THE SYNTHESIS AND ANTISPASMODIC ACTIVITY OF 4-PHENYLPYRROLIDONE-2-ACETAMIDES

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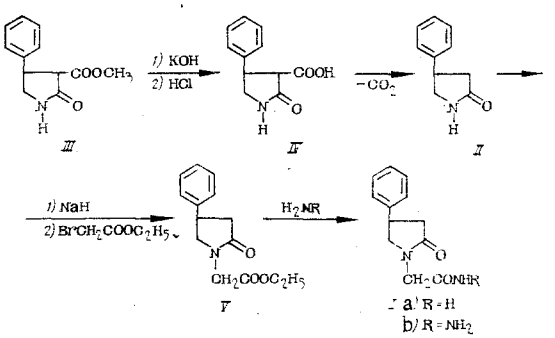
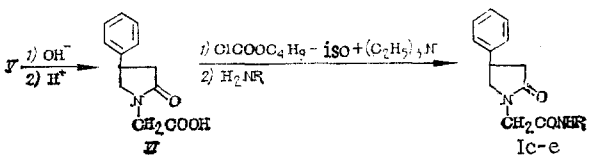
It is well known [1] that the antispasmodic property of various compounds frequently is connected with the presence of structural elements which include a phenyl radical or a benzene ring specifically oriented with respect to an amide group which, as a rule, is a fragment of an heterocyclic system (barbituric acid, hydantoin, pyrazolidindione, succinimide, etc.). Phenyl derivatives of pyrrolidone-2 satisfy these requirements, and, in fact, compounds possessing antispasmodic activity have been discovered among the derivatives of 5-phenylpyrrolidone-2 [2]. Therefore, it may be possible that a definite antispasmodic effect could be shown by derivatives of 4-phenylpyrrolidone-2, which, as indicated, are the most active of the phenylsubstitute 2-pyrrolidones in some other pharmacological properties [3]. It is also established that the introduction of substituents such as the acetamide group on the nitrogen atom of pyrrolidone-2 leads to the development of new types of pharmacological activity and to lower toxicity, such as the known preparation piracetam (2-pyrrolidinoacetamide) [4, 5].

In order to study the influence of the acetamide group in position 1 of 4-phenylpyrrolidone-2 (I) on pharmacological activity, the synthesis of compounds Ia-e was carried out, starting from phenylpyrrolidone (II);



By analogy with the synthesis of 4-substitute pyrrolidone-2 [6, 7], compound II was obtained from the ester (III) through the acid (IV). Condensation of the sodium salt of II with ethyl bromoacetate in dioxane gave the ethyl ester 4-phenylpyrrolidone-2-acetic acid (V) from which, by the mixed anhydride method with subsequent treatment with the corresponding amine, were obtained the amides Ic-e, containing the hydrophobic cyclohexyl and 1- and 2-adamantyl residues.



Ic, R = cyclohexyl; Id, R = 1-adamantyl; Ie, R = 2-adamantyl

The structures of the amides Ia-e were established by elemental analysis and by IR and mass-spectral data.

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TABLE 1. Antispamodic Activity of 2-Oxo-4-phenylpyrrolidine-1-acetic Acid Derivatives and Related Compounds in the Maximal Electroshock Test

Compound	ED_{50}, mg/kg
Ia	52 (29—94)
Ib	310 (250—380)
Ic	Inactive
Id	"
Ie	"
VI	"
Morfolep	55 (48—63)
4-Phenylpyrrolidone	127 (105—149)
Piracetam	Inactive

Note: The limits of variation for ED_{50} are given in parentheses.

EXPERIMENTAL

Chemistry

IR spectra were obtained on a Perkin-Elmer 475 instrument (England) in mineral oil, in KBr pellets, or in CCl_4 solution. PMR spectra were recorded on a Varian T-60 instrument (USA) (on the δ scale). Mass-spectra were obtained on a Varian MAT-112 (USA), with the sample directly introduced into the ion source at a temperature of 100 °C and an ionization potential of 70 eV. Basic Al_2O_3 (degree of activity II, solvent benzene) was used for TLC.

3-Carboxy-4-phenylpyrrolidone-2 (IV). A mixture of 9.52 g (0.0434 mole) of 3-methoxycarbonyl-4-phenylpyrrolidone-2 (III) and 30 ml of a 10% KOH solution was boiled for 5 h until the ester III was completely hydrolyzed, the filtrate was acidified with 10% aqueous HCl to pH 2.0, the residue was separated and washed with water to give 7.25 g (89.6%) of IV, mp 140.5-141 °C (from water). IR spectrum (in mineral oil), ν, cm^{-1}: 3250 (NH), 1735 (C=O of the carboxyl group), 1670 (C=O of the lactam). Found, %: C 64.4; H 5.5; N 7.1. $C_{11}H_{11}NO_3$. Calculated, %:C 64.4; H 5.5; N 6.8.

4-Phenylpyrrolidone-2 (II). Acid IV (7.25 g, 0.0353 mole) was heated at 190 °C for 30 min until CO_2 evolution ceased. After cooling, the residue was extracted several times with boiling petroleum ether or pentane to give 3.3 g (58%) of II, mp 75 °C [6].

Ethyl 2-oxo-4-phenylpyrrolidine-1-acetate (V). To a suspension of 1.13 g (0.047 mole) of NaH in 25 ml of dry dioxane was added dropwise a solution of 6.9 g (0.0428 mole) of phenylpyrrolidone II in 110 ml of dioxane, and the mixture was heated at 90 °C for 1 h. After cooling, a solution of 7.86 g (0.047 mole) of ethyl bromoacetate in 25 ml of dioxane was added dropwise and the mixture was heated at 125 °C for 5 h and kept overnight. After filtration, the residue was washed with CCl_4 and the combined solutions concentrated under vacuum. Distillation of the residue at 198-204 °C (4-5 mm) gave 5.57 g (52.7%) of V, R_f 0.31. IR spectrum (in CCl_4), ν, cm^{-1}: 1750 ($COOC_2H_5$), 1709 (CONH). PMR spectrum (CCl_4), δ ppm: 1.10, triplet (CH_3); 2.49, multiplet (3-CH_2); 3.62, unresolved signal (4-CH and 5-CH_2); 4.04, singlet (CH_2CO); 4.26, quartet (OCH_2), 7.44 (C_6H_5).

2-Oxo-4-phenylpyrrolidine-1-acetamide (I). Ammonia was passed throygh a solution of 0.49 g (1.98 mmoles) of the ester V in 30 ml of absolute methanol for 5 h at 45-50 °C, the solution was concentrated, and the oily residue was triturated with ether and the crystals were separated to give 0.43 g (100%) of I, mp 129.5-130.5 °C (from ethyl acetate). IR spectrum (in KBr), ν, cm^{-1}: 3370 and 3200 (NH_2), 1670 (broad, two C=O groups). Mass spectrum, m/e (relative intensity, %): 219 (8), M^+ 218 (44), 201 (7), 175 (19), 174 (75), 161 (19), 160 (64), 159 (10), 146 (19), 145 (47), 144 (10), 132 (17), 141 (13), 130 (13), 129(26), 127

TABLE 2. Neurotropic Activity Spectra of Ia, 4-Phenylpyrrolidone-2, Morfolep, and Piracetam

Compound	Antagonism			Depression of exploratory behavior ("screen climbing")	Influence on Motor coordination ("Rotating Rod")	Suppression of induced aggression	LD_{50}
	pentylene tetrazole	picrotoxin	nicotine				
	ED_{50}, mg/kg						
Ia	300 (113—487)	164 (145—183)	105 (72—138)	382 (344—420)	455 (396—514)	366 (210—322)	1100 (850—1430)
4-Phenylpyrrolidone-2	168 (132—204)	—	—	64 (57—71)	124 (92—156)	88 (52—124)	352 (280—442)
Morfolep	65 (42—88)	100 (78—122)*	82 (73—91)*	50 (20—80)	270 (263—287)	120 (97—143)	480 (472—488)
Piracetam	Inactive*	Inactive*	Inactive*	>10 000	>10 000	Inactive*	>10 000

*Characteristic results according to the literature [9].

Note: The limits of variation of the effects are given in parentheses; $P < 0.05$.

(9), 120(8), 118(9), 117(56), 116(7), 115(23), 105(28), 104(100), 103(38), 102(7). Found, %: C 66.0; 6.5; N 12.8. $C_{12}H_{14}N_2O_2$. Calculated, %: C 66.0; H 6.5; N 12.8.

2-Oxo-4-phenylpyrrolidine-1-acetic Acid Hydrazide (Ib). A mixture of 2.47 g (0.01 mole) of ester V and 2 g (0.08 mole) of hydrazine hydrate in 10 ml of alcohol was boiled for 8 h and the solution was concentrated under vacuum. The residue was washed with ether and dried over P_2O_5 to give 1.56 g (67%) of hydrazide Ib, mp 154-155 °C (from water). Found, %: C 61.8; H 6.8; N 18.1 $C_{12}H_{15}N_3O_2$. Calculated, %: C 61.8; H 6.5; N 18.1.

2-Oxo-4-phenylpyrrolidine-1-acetic Acid (VI). Ester V (2.31 g 9.3 mmoles) was added to a solution of 0.56 g (10 mmoles) of KOH in 6 ml of water and 6 ml of alcohol and boiled for 3 h. The alcohol was distilled under vacuum and the residue was acidified to pH 2.0 with 10% hydrochloric acid. The resulting precipitate was filtered, washed with water, and dried over P_2O_5 to give 2.3 g (80%) of acid VI, mp 162.5-163 deg C (from water). Found, %: C 65.8; H 6.0; N 6.7. $C_{12}H_{13}NO_3$. Calculated, %: C 65.8; H 6.0; N 6.4.

N-Cyclohexyl-2-oxo-4-phenylpyrrolidine-1-acetamide (Ic). To a solution of 2.19 g (0.01 mole) of acid VI and 1.01 g (0.01 mole) of triethylamine in 50 ml of dry toluene was added dropwise at 9-7 °C a solution of 1.37 g (0.01 mole) of isobutylchloroformate in 5 ml of toluene. After stirring the mixture for 30 min, a solution of 0.99 g (0.01 mole) of cyclohexylamine in 5 ml of toluene was added dropwise at −8 °C and the mixture was stirred for 4 h, gradually increasing the temperature to 20 °C. After the addition of 100 ml of water, the toluene layer was washed with sodium bicarbonate solution, then water, and dried over magnesium sulfate. Concentration of the solution gave 1.7 g (56.7%) of amide Ic, mp 92-93°C (from pentane). IR spectrum (in KBr), ν, cm^{-1}: 3405 (NH), 1663 (broad, two C=O groups). Mass spectrum, m/e (relative intensity, %): 300 (28), 175 (100), 174 (58), 145 (20). Found, %: C 71.8; H 8.1, N 7.3. $C_{18}H_{24}N_2O_3$. Calculated, %: C 72.0; H 8.1; N 9.3.

N-(1-adamantyl)-2-oxo-4-phenylpyrrolidine-1-acetamide (Id). To a solution of 2.19 g (0.01 mole) of acid VI and 2.02 g (0.02 mole) of triethylamine in 50 ml of dry toluene was added dropwise at -9 °C a solution of 1.37 g (0.01 mole) of isobutylchloroformate in 5 ml of toluene. The mixture was stirred for 30 min and then a suspension of,1.87 g (0.01 mole) of 1-adamantylamine hydrochloride in 50 ml of toluene was added and the mixture was stirred for 4 h and kept overnight. To the resulting suspension was added 100 ml of water, the toluene layer separated, washed with aqueous sodium bicarbonate, dried over magnesium sulfate, and concentrated under vacuum to give an oily residue which was triturated with petroleum ether to give 2.2 g (62.5%) of amide Id, mp 108-109 °C (from pentane). Mass-spectrum, m/e (relative intensity, %): 352 (8), 176 (14), 175 (100). Found, %: C 75.1; H 8.0; N 7.9. $C_{22}H_{28}N_2O_2$. Calculated, %: C 75.0; H 8.0; N 7.9.

N-(2-adamantyl)-2-oxo-4-phenylpyrrolidine-1-acetamide (Ie). This compound was prepared analogously to amide Id, yield 1.86 g (52.8%), mp 142-143 °C (from benzene and pentane). IR spectrum (in KBr), ν, cm^{-1}: 3325 (NH), 1685 (C=O). Mass-spectrum, m/e (relative intensities, %): 352 (13), 175 (76), 164 (18). Found, %: C 75.1; H 8.0; N 8.0. $C_{22}H_{28}N_2O_3$. Calculated, %: C 75.0; H 8.0; N 7.9.

Pharmacology

The antispasmodic activity spectrum of the subject compounds was studied in white mice by antagonism of the effect of maximal electroshock, pentylene tetrazole, picrotoxin, or nicotine. The influence of the substances on induced aggression (electrical pain stimulation) and on motor coordination and muscle tone by the "screen climbing" and "rotating rod" tests also was studied. Acute daily toxicity was determined by standard methods. The calculation of median effective dose was carried out by the method of Litchfield and Wilcoxon [8]. The pharmacological activity of the compounds was compared with the activity of known compounds whose structures were analogous to the studied substances: morfolep (3-methyl-1-morpholinomethyl-3-phenylpyrrolidine-2,5-dione), phenylpyrrolidone (4-phenylpyrrolidone-2), and piracetam.

Data on the antispasmodic activity of amides Ia-e, morfolep, phenylpyrrolidone, and piracetam in the maximal electroshock test are given in Table 1, from which it can be seen that antispasmodic activity is indeed shown by compounds whose structure contains a phenyl radical with an amide group attached to a pyrrolidone ring. Maximum antispasmodic activity requires that the acetamide group in the side chain must have an unsubstituted amino nitrogen

(Compound Ia). The substitution or absence of the exocyclic amide group leads to sharply decreased antispasmodic activity in the maximal electroshock test (Compounds Ib-e and VI).

It should be noted that the presence of the morpholinomethyl substituent on the cyclic nitrogen atom of morfolep does not decrease its antispasmodic effect in the maximal electroshock test, but strengthens its psychologically disruptive effects. It is possible therefore that it also increases the morfolep antagonism of the effect of convulsants. This situation is illustrated in Table 2, in which are compared the activities of morfolep and compound Ia in the antagonism of convulsants, as well as the "screen climbing" and "rotating rod" tests. Likewise, the substitution of the hydrogen on the cyclic nitrogen of the pyrrolidone ring by the acetamide group gives a decrease in the psychosedative effect, which is apparent by comparing the psychologically disruptive activities of phenylpyrrolidone and compound Ia. (cf. Table 2). In addition, it is known that pyrrolidone-2 itself possesses elements of a depressive type of neurotropic action (suppression of convulsions produced by strychnine [9]), while piracetam lacks this activity and shows certain properties characteristic of psychostimulants. The acetamide group on the nitrogen of the purrolidone ring probably lowers the acute toxicity of the compounds, as is shown in Table 2, and also in the literature [5, 10]. The compounds which were studied are structurally related to γ-aminobutyric acid (GABA); it is known that 4-phenylpiracetam does not influence the desorption of amino acids from synaptosomes isolated from rat brain [11]. It was shown earlier [12], that phenylpyrrolidone also does not influence this process. We obtained data on the effect of compound Ia and morfolep on the convulsive activity of picrotoxin on specific receptors for GABA antagonists which suggest that these substances do not enter into the interaction of amino acids with their receptors, or in the inactivation of GABA by desorption. The results obtained in this study indicate the desirability of further and deeper study of derivatives of pyrrolidone as antispasmodic and anti-epileptic materials.

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