ANTICONVULSANT ACTIVITY OF OXINDOLE DERIVATIVES AND 1,3-DISUBSTITUTED INDOLES

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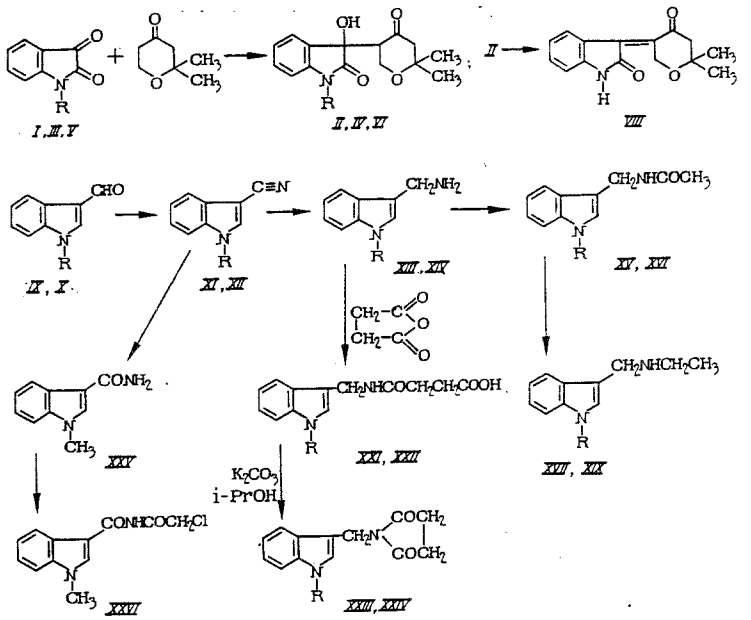
In order to find new compounds that have significant anticonvulsant activity (ACA), we have synthesized heterocyclic derivatives of 1-substituted oxindoles as well as some derivatives of 1-substituted 3-aminomethylindoles containing substituents in the side chain.



R=H(I,II), CH_3(III, IV, IX, XI, XIII, XV, XVII, XVIII, XXI, XXIII),morpholinomethyl (V, VI, VII), $CH_2C_6H_5$ (X, XII, XIV, XVI, XIX, XX, XXII, XXIV).

From the literature [10] and according to our findings [1] derivatives of 3-acetonyl-3-hydroxy-1-substituted oxindoles are known to display some ACA.

Condensation of isatins I, III, and V [5, 6] with 2,2-dimethyl-4-tetrahydropyranone in alcohol in the presence of a catalytic quantity of diethylamine gave tetrahydropyranonyl derivatives of oxindoles (II, IV, and VI). Compound VIII was obtained by dehydration of II.

1-substituted 3-N-ethylaminomethylindoles XVII and XIX were synthesized by acetylation of 1-substituted 3-aminomethylindoles XIII and XIV, obtained by reduction of the corresponding nitriles XI and XII, followed by reduction.

Condensation of aminomethylindoles with succinic anhydride gave the corresponding succinic acid monoamides XXI and XXII, cyclization of which resulted in the formation of succinimide derivatives XXIII and XXIV. 1-Methylindole-3-carboxylic acid chloroacetamide (XXVI) was also synthesized.

EXPERIMENTAL (CHEMISTRY)

IR spectra were recorded on a UR-20 spectrophotometer (GDR) in petrolatum oil. Mass spectra were recorded on an MX-1320 instrument with direct introduction of sample into the

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ionization zone at electron ionizing energy of 60-65 eV and at a temperature of 20-30°C below the melting point of the compounds. PMR spectra were recorded on a Varian T-60 spectrometer, with TMS as internal standard. TLC was performed on Silufol UV-254 plates in the solvent system chloroform–acetone; iodine vapor was used for developing. Melting points were determined on a Boetius (GDR) microheating stage.

3-Hydroxy-3-(2,2-dimethyl-4-tetrahydropyranonyl)oxindole (II). A mixture of 2.94 g (0.02 mole) of isatin, 3.2 g (0.025 mole) of 2,2-dimethyl-4-tetrahydropyranone [5], and 2 ml of dry diethylamine in 40 ml of absolute ethanol was agitated at room temperature (28-30°C) for 48 h. The crystals that formed were filtered off and washed with hexane or ether. Compound II was obtained (4.7 g) in 85.4% yield, mp 192-193°C (from ethanol), R_f 0.47 (chloroform–acetone, 2:1). Found: C 65.20; H 6.70; N 5.50%. $C_{15}H_{17}NO_4$. Calculated: C 65.44; H 6.22; N 5.09%. Mass spectrum,* m/z: 275 M^+ (10), 147 (100), 128 (50). IR spectrum, ν_{max}, cm^{-1}: 3350 (OH), 3280 (NH), 1720 (C=O), 1620 (arom.). PMR spectrum (CD_3OD), δ, ppm: 1.1 s (3H, CH_3); 1.4 s (3H, CH_3); 2.4 d (2H, CH_2); 3.6 (CH); 4.4 d (2H, OCH_2); 7.0-7.6 m (5H, arom. and indole NH).

1-Methyl-3-hydroxy-3-(2,2-dimethyl-4-tetrahydropyranonyl)oxindole (IV). From 1-methylisatin [5] using the method described above was obtained IV in 72% yield, mp 153-154°C (from ethanol), R_f 0.56 (chloroform–acetone, 2:1). Found: C 66.20; H 6.30; N 4.40%. $C_{16}H_{19}NO_4$. Calculated: C 66.43; H 6.61; N 4.84%. Mass spectrum, m/z: 289 M^+ (100), 151 (80), 128 (40). IR spectrum, ν_{max}, cm^{-1}: 3370 (OH), 1730, 1720 (C=O). PMR spectrum (CD_3OD), δ, ppm: 1.2 s (3H, CH_3); 1.4 (3H, CH_3); 2.25 d (2H, CH_2); 3.2 s (3H, NCH_3); 3.45 m (1H, CH); 4.44 m (2H, OCH_2); 6.8-7.50 m (4H, arom.).

1-Morpholinomethyl-3-hydroxy-3-(2,2-dimethyl-4-tetrahydropyranonyl)oxindole (VI). From 1-morpholinomethylisatin [6] using the method desribed above was obtained VI in 83.7% yield, mp 170-171°C (from ethanol), R_f 0.60 (chloroform–acetone, 1:1). Found: C 64.58; H 6.90; N 7.02%. $C_{20}H_{26}N_2O_5$. Calculated: C 64.15; H 6.99; N 7.48%. Mass spectrum, m/z: 374 M^+ (30), 275 (25), 128 (15), 100 (100). IR spectrum, ν_{max}, cm^{-1}: 3365 (OH), 1720 (broad band, C=O), 1620 (arom.).

Hydrochloride of VI (VII). Had mp 160-161°C (from ethanol). Found: C 57.92; H 6.09; N 7.12; Cl 8.78%. $C_{20}H_{27}ClN_2O_5$. Calculated: C 58.47; H 6.60; N 6.82; Cl 8.63%.

3-(2,2-Dimethyltetrahydropyranyliden-4-one)oxindole (VIII). Compound II (1.5 g, 0.005 mole) in 8 ml of acetic acid was heated for 2 h on a steam bath with a catalytic quantity of HCl [7]. As II dissolved the solution took on a reddish brown tint. After cooling, the reaction mixture was poured onto ice (100 g). The crystals that formed were filtered off, washed with water, and dried. Compound VIII was obtained (1 g) in 73.5% yield, mp 187-189°C (from ethanol), R_f 0.42 (chloroform–acetone, 2:1). Found: C 69.44; H 5.50; N 6.00%. $C_{15}H_{15}NO_3$. Calculated: C 70.02; H 5.88; N 5.44%. Mass spectrum, m/z: 257 M^+ (100), 201 (60), 173 (16), 145 (26), 117 (16). IR spectrum, ν_{max}, cm^{-1}: 3275 (N–H), 1725-1650 (C=O), 1620 (arom.). PMR spectrum ($CDCl_3$), δ, ppm: 1.25 m (6H, $2CH_3$); 2.6 s (2H, CH_2); 4.25 s (2H, OCH_2); 6.9-7.3 m (5H, arom. and indole NH).

1-Methylindole-3-carbonitrile (XI). A mixture of 15.9 g (0.1 mole) of 1-methylindole-3-aldehyde [7] (IX), 11.8 g (0.17 mole) of hydroxylamine hydrochloride, and 78 ml of pyridine was heated to 85°C, and 55 ml of acetic anhydride was added dropwise over a period of an hour at this temperature with agitation. The reaction mixture was boiled for another 2 h at the same temperature and after cooling was poured on to crushed ice (500 g). The crystals that formed were filtered off and washed with water. Compound XI was obtained (13.5 g) in 85.5% yield, mp 55-56°C (from methanol), R_f 0.7 (chloroform–acetone, 1:1). Found: C 77.10; H 5.43; N 17.80%. $C_{10}H_8N_2$. Calculated: C 76.90; H 5.16; N 17.94%. Mass spectrum, m/z: 156 M^+ (100), 128 (10), 114 (12). IR spectrum, ν_{max}, cm^{-1}: 2228 (C≡N).

1-Benzylindole-3-carbonitrile (XII). This was obtained by the method described above from 1-benzylindole-3-aldehyde [8] (X) in 94% yield, mp 68-69°C (from methanol), R_f 0.68 (chloroform–acetone, 1;1). Found: C 83.10; H 5.35; N 11.67%. $C_{16}H_{12}N_2$. Calculated: C 82.73; H 5.20; N 12.06%. IR spectrum, ν_{max}, cm^{-1}: 2220 (C≡N).

1-Methyl-3-aminomethylindole (XIII). To an ether suspension prepared from 3.8 g (0.1 mole) of $LiAlH_4$ in 150 ml of dry ether was added dropwise a solution of 6.24 g (0.04 mole)

*The figures in front of the brackets indicate the ion masses, those in the brackets are the peak intensities as a percentage of the maximum peak.

of 1-methylindole-3-carbonitrile in 20 ml of dry THF. The reaction mixture was heated for 12 h. After the usual treatment, 5.2 g of XIII was obtained in 81.2% yield. Found: C 74.63; H 7.00; N 17.30%. $C_{10}H_{12}N_2$. Calculated: C 74.96; H 7.54; N 17.48%. Mass spectrum, m/z: 160 M^+ (100), 145 (20), 129 (40). IR spectrum, ν_{max}, cm^{-1}: 3350, 3290 (amino NH), 1610 (arom.).

Hydrochloride of (XIII). Had mp 155-156°C (from ethanol). Found: Cl 18.50%. $C_{10}H_{13}N_2Cl$. Calculated: Cl 18.02%.

1-Benzyl-3-aminomethylindole (XIV). This was obtained in 90.5% yield from XII by the method described above. Found: C 81.08; H 6.60; N 11.50%. $C_{16}H_{16}N_2$. Calculated: C 81.32; H 6.82; N 11.86%. Mass spectrum, m/z: 235 M^+ (100), 135 (100), 205 (10). IR spectrum, ν_{max}, cm^{-1}: 3375, 3295 (amino NH), 1610 (arom.).

Hydrochloride of (XIV). Had mp 172°C (from ethanol). Found: Cl 13.03%. $C_{16}H_{17}ClN_2$. Calculated: Cl 12.99%.

1-Methyl-3-acetylaminomethylindole (XV). A mixture of 1.6 g (0.01 mole) of XIII, 1.02 g (0.01 mole) of acetic anhydride, and 10 ml of benzene was heated for 12 h then after cooling was poured into ice-cold water (50 ml). The aqueous solution was extracted with ether, the ether layer was washed with a 10% solution of $NaHCO_3$ and with water, and after drying over Na_2SO_4 the solvent was evaporated. Compound XV was obtained (1 g) in 50% yield, mp 108-109°C (from ethanol), R_f 0.42 (chloroform–acetone, 1:1). Found: C 70.90; H 6.50; N 13.40%. $C_{12}H_{14}N_2O$. Calculated: C 71.26; H 6.97; N 13.85%. IR spectrum, ν_{max}, cm^{-1}: 3310 (amide NH), 1640 (CO), 1580 (arom.).

1-Benzyl-3-acetylaminomethylindole (XVI). This was obtained in 50.3% yield from XIV by the method described above, mp 130-131°C (from ethanol), R_f 0.73 (chloroform–acetone, 1:1). Found: C 77.04; H 6.99; N 10.02%. $C_{18}H_{18}N_2O$. Calculated: C 77.66; H 6.51; N 10.06%. IR spectrum, ν_{max}, cm^{-1}: 3300 (amide NH), 1650 (CO), 1610 (arom.).

1-Methyl-3-ethylaminomethylindole (XVII). To an ether suspension of 0.91 g (0.024 mole) of $LiAlH_4$ and 100 ml of dry ether was added a solution of 4.04 g (0.02 mole) of XV in 20 ml of dry THF. The reaction mixture was boiled for 18 h. After the usual treatment, 2.5 g of XVII was obtained, yield 66%. Found: C 76.81; H 8.88; N 14.50%. $C_{12}H_{16}N_2$. Calculated: C 76.55; H 8.57; N 14.88%. Mass spectrum, m/z: 188 M^+ (25), 144, 115 (100). IR spectrum, ν_{max}, cm^{-1}: 3300 (amino NH), 1610, 1590 (arom.).

Hydrochloride of XVII (XVIII). Had mp 153-154°C (from ethanol). Found: C 63.70; H 8.15; N 12.61; Cl 16.30%. $C_{12}H_{17}ClN_2$. Calculated: C 64.08; H 7.71; N 12.45; Cl 15.76%.

1-Benzyl-3-ethylaminomethylindole (XIX). This was obtained in 75.9% yield by reduction of XVI. Found: C 81.60; H 7.55; N 10.09%. $C_{18}H_{20}N_2$. Calculated: 81.77; H 7.62; N 10.59%. Mass spectrum, m/z: 264 M^+ (52), 220 (100), 129 (10), 91 (24). IR spectrum, ν_{max}, cm^{-1}: 3300 (amino NH), 1610, 1590 (arom.).

Hydrochloride of XIX (XX). Had mp 181-183°C (from ethanol). Found: C 71.57; H 6.80; N 8.91; Cl 12.09%. $C_{18}H_{21}ClN_2$. Calculated: C 71.86; H 7.04; N 9.31; Cl 11.78%.

Succinic Acid 1-Methyl-3-indolylmethylamide (XXI). To a solution prepared from 1.6 g (0.01 mole) of XIII in 20 ml of benzene was added 1 g (0.01 mole) of succinic anhydride in small portions at room temperature (20-25°C). The reaction mixture was then boiled for 12 h. The precipitate that formed was filtered off and washed with ether. Compound XXI was obtained (2 g), yield 76.9%, mp 166-167°C (from ethanol), R_f 0.33 (chloroform–acetone, 1:1). Found: C 64.99; H 5.83; N 11.30%. $C_{14}H_{16}N_2O_3$. Calculated: C 64.60; H 6.19; N 10.76%. Mass spectrum, m/z: 260 M^+ (80), 159 (48), 144 (100). IR spectrum, ν_{max}, cm^{-1}: 3345 (amide NH), 1710, 1675 (C=O), 1635, 1620 (arom.).

Succinic Acid 1-Benzyl-3-indolylmethylamide (XXII). From XIV was obtained XXII by the method described above, yield 70%, mp 159-169°C (from ethanol), R_f 0.53 (chloroform–acetone), 1:1). Found: C 71.16; H 6.12; N 7.90%. $C_{20}H_{20}N_2O_3$. Calculated: C 71.41; H 5.99; N 8.33%. Mass spectrum, m/z: 336 M^+ (41), 318 (17), 235 (30), 220 (45), 145 (17), 91 (100). IR spectrum, ν_{max}, cm^{-1}: 3390 (amide NH), 1715 shld, 1685 (C=O), 1620, 1590 (arom.).

1-Methyl-3-(1-succinimidomethyl)indole (XXIII). A mixture of 1.64 g (0.0063 mole) of XXI and 1.13 g (0.0082 mole) of dry potassium carbonate in 100 ml of dry isopropyl alcohol was heated for 12 h. The alcohol was then distilled off, and the residue was dissolved in water and extracted with ethyl acetate. The extract was washed with water and dried; after evaporation of the solvent, 1.1 g of XXIII was obtained, yield 70%, mp 145°C (from ethanol),

R_f 0.62 (chloroform–acetone, 2:1). Found: C 69.40; H 5.80; N 12.04%. $C_{14}H_{14}N_2O_2$. Calculated: C 69.40; H 5.82; N 11.56%. Mass spectrum, m/z: 242 M^+ (100), 157 (45), 144 (95). IR spectrum, ν_{max} cm^{-1}: 1780, 1710, 1680 shld (imide), 1580 (arom.). PMR spectrum ($CDCl_3$), δ, ppm: 2.45 s (4H, CH_2CH_2), 3.85 s (3H, NCH_3), 4.70 s (2H, NCH_2); 7.2-7.8 m (5H, arom.).

1-Benzyl-3-(1-succinimidomethyl)indole (XXIV). This was obtained in 78% yield from XXII by the method described above, mp 162°C (from ethanol), R_f 0.33 (chloroform–acetone, 1:1). Found: C 76.00; H 5.57; N 9.00%. $C_{20}H_{18}N_2O_2$. Calculated: C 75.45; H 5.69; N 8.80%. Mass spectrum, m/z: 318 M^+ (L00), 239 (45), 220 (40), 91 (100). IR spectrum, ν_{max}, cm^{-1}: 1785, 1715, 1685 shld (imide), 1570 (arom.). PMR spectrum ($CDCl_3$), δ, ppm: 2.44 s (4H, CH_2CH_2); 4.82 s (2H, NCH_2); 5.15 s (2H, benzyl CH_2); 7.2-7.8 m (10H, arom.).

1-Methylindole-3-carboxylic Acid Amide (XXV). A solution of 5 g (0.032 mole) of XI in 50 ml of a 10% solution of sodium hydroxide was boiled for 4 h. After cooling, the crystals that had formed were filtered off and washed with water until there was a neutral reaction. Compound XXV was obtained (4.5 g) in 80.7% yield, mp 183-184°C (from methanol), R_f 0.45 (chloroform–acetone, 1:1). Found: C 69.40; H 5.54; N 15.80%. $C_{10}H_{10}N_2O$. Calculated: C 68.88; H 5.78; N 16.08%. Mass spectrum, m/z: 174 M^+ (66), 158 (100), 144 (10), 130 (13), 103 (11). IR spectrum, ν_{max}, cm^{-1}: 3390, 3180 (amide NH), 1640 (CO). PMR spectrum ($CDCl_3$), δ, ppm: 3.62 s (3H, NCH_3); 6.7-7.4 m (4H, arom.); 7.8 s (1H, 4H-indole).

1-Methylindole-3-carboxylic Acid Chloroacetamide (XXVI). To a solution of 1.74 g (0.01 mole) of XXV in 40 ml of dry THF was added dropwise 1.13 g (0.01 mole) of monochloroacetyl chloride; the mixture was boiled for 48 h. After cooling, the crystals that had formed were filtered off, washed with ether, and dried. Compound XXVI was obtained (0.9 g) in 36% yield, mp 189-190°C (from ethanol), R_f 0.74 (chloroform–acetone, 1:3). Mass spectrum, m/z: 250 M^+ (100), 214 (98), 158 (98). IR spectrum, ν_{max}, cm^{-1}: 3275 (amide NH), 1715, 1680 (CO), 1580 (arom.). Found: C 57.55; H 4.51; N 11.20; Cl 14.10%. $C_{12}H_{22}ClN_2O_2$. Calculated: C 57.49; H 4.42; N 11.17; Cl 14.14%.

EXPERIMENTAL (PHARMACOLOGY)

Anticonvulsant activity of the compounds was studied on white mongrel mice of both sexes. Convulsions produced by electrical stimulation and by means of chemical agents (Corazole, nicotine, arecoline) served as standards.

A supramaximal current (maximum electric shock method) was used for electrical stimulation. Prevention of the tonic extension phase served as an indicator of ACA [12].

In order to investigate the compounds in a Corazole test, a method using subcutaneous administration of Corazole on the basis of 90 mg per 1 kg weight of animal was employed [11].

Central H- and M-cholinolytic action of the compounds was studied with respect to the prevention of nicotine-induced convulsions and arecoline-induced tremor [2, 4].

Acute toxicity of the compounds was determined by intraperitoneal administration. In order to calculate the 50% effective (ED_{50}) and 50% lethal (LD_{50}) doses, the statistical Probit method of Litchfield and Wilcoxon [9] was used.

TABLE 1. ACA and Toxicity Parameters of Compounds VIII, XVIII, XX, and Zarontin

Compound	ACA — ED_{50}, mg/kg ($p=0,05$)		LD_{50}, mg/kg	Therapeutic index (TI = LD_{50}/ED_{50})	
	corazole antagonism	maximum electric shock antagonism		corazole	electric shock
VIII	135 (71—256,5)	265 (192—358)	2050 (1934—2173)	15,2	7,7
XVIII		68 (48,6—95,2)	120 (100—144)	—	1,76
XX		28,5 (22,6—35,6)	105 (87,3—124,9)	—	3,68
Zarontin	155 (117,5—204,5)	—	1325 (1200—1462)	8,55	—

Note. Range limits are shown in brackets.

The known anticonvulsant agent Zarontin (α-methyl, α-ethylsuccinimide) was used as a control.

DISCUSSION OF RESULTS

The oxindole derivatives – compounds II, IV, VI, and VIII – prevent Corazole-induced convulsions in 40% of the animals. The most active in this series proved to be compound VIII, [3-(2,2-dimethyltetrahydropyranyliden-4-one)oxindole] (see Table 1).

As can be seen from Table 1, compound VIII is considerably superior to Zarontin in terms of activity and also range of pharmacological action (TI 15.2); moreover, the latter is inactive in the maximum electric shock test.

It may be concluded that the presence of a substituent at the 1-position and an OH group at the 3-position of the oxindole ring reduces the ACA.

Among the derivatives of 1,3-substituted indoles, compound XX (1-benzyl-3-ethylaminomethylindole hydrochloride) stands out. The average effective dose for prevention of the tonic phase of maximum electric shock is 28.5 mg/kg, but the compound is quite toxic (LD_{50} 105 mg/kg). Replacement of the benzyl group by a methyl group leads to a reduction in anti-electric shock activity almost by a factor of 2 (compound XVIII), while introduction of methylsuccinimide and chloroacetamide substituents into the 3-position considerably lessen the anticonvulsant activity (compounds XXIII, XXIV, and XXVI).

Whatever their structure none of the compounds studied had an effect on nicotine-induced convulsions or arecoline-induced tremor, in other words, they had no central H- or M-cholinolytic action.

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