# SYNTHESIS AND NOOTROPIC ACTIVITY OF OXAMOYLAMINO ACIDS

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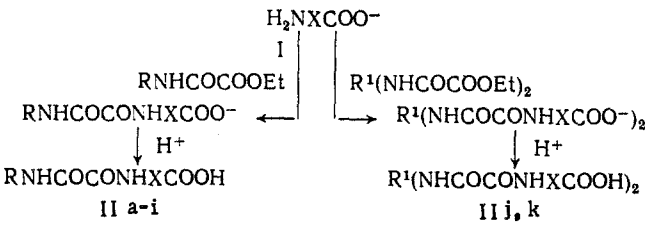
Amino acids are known to possess a zwitterionic structure [2], and they are acylated by acid halides [4-6] or acid anhydrides [1, 4, 7]. For the synthesis of N-R-oxamoyl derivatives of amino acids, it was desirable to use the more accessible oxamate esters rather than the above mentioned acylating agents.

Attempts to obtain oxamoylamino acids by the direct reaction of amino acids with an ester were unsuccessful, as a result of the reduced nucleophilicity of the amino group in the zwitterionic form. For this reason, it was desirable to carry out the reaction between the ester and the amino acid in the presence of an equivalent amount of alkali, when the nucleophilicity of the amino-group in the amino acid should be increased as a result of the existence of the anion (I).

The reaction between the amino acid and the ester was carried out in an aqueous organic solvent in the presence of KOH at room temperature, as follows:




R = 1-adamantyl (IIa, b,), 4-AcNHC$_6$H$_4$ (IIb-d), 4-antipyryl (IIe), PhCH$_2$ (IIf), C$_{10}$H$_{21}$ (IIg) n-C$_{17}$H$_{35}$ (IIi); R$^1$ = 1,2-phenylene (IIj), 4-methyl-1,3-phenylene (IIk); X = = CH$_2$ (IIa, c, e,), (CH$_2$)$_2$ (IIb), (CH$_2$)$_3$ (IIf-k), CHCH$_2$COOH (IId).

Completion of the reaction was indicated by disappearance of the alkali (universal indicator paper). The reaction took from a few minutes to several hours. The reaction mixture was acidified with HCl to pH 1.0-2.0, and the desired product isolated in the usual way. The yields of product were 59-81%.

The oxamoylamino acids (II) were obtained (Table 1) as colorless, crystalline solids, soluble in solutions of alkalies and in organic solvents, but sparingly soluble in water. The structures of (II) were confirmed by their UV and IR spectra, and by elemental analysis (Table 1). The purity of the compounds was shown by chromatography.

The UV spectra of (IIb-d), f, j, k) showed "benzene absorption" at 268-294 nm (lg ε 4.15-4.04).

The IR spectra showed no absorption for $\overset{+}{N}H_3$ or $COO^-$ at 3070 and 1600-1500 cm$^{-1}$, characteristic of amino acids. Stretching vibrations of the NH groups were seen as broad bands at 3380-3250 cm$^{-1}$. A series of bands located at 3030-2500 cm$^{-1}$ were due to vibrations of the carboxyl hydroxy groups. COOH carbonyl absorption was present at 1760-1710 cm$^{-1}$, and CONH vibration at 1700-1660 cm$^{-1}$.

The ionization constants of some of the compounds were measured (Table 1). The $pK_a$ values show that the oxamoylamino acids are less strongly acidic than the parent amino acids. This effect of acylation on the acid properties of the amino acids is due to the less pronounced electron-acceptor properties of the amide group as compared with the ammonium group.

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TABLE 1. Properties of Compounds (IIa-k)

| Compound | Yield, % | mp, °C | Found, N, % | Empirical formula | Calculated, N, % | $R_f$ | $pK_a$ |
|---|---|---|---|---|---|---|---|
| IIa | 73 | 159—60 | 10,2 | $C_{14}H_{20}N_2O_4$ | 10,0 | — | — |
| IIb | 68 | 279—80 | 14,2 | $C_{13}H_{15}N_3O_5$ | 14,3 | 0,63 | 4,2 |
| IIc | 61 | 282—4 | 14,9 | $C_{12}H_{13}N_3O_5$ | 15,0 | 0,67 | 5,2 |
| IId | 59 | 211—2 | 12,3 | $C_{14}H_{15}N_3O_7$ | 12,4 | 0,82 | — |
| IIe | 70 | 265 (decomp.) | 17,1 | $C_{15}H_{16}N_4O_5$ | 16,9 | 0,52 | — |
| IIf | 65 | 203—5 | 10,4 | $C_{13}H_{16}N_2O_4$ | 10,6 | — | — |
| IIg | 64 | 58—60 | 8,8 | $C_{16}H_{30}N_2O_4$ | 8,9 | 0,82 | — |
| IIh | 68 | 246—8 | 9,3 | $C_{16}H_{24}N_2O_4$ | 9,1 | 0,55 | 4,9 |
| IIi | 55 | 130—2 | 10,1 | $C_{13}H_{24}N_2O_4$ | 10,3 | 0,75 | 4,1 |
| IIj | 81 | 66—8 | 13,0 | $C_{18}H_{22}N_4O_8$ | 13,3 | — | — |
| IIk | 69 | 149—51 | 12,9 | $C_{19}H_{24}N_4O_8$ | 12,8 | — | — |

TABLE 2. Antiamnesic and Antihypoxic Activity of (IIf-h, k) and Aminalone

| Compound | Dose, mg/kg | Conditioned reflex amnesia, % | Pressure chamber | |
|---|---|---|---|---|
| | | | mean lifespan, sec | number of animals surviving, % |
| IIf | 300 | 100 | 72±8 | 17 |
| | 500 | — | 98±22 | 60 |
| IIg | 300 | 67 | 73±7 | 34 |
| | 500 | — | 73±3 | 40 |
| IIh | 300 | 50 | 55±15 | 75 |
| IIk | 300 | 100 | 50±1 | 60 |
| | 500 | — | 72±18 | 60 |
| Aminalone | 300 | 67 | 45±6 | 0 |
| | 500 | — | 54±3 | 0 |
| Control | — | 72 | 48±4 | 0 |

## EXPERIMENTAL (CHEMISTRY)

UV spectra were obtained on an SF-26 spectrophotometer (USSR) in 0.05 N KOH, and IR spectra on a UR-20 (East Germany) in KBr disks (c 0.5%). Ionization constants were measured by potentiometric titration in 60% aqueous dioxane using an EV-74 pH meter (USSR).

Chromatography was carried out on Silufol UV-254 plates in the solvent system n-butanol—AcOH—water (4:2:2.2). Development was by iodine vapor and UV light.

4-Acetylaminophenyloxamoyl-β-aminopropionic Acid (IIb). To a solution of 2.51 g (0.01 mole) of ethyl 4-acetylaminooxanilate in 5 ml of DMF was added 2 ml of an aqueous solution containing 0.89 g (0.01 mole) of β-aminopropionic acid and 0.56 g (0.01 mole) of KOH, and the mixture stirred. After a few minutes, the mixture began to crystallize throughout its bulk [the K salt of acid (IIb)], and became neutral as shown by testing with universal indicator paper. The mixture was then treated with 10 ml of water, and acidified with HCl (1:1) to pH 2.0. The solid which separated was filtered off and crystallized. Compounds (IIc-g, i) were obtained similarly.

The oxamoylamino acids (IIa, h) were obtained as described above, but using dioxane as the organic solvent.

1,2-Phenylenedioxamoylbis(γ-aminobutyric acid) (III). To a solution of 1.54 g (0.005 mole) of diethyl 1,2-phenylenedioxamate in 3 ml of DMF was added a solution containing 1.33 g (0.01 mole) of γ-aminobutyric acid and 0.56 g (0.01 mole) of KOH, and the reaction mixture acidified with HCl (1:1) to pH 2.0. The solid which separated was filtered off and recrystallized. (IIk) was obtained similarly.

## EXPERIMENTAL (PHARMACOLOGY)

The oxamoylamino acids (IIf, g, h, k) were tested for nootropic activity. The compounds were examined in two tests, namely ability to modify memory (antiamnesic activity), and ability to reduce the oxygen requirement of the brain (antihypoxic activity) [3]. In examining antiamnesic activity in rats, a conditioned reflex (CRF) was established to passive avoidance

of a darkened chamber in response to an electrical pain stimulus while the animal was located therein. Immediately after this, an electric shock was administered. The test compounds, together with the reference drug aminalone, were administered to the animals in a dose of 300 mg/kg intraperitoneally in starch mucilage one hour before establishment of the CRF. Persistence of the CRF was checked 24 h following its establishment, by placing the rats for 3 min in a lightened section of the apparatus. If they entered the dark chamber during this time, they were regarded as having amnesia for the CRF [8].

The test results are shown in Table 2, from which it will be seen that in the control test using rats, amnesia developed in 72% of cases. Compound (IIg) and aminalone had no effect on the development of amnesia in the animals, while (IIf) and (IIk) even increased it, the number of amnesiac rats being increased to 100%. The effect of (IIh) was limited to slight inhibition without disturbance, and gave rise to amnesia in only 50% of the rats. This compound therefore shows antiamnesic activity.

The antihypoxic effects were examined in mice in a pressure chamber, the atmospheric pressure in which was reduced to 198 mm (the "lethal platform"), and held at this level for 3 min. The test compounds and aminalone were administered intraperitoneally in starch mucilage 1.5 h before introduction into the pressure chamber, in doses of 300-500 mg/kg. After the pressure chamber, the mean lifespan of the animals was measured, together with the number of surviving animals. It will be seen from Table 2 that all the test compounds increased the mean lifespan and the survival of the animals following the pressure chamber, i.e., they showed antihypoxic activity. Compound (IIh) was of greatest interest, displaying types of activity characteristic of nootropic compounds (antiamnesic and antihypoxic), being superior in these respects to the reference compound aminalone. These results encourage an extension of the search for nootropic compounds in oxamoyl derivatives of γ-aminobutyric acid.

## LITERATURE CITED


1. Author's Cert. (USSR) No. 761,455; Otkrytiya, No. 33 (1980).
2. D. Greenstein and M. Vinits, The Chemistry of Amino Acids and Peptides [Russian translation[, Moscow (1965), p. 823.
3. M. D. Mashkovskii, L. F. Roshchina, and A. I. Poletaeva, Farmakol. Toksikol., No. 6, 676-684 (1977).
4. Polish Pat. No. 87,745; Ref. Zh. Khim., 19 O 347 (1978).
5. West German Pat. No. 2,940,258; Ref. Zh. Khim., 2 N 94 (1982).
6. French Pat. No. 1,479,260; Ref. Zh. Khim., 3N 309P (1969).
7. Japanese Pat. No. 56-12,351; Ref. Zh. Khim., 8 N 48 (1982).
8. P. D. Shabanov and I. Ya. Aleksandrova, Farmakol. Toksikol., No. 4, 28-33 (1984).