3. B. A. Arbuzov, A. O. Vizel', M. A. Zvereva, et al., Izv. Akad. Nauk SSSR, Ser. Khim., No. 10, 1848-1850 (1966).
4. L. S. Afonskaya and E. K. Naumova, The Pharmacology and Toxicology of Organophosphorus Compounds and Other Biologically Active Substances [in Russian], Kazan (1969), pp. 19-20.
5. M. L. Belen'kii, Elements of the Quantitative Evaluation of Pharmacological Effects [in Russian], Leningrad (1963).
6. R. S. Garaev, R. Kh. Khafiz'yanova, B. A. Arbuzov, et al., The Pharmacology and Toxicology of Organophosphorus Compounds and Other Substances [in Russian], Kazan (1974), pp. 17-23.
7. V. S. Genes, Tables of Reliable Differences between Groups of Observations for Qualitative Indices [in Russian], Moscow (1964).
8. I. P. Lapin and M. L. Samsonova, Byull. Eksp. Biol., No. 11, 66-70 (1964).
9. E. V. Montsevichyute-Eringene, Pat. Fiziol., No. 4, 71-78 (1964).
10. N. I. Rizpolozhenskii, F. S. Mukhametov, and R. R. Shagudillin, Izv. Akad. Nauk SSSR, Ser. Khim., No. 5, 1121-1125 (1969).
11. R. R. Shagidullin, E. P. Trutneva, and F. S. Mukhametov, Izv. Akad Nauk SSSR, Ser. Khim.,
12. No. 3, 667-670 (1978).
R. R. Shagidullin, Yu. Yu. Samitov, F. S. Mukhametov, and N. I. Rizpolozhenskii, Izv. Akad Nauk SSSR. Ser. Khim., No. 7, 1604-1612 (1972).
13. G. R. Boissier, P. Simon, and G. N. Lwoff, Therapie, 19, 571-583 (1964).

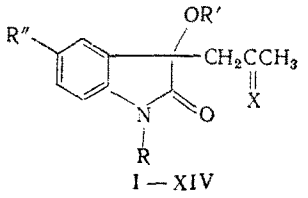
SYNTHESIS AND ANTICONVULSANT ACTIVITY OF OXIMES OF 1-R-3-ACETONYL-3-HYDROXY-OXINDOLE AND ITS DERIVATIVES.

K. A. Gevorkyan, G. L. Papayan,
S. G. Chshmarityan, R. G. Paronikyan,
N. E. Akopyan, and A. P. Engoyan

UDC 615.213:547:756].012.1

Some carbonyl derivatives of oxindole display anticonvulsant activity [3]. No biological data are, however, available for the known oximes of this series, which are used in the synthesis of tryptamides.

We here describe the synthesis of the oximes and O-acetyl derivatives of some 1-substituted 3-acetonyl-3-hydroxyoxindoles [4, 10], and their testing for anticonvulsant activity.



I—XIV

I:R = Me, R′ = R″ = H, X = O; II:R = Me, R′ = R″ = H, X = NOH; III:R = Me, R′ = Ac, R″ = H, X = NOAc; IV:R = Me, R′ = Ac, R″ = H, X = O; V:R = Me, R′ = Ac, R′ = H, X = NOH; VIII:R = Pr, R′ = R″ = H, X = O; IX:R = Me, R′ = H, R″ = Br, X = O; X:R = morpholinomethyl R′ = R″ = N, X = O; XI:R = Pr, R′ = R″ = H, X = NOH; XII:R = Me, R′ = H, R″ = Br, X = NOH, XIII:R = R′ = R″ = H, X = NOH;
XIX: R= morpholinomethyl, R′ = R″ = H, X = NOH.

From the ketone (I) there was obtained the oxime (II) [5], which was converted by treatment with acetic anhydride into the diacetate (III). PMR spectral data (CD_3OD, δ, ppm): 1.95, 1.98, and 2.0 (9H, s.s.s) Ac and N=CCH_3; 2.94 (2H, s, CH_2), 3.18 (3H, s, NCH_3), 6.8-7.45 (4H, t. arom. H).

The acetylated ketone (IV), obtained from (I), was converted into the oxime (V). PMR spectral data (DMSO-d_6, δ, ppm): 1.6 (3H, s, N=CCH_3), 2.0 (3H, s, C—CH_3), 2.7 (2H, m, AB system, J 13.5 Hz, CH_2), 3.03 (3H, s, 11-CH_3), 6.7-7.3 (4H, m, arom. H). Acetylation of the oxime (V) gave a mixture of compounds which we were unable to separate and identify, even though all the PMR signals for the diacetate (III) were present.

In addition to these compounds, also obtained were 1-n-propylisatin (VI) [10], 1-(N-morpholinomethyl)isatin (VII) [7], and their acetyl derivatives (VIII) and (X). Oximes (XI)

A. L. Mndzhoyan Institute of Fine Organic Chemistry (ITOKh). Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 21, No. 2, 167-170, February, 1987. Original article submitted August 17, 1985.

and (XII) were obtained by the method described above, from (VIII) and (IX), respectively, but this method was unsuitable for the oxime (XIV). The latter was obtained by aminomethylating the oxime (XIII) [6].

In the IR spectra (obtained in vaseline oil) of all the final products, absorption was present at 1640-1610 cm^{-1} (C=N) and 1720-1710 cm^{-1} (C=O), together with absorption corresponding to N–OH and C–OH (3360 and 3300 cm^{-1}).

1-Methyl-3-acetonyl-3-hydroxy-5-bromooxindole (IX) was obtained from 1-methyl-5-bromoisatin [2], and was used without further purification.

EXPERIMENTAL CHEMICAL

IR spectra were obtained on a UR-20 (East Germany), and mass spectra on an MX-1320 with direct introduction of the sample into the ionization zone, ionizing electron energy 60-65 eV, and temperature 20-30°C below the melting point of the compound.

TLC was carried out on Silufol UV-254 plates in the solvent system chloroform–acetone (1:2), developer iodine vapor.

Melting points were determined on a Boetius micro-hot plate (East Germany).

1-Methyl-3-acetoxy-3-acetonyloxiindole Acetoxyimine (III). To a solution of 2 g of (II) [10] in 10 ml of pyridine was added 5 ml of acetic anhydride. The mixture was kept at room temperature (20-22°C) for 24 h, then it was poured into ice-water, and acidified to pH 4.0 with dilute sulfuric acid. The product was isolated by extraction with ether. Removal of the ether gave 2 g (73.8%) of (III) as a colorless crystalline solid, mp 109-110°C (from ethanol). R_f 0.64. Found, %: C 60.09; H 5.51; N 8.64, $C_{16}H_{18}N_2O_5$. Calculated, %: C 60.36; H 5.69; N 8.80. Mass spectrum, m/z: 318 (100), 217 (70), 199 (30), 159, 160 (25). IR spectrum, ν_{max}, cm^{-1}: 1630 (C=N), 1730, 1720 (C=O).

1-Methyl-3-acetoxy-3-acetonyloxindole (IV). Obtained as described above from (I), yield 64.7%, mp 109-110°C (from ethanol). R_f 0.70. Found, %: C 64.15; H 5.90; N 5.36, $C_{14}H_{15}NO_4$. Calculated, %: C 64.36; H 5.78; N 5.36. Mass spectrum, m/z 261. IR spectrum, ν_{max}, cm^{-1}: 1740, 1720 (C=O).

1 Methyl-3-acetoxy-3-acetonyloxindole Oxime (V). To a boiling solution of 3.26 g (0.0125 mole) of (IV) in 10 ml of alcohol was added dropwise an aqueous solution of 1.12 g (0.014 mole) of hydroxylamine hydrochloride and 1.64 g (0.02 mole) of sodium acetate in 20 ml of water. The mixture was boiled for 2 h, then the alcohol was removed, and the crystals which separated were filtered off, washed with water, and dried to give 2.7 g (78.4%) of (V), mp 172-173°C (from ethanol). R_f 0.68. Found, %: C 60.80; H 5.83; N 10.40. $C_{14}H_{16}N_2O_4$. Calculated, %: C 60.24; H 5.80; N 10.16. Mass spectrum m/z: 276 (100), 216 (64), 199 (95), 188 (85), 175 (58), 162 (78), 155 (85), 147 (65), 130 (54). IR spectrum, ν_{max}, cm^{-1}: 3360 (N=OH), 1700 (C=O), 1620 (C=N).

1-n-Propyl-3-acetonyl-3-hydroxyoxindole (VIII). Obtained as described in [4] from (VI) [2], yield 53%, mp 130-131°C (from ethanol). R_f 0.64. Found, %: C 68.50; H 7.45; N 5.86. $C_{14}H_{17}NO_3$. Calculated, %: C 67.99; H 6.92; N 5.66. IR spectrum, ν_{max}, cm^{-1}: 3330 (OH), 1720, 1710 (C=O).

1-Morpholinomethyl-3-acetonyl-3-hydroxyoxindole (X). Obtained from (VII) [7] as described in [4], yield 80.9%, mp 158-159°C (from ethanol). R_f 0.33. Found, %: C 64.04; H 6.18; N 9.3. $C_{16}H_{20}N_2O_4$. Calculated, %: C 63.56; H 6.00; N 9.26. Mass spectrum, m/z: 304 (100), 162 (30), 148, 132 (100), 100 (105). IR spectrum, ν_{max}, cm^{-1}: 3240 (OH). 1700, 1618 (C=O).

1-Propyl-3-acetonyl-3-hydroxyoxindole Oxime (XI). To a boiling alcoholic solution of 6.18 g (0.025 mole) of (VIII) in 30 ml of ethanol was added dropwise an aqueous solution of 4.59 g (0.028 mole) of hydroxylamine sulfate and 3.28 g (0.04 mole) of sodium acetate in 30 ml of water. The crystals which separated on removal of the alcohol were filtered off, washed with water, and dried to give 5.3 g (80.85%) of (XI), mp 155-156°C (from ethanol). R_f 0.54. Found, %: C 63.67; H 6.75; N 10.65. $C_{14}H_{18}N_2O_3$. Calculated, %: C 64.10; H 6.91; N 10.68. Mass spectrum, m/z: 262 M^+ (22), 245, 227, 160 (7), 190 (100), 148 (77), 146, 130 (15). IR spectrum, ν_{max}, cm^{-1}: 3330, 3210 (OH), 1700 (C=O), 1660, 1640 (C=N).

1-Methyl-3-acetonyl-3-hydroxy-5-bromooxindole (XII). Obtained as described above from 1-methyl-3-acetonyl-3-hydroxy-5-bromooxindole (IX), yield 92.6%, mp 184-186°C (from ethanol). R_f 0.56. Found, %: C 46.50; H 4.60; Br 26.00; N 9.23. $C_{12}H_{13}BrN_2O_3$. Calculated, %: C 46.02;

TABLE 1. Anticonvulsant Activity and Toxicities of (II), (III), (V), and Zarontin

Compound	Anticonvulsant activity, ED_{50}, mg/kg		ED_{50}, mg/kg	Protective index, PI	
	antagonism to corazole	antagonism to electroshock		corazole	electroshock
II	110 (66,6—181,5)	210 (143—308)	1200 (1025—1404)	10,9	5,7
III	220 (137,5—352)	203 (185—233)	680 (607—762)	3,09	3,35
V	220 (137,5—352)	>(250)	1000 (714—1400)	4,5	4
Zarontin	155 (117,5—204,5)	—	1325 (1200—1462)	8,55	—

Note. Range of variation given in brackets; protective index $PI = LD_{50}/ED_{50}$.

H 4.15; Br 25.51; N 8.94. Mass spectrum, m/z: 212, 314 (10), 214, 296 (45), 277, 279 (20.18), 252, 254 (55, 60), 240, 242 (100), 209, 210 (40, 52), 182, 184 (15, 30). IR spectrum, ν_{max}, cm^{-1}: 3320, 3200 (OH), 1710 (C=O), 1660, 1640 (C=N).

1-Morpholinomethyl-3-hydroxy-3-acetonyloxindole (XIV). To 2.2 g (0.01 mole) of (XIII) [6] was added 4 ml of formalin, followed by the dropwise addition with stirring and cooling of 0.86 g (0.01 mole) of morpholine. The reaction was exothermic, the starting material dissolving to give a homogeneous mass. Crystallization occurred on prolonged storage (approximately one month). Yield of (IV) 2 g (89.9%), mp 158-159°C (from ethanol). R_f 0.42. Found, %: C 60.00; H 6.20; N 13.16. $C_{16}H_{21}N_3O_4$. Calculated, %: C 60.17; H 6.63; N 13.16. Mass spectrum, m/z 319 (20), 301 (5), 220 (23), 202 (100), 186 (65), 170 (43), 142 (55), 100 (100). IR spectrum, ν_{max}, cm^{-1}: 3280, 3270 (OH), 1710 (C=O), 1690, 1620 (C=N).

EXPERIMENTAL PHARMACOLOGICAL

The anticonvulsant activity of (II), (III), (V), (X-XII), and (XIV) was examined in white mice weighing 18-22 g. Convulsions were induced by electrical stimulation and by the administration of convulsants.

The electrical stimulus was provided by the use of supramaximal current (maximum electroshock method). The indication of anticonvulsant activity was the prevention of the tonic extension phase [11].

In testing the compounds using the corazole test, the minimum corazole convulsion method was employed (the corazole was administered subcutaneously in a dose of 90 mg per kg of body weight) [9]. Effects on the central H- and M-choline-reactive systems were assessed by the ability of the compounds to prevent the effects of nicotine and arecoline. Anticonvulsant activity was assessed on a three-point scale [1]. The test compounds were administered intraperitoneally 30 min prior to the administration of the convulsants.

To determine the mean effective doses (ED_{50}) and to carry out a comparative, quantitative assessment of the anticonvulsant activity of the test compounds, the statistical probit analysis method of Litchfield and Wilcoxon [8] was employed. The acute daily toxicites of the compounds by the intraperitoneal route were also determined.

The test results showed that some of the compounds tested display antagonism to corazole, and they also eliminte the tonic phase in maximum electroshock (Table 1).

As will be seen from Table 1, the most interesting of the oxindolylacetone derivatives is the oxime (II). The ED_{50} of (II) in respect of anticorazole activity is 110 mg/kg, and in preventing the tonic extension phase in maximum electroshock, 210 mg/kg. In its activity and breadth of pharmaceutical effects (PI), (II) is superior to the antiepileptic drug Zarontin, a drug of the succinimide group, and furthermore Zarontin is inactive in the maximum electroshock test.

Replacement of the methyl group in (II) by propyl or morpholinomethyl, or the introduction of a bromine atom into the benzene ring, results in a considerable reduction in anticonvulsant activity (compounds X-XII and XIV).

None of the compounds tested, of whatever structure, had any effects on nicotine convulsions or arecoline tremor, i.e., they had no central H- or M-cholinolytic activity.

These hydroxyindolylacetone derivatives have thus shown anticonvulsant activity in respect of antagonism to corazole and electroshock. Of these compounds, one (II) is superior to Zarontin in its anticonvulsant activity and protective index.

LITERATURE CITED

1. M. Ya. Mikhel'son and Ya. R. Savinskii, Farmakol. Toksikol., 18, No. 3, 28-33 (1955).
2. G. Heller, Ber. Chem. Ges., 53, 1545-1551 (1920).
3. F. D. Poppo, J. Heterocycl. Chem., 19, 589-592 (1982).
4. F. Braude and H. G. Lindwall, J. Am. Chem. Soc., 55, 325-327 (1933).
5. P. J. Islip and A. C. White, J. Chem. Soc., No. 4, 1201-1204 (1964).
6. C. S. Franklin and A. C. White, J. Chem. Soc., No. 2, 1335-1337 (1963).
7. H. Hellmann and I. Löschman, Ber. Chem. Ges., 87, 1684-1690 (1954).
8. J. T. Litchfield and F. Wilcoxon, J. Pharmacol. Exp. Ther., 96, 99-113 (1949).
9. E. A. Swinyard, W. C. Brown, and L. S. Goodman, J. Pharmacol. Exp. Ther., 106, 319-330 (1952).
10. G. Tacconi, P. P. Richetti, and G. Desimoni, J. Parkt. Chem. 135, 339-344 (1973).
11. J. E. P. Toman, E. A. Swinyard, and L. S. Goodman J. Neurophysiol., 9, 231-240 (1946).

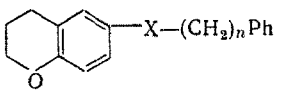
SYNTHESIS AND LOCAL ANESTHETIC ACTIVITY OF 6-[α-AMINO-ω-PHENYLALKYL]CHROMANS

V. K. Daukshas, O. Yu. Pyatrauskas,
Yu. Yu. Ramanauskas, I. Yu. Yautakene,
V. V. Lapinskas, and R. S. Maskalyunas

UDC 615.216.2:547.814].012.1

Local anesthetic activity is exhibited by the 6-(ω-amino-ω-phenylalkyl)-1,4-benzodioxanes [3]. Therefore, in order to investigate possible new local anesthetic agents we synthesized and studied previously unknown chroman derivatives whose structures are similar to the indicated derivatives of 1,4-benzodioxane.

We obtained the 4 (α-amine-ω-phenylalkyl)chromans (IIIa-d) by reducing sodium in an n-butanol solution of oximes (IIa-d) synthesized by reacting the previously known 6-(ω-phenylacyl)chromans (Ia-d) [2, 7, 9] with hydroxylamine HCl in a pyridine solution.



Ia-d, IIa-d, IIIa-d

Ia-d; X = C=O; IIa-d: X = C=NOH;
IIIa-d : X = CH—NH_2 a: $n = 0$; b $n = 1$, c: $n = 2$;
d : $n = 3$.

The IIIa-d amines were precipitated in the form of hydrochlorides. Inasmuch as the IIIc amine hydrochlorides turned out to be only slightly water soluble, we also obtained the amine lactates. However, the IIId amine lactate was also only slightly soluble.

Stretch vibrations of the HO-group in the IR spectra of all of the IIa-d oximes were manifested at 3250 cm^{-1}. However, the UV spectrum of the IIa oxime which has both aromatic rings conjugated with a C=NOH bond, was distinctive by a bathochromatic shift in the long-wave absorption band. There were no significant differences between the UV spectra of any of the IIIa-d amine hydrochlorides. The structure of the synthesized eompounds was confirmed by PMR spectral data (Table 1).

The IIIa-c chroman derivatives were found to exhibit the highest degree of local anesthesia activity, but they were also found to be more toxic and more irritating to the tissue than the known derivatives of 1,4-benzodioxane which have a similar structure [3].

V. Kapsukas Vilnius University.

Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 21, No. 2, pp. 170-174, February, 1987. Original article submitted September 17, 1985.

0091-150X/87/2102-0098$12.50