound IXa ($\nu_{max} = 1675\ cm^{-1}$).

The oxindole derivatives, including 3-aminomethylene ones, are known to possess a significant pharmacological activity [1]. Therefore, we have studied the activity of compounds V – VII, Xa, Xb, XIa, and XII synthesized in this work, together with the activity of indolinones IXb, XIb, and XIc obtained previously.



XIa: R = H;
XIb: R = NO_2;
XIc: R = NHAc.

XII

Compound XIa (most active among the 3-aminomethyleneindolin-2-ones studied) introduced perorally in the dose range 12.5 – 200 mg/kg prevented convulsions induced in test animals by the maximum electroshock (ED_{50} = 35 mg/kg) and by the injections of bicuculline (ED_{50} = 86 mg/kg) or 3-mercaptopropionic acid (ED_{50} = 110 mg/kg). At the same time, compound XIa in the dose range studied did not prevent the convulsions induced by corazole, although it increased 1.5 – 2 times the latent period before the onset of clonic convulsions.

3-Aminomethyleneindolinone XIa also exhibited a pronounced antihypoxic effect (with ED_{50} = 80 mg / kg on the hypoxic hypoxia model) and produced analgesic action (ED_{50} = 35 mg / kg for the "vinegar" convulsions and 200 mg / kg for the hot plate test).

Compound XIa was also found to possess a general depressant activity, being capable of inducing hypodynamia, ataxia, myorelaxation, and potentiating the action of thiopental sodium.

Indolinones VII and XII prevented the convulsions induced by the maximum electroshock (ED_{50} = 36 and 34 mg / kg, respectively), but did not protect against the corazole effect. Compound XII, in contrast to VII, also prevented the convulsive effect of bicuculline (ED_{50} = 70 mg / kg).

Indolinones VII and XII exhibited a weak analgesic action in the hot plate test.

The other synthesized compounds showed no evidence of neurotropic activity.

Compounds XIa, VII, and XII possess low toxicity (LD_{50} > 1000 mg / kg for peroral administration).

Thus, the results of our pharmacological tests show that some of the synthesized compounds possess anticonvulsive properties and produce antihypoxic and moderate analgesic action.

EXPERIMENTAL CHEMICAL PART

The IR spectra of synthesized compounds were measured on a Perkin-Elmer spectrophotometer using samples prepared as vaseline oil suspensions. The mass spectra were obtained using a Finnigan SSQ 710 mass spectrometer with direct injection of samples into the ion source (electron impact ionization energy, 70 eV; ionization chamber temperature, 180°C). The ^{1}H NMR spectra were measured on the Varian XL-200 and Unity Plus 400 spectrometers using DMSO-d_6 as the solvent and TMS as the internal standard. The course of reactions was monitored and the purity of products checked by TLC on Silufol UV-254 plates with the spots visualized by UV illumination.

1-(2,6-Dichlorophenyl)-3-(piperidin-2-ylidene)indoli n-2-one (IVa). A mixture of 0.5 g (1.7 mmole) of indolinone Ia and 1 ml of O-methylvalerolactim (II, n = 1) [9] was boiled for 1 h 45 min and cooled. The precipitate was separated by filtration and washed with petroleum ether to obtain 0.61 g of compound IVa. The yields and physicochemical properties of compounds IVa – IVc are listed in Table 1.

1-(2,6-Dichlorophenyl)-3-(hexahydroazepin-2-yliden e)indolin-2-one (IVb). Compound IVb was obtained similarly to compound IVa from a mixture of 4.5 g (16.1 mmole) of indolinone Ia and 35 ml of O-methylcaprolactim (II, n = 2) boiled for 1 h.

1-(2,6-Dichlorophenyl)-3-(hexahydroazepin-2-yliden e)-5-nitroindol in-2-one (IVc). Compound IVb was obtained similarly to compound IVa from a mixture of 5.0 g (15.4 mmole) of nitroindolinone Ib and 20 ml of O-methylcaprolactim (II, n = 2) boiled for 1 h.

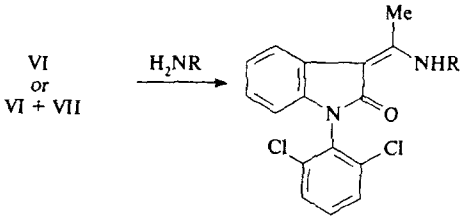
1-(2,6-Dichlorophenyl)-3-ethoxymethyleneindolin-2-one (V). A mixture of 38.7 g (138.9 mmole) of indolinone Ia, 96 ml of orthoformic ether, and 154 ml acetic anhydride was boiled for 9 h, cooled, and evaporated in vacuum. The residue was triturated with 70 ml of heptane, after which the precipitate was filtered and washed with heptane and ethanol to obtain 34.64 g (57%) of compound V; m.p., 161 – 162°C (ethanol); $C_{17}H_{13}Cl_2NO_2$; mass spectrum (m/z): M^+, 333; ^{1}H NMR spectrum (δ, ppm): 7.13, 7.23 (2m, 2H, H-$C^{5,6}$), 6.28 (m, 1H, H-C^7), 7.55 – 7.75 (m, 4H, H-C^4, H-$C^{3',4',5'}$), 7.93 (s, 1H, CHOEt), 1.40 (t, 3H, J 7.6 Hz, OCH_2CH_3), 4.45 (q, 2H, J 7.6 Hz, OCH_2CH_3).

1-(2,6-Dichlorophenyl)-3-(1-ethoxyethylidene)indolin -2-one (VI). To a suspension of 10.0 g (35.9 mmole) of indolinone Ia in 40 ml of 2-propanol was added 10.0 g (62.0 mmole) of dimethylacetamide acetal and the mixture was stirred for 1.5 h at 20°C. Then was added 6 g (37.2 mmole) of acetal III and the stirring was continued for another 2.5 h. The precipitate was filtered and washed with 10 ml of 2-propanol to obtain 6.67 g (53%) of compound VI; m.p., 209 – 210°C (CH_3CN – DMF, 10 : 1), 207 – 208°C (methanol; $C_{18}H_{15}Cl_2NO_2$; mass spectrum (m/z): M^+, 347; ^{1}H NMR spectrum (δ, ppm): 7.06 (m, 2H, H-$C^{5,6}$), 6.31 (m, 1H, H-C^7), 7.53 – 7.80 (m, 4H, H-C^4, H-$C^{3',4',5'}$), 2.73 (s, 3H, CH_3), 1.46 (t, 3H, OCH_2CH_3), 4.42 (q, 2H, OCH_2CH_3); IR spectrum (ν_{max}, cm^{-1}): 1680, 1620, 1610.

1-(2,6-Dichlorophenyl)-3-(1-ethoxyethylidene)indolin -2-one (VII). A suspension of 4.72 g (13.4 mmole) of ethoxyethylidene derivative VI in 40 ml of methanol saturated with dimethylamine was stirred for 48 h at 20°C and cooled to 2°C. The precipitate was filtered to obtain 4.45 g (95%) of compound VII; m.p., 157.5 – 159.5°C (methanol – DMF, 3 : 1); $C_{18}H_{16}Cl_2N_2O$; mass spectrum (m/z): M^+, 346; ^{1}H NMR spectrum, (δ, ppm): 7.29 (bs, 1H, H-C^4), 6.84, 6.93 (2m, 2H, H-$C^{5,6}$), 6.25 (bd, 1H, J 8 Hz, H-C^7), 7.48 – 7.72 (3H, A_2B-system, H-$C^{3',4',5'}$), 2.65 (bs, 3H, CH_3), 3.16, 3.17, 3.23 (s, s, bs, 6H, NMe_2).

1-(2,6-Dichlorophenyl)-3-(1-aminoethylidene)indolin -2-one (Xa). To a suspension of 0.5 g (1.7 mmole) of indolinone Ia in 2 ml of benzene was added 0.5 ml (2.8 mmole) of acetal III and the mixture was kept for 18 h at 20°C. The precipitate was filtered to obtain 0.35 g of a mixture of compounds VI and VII, 1 : 9 (^{1}H NMR data). This mixture was stirred for 4 h in a saturated methanol solution of ammonia and evaporated in vacuum to obtain 0.3 g (53%) of compound Xa; m.p., 219°C (ethyl acetate); $C_{16}H_{12}Cl_2N_2O$; mass spectrum (m/z): M^+, 318; ^{1}H NMR spectrum, (δ, ppm): 6.99 (m, 1H, H-C^4), 6.95 (m, 2H, H-$C^{5,6}$), 6.33 (m, 1H, H-C^7), 7.36 – 7.63 (3H, A_2B-system, H-$C^{3',4',5'}$), 9.17, 8.32 (bs, 2H, NH_2), 2.47 (s, 3H, CH_3).

1-(2,6-Dichlorophenyl)-3-(1-benzylaminoethylidene) indolin-2-one (Xb). A mixture of compounds VI and VII (0.35 g, see the synthesis of compound Xa), 0.23 ml (2.1 mmole) of benzylamine, and 5 ml of 2-propanol was boiled for 8 h and cooled. The precipitate was filtered and



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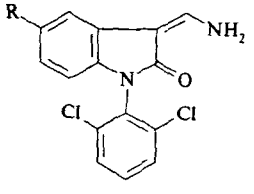

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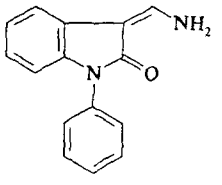

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H NMR spectrum in DMSO-d_6 (δ, ppm)

.88, 6.97 (2m, 2H, H-$C^{5,6}$), 6.32 (m, 1H, H-C^7), 7.54 – 7.71
$^{3',4',5'}$), 1.84 (m, 4H, 4",5"-CH_2), 3.00 (t, 2H, 3"-CH_2), 3.45
2 (bs, 1H, NH)

.91, 6.97 (2m, 2H, H-$C^{5,6}$), 6.33 (m, 1H, H-C^7), 7.5 – 7.8
$^{3',4',5'}$), 1.61, 1.79, 3.27, 3.58 (4m, 10H, 4",5", 6", 7"-CH_2),
t, 1H, NH)

38 (q, 1H, H-C_6), 6.60 (d, 1H, H-C^7),
system, H-$C^{3',4',5'}$), 1.63, 1.83, 3.18, 3.66 (4bs, 10H,
.63 (bs subspl. into t, 1H, NH)

ticonvulsive activity was studied on a model of s induced by maximum electroshock (MES) and al agents corazole (130 mg / kg, s.c.), 3-mercapto- icid (3-MPA) (0.32 mg / kg, i.p.), and bicuculline kg, i.v.). The effects were evaluated by determinber of animals with convulsions, the onset of conid the loss of the test animals; the protective effect sed as ED_{50}.

algesic activity of the synthesized compounds was the models of chemical and thermal irritation. The ritation (vinegar convulsions test) was induced by teal injections of 0.25 ml of a 1% acetic acid solu- The response to thermal irritation was studied by t mice onto a metal plate of a Ugo Basile anal- Italy) heated to 56°C [15]. The antihypoxic activ- died on the model of hypoxic hypoxia with hyperimals placed into hermetically sealed compart- effect was evaluated as a percentage increase in (with respect to control).

st compounds were introduced at a dose of 0.1 or o perorally 40 min before testing in the form of s in a 1% carboxymethylcellulose solution with additives.

/LEDGMENTS

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NCES

covich, V. A. Azimov, S. Yu. Ryabova, et. al., *Khim.-*., **29**(2), 22 – 27 (1995).

ovich, S. Yu. Ryabova, L. M. Alekseeva, and V. G. Gra- *n.-Farm. Zh.*, **29**(12), 44 – 48 (1995).

ovich, S. Yu. Ryabova, L. M. Alekseeva, and V. G. Gra- *n.-Farm. Zh.*, **30**(9), 35 – 39 (1996.

anik, *Khim. Geterotsikl. Soed.*, No. 6, 762 – 781 (1992).

lovko, N. P. Solov'eva, G. A. Bogdanova, et al., *Khim. ikl. Soed.*, No. 6, 1190 – 1198 (1991).

6. A. V. Komkov, A. M. Sakharov, V. S. Bogdanov, and V. A. Dorokhov, *Izv. Akad Nauk SSSR*, Ser. Khim., No. 7, 1324 – 1328 (1995).
7. J. Shvo and H. Shanan-Atidi, *J. Am. Chem. Soc.*, **91**(24), 6683 – 6689 (1969).
8. J. Shvo and H. Shanan-Atidi, *J. Am. Chem. Soc.* **91**(24), 6689 – 6696 (1969).
9. V. G. Granik, A. M. Zhidkova, N. S. Kuryatov, et al., *Khim. Geterotsikl. Soed.*, No. 11, 1532 – 1535 (1973).
10. R. Sarges, H. R. Howard, B. K. Koe, and A. Weissman, *J. Med. Chem.*, **32**(2), 437 – 444 (1989).
11. T. G. Svensson and C. R. Thime, *Psychopharmacology*, **14**, 157 – 163 (1969).
12. N. W. Dunham and T. A. Mija, *J. Am. Pharm. Assoc. Sci.*, **46**, 208 – 209 (1957).
13. C. A. Winter, *J. Pharmacol. Exp. Ther.*, **94**, 7 – 11 (1948).
14. P. Taberner, *Eur. J. Pharmacol.*, **39**, 305 (1976).
15. G. Woolfe and A. MacDonald, *J. Pharmacol. Exp. Ther.*, **80**, 300 – 308 (1944).