SYNTHESIS AND BIOLOGICAL ACTIVITY OF SOME N-SUBSTITUTED 2-PYRROLIDONES

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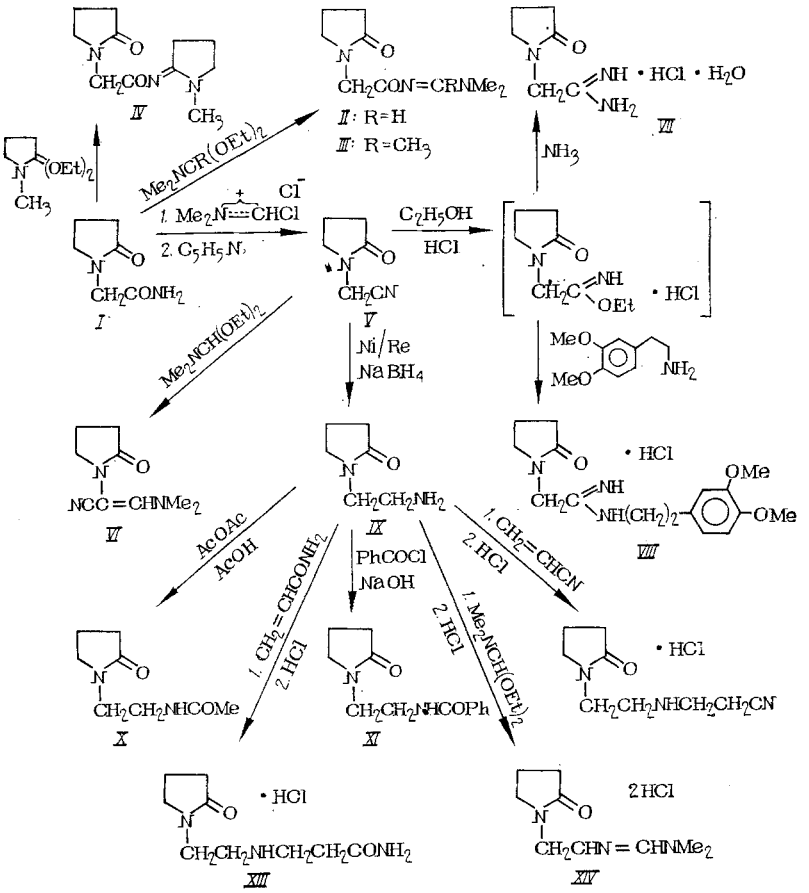
Continuing a search for biologically active compounds by modifying the pyracetamide [1-carbamoylmethyl-2-pyrrolidone (I)] molecule [1], we here report the synthesis and biological activity of some 2-pyrrolidones obtained from (I) and its chemical conversion products.



In the first stage of this investigation, the acylamidines (II-IV) were synthesized by the reaction of (I) with the diethyl acetals of dimethylformamide, dimethylacetamide, and N-methyl-2-pyrrolidone. The reactions proceeded selectively at the amide NH_2 group without involving the 3-methylene group, as shown conclusively by their NMR spectra. For example, the PMR spectrum of the amidine (III) in $CDCl_3$ contained signals for the C—CH_3, $N(CH_3)_2$, and NCH_2CO groups at 2.22, 3.04, and 3.99 ppm, respectively, and signals for the 4-CH_2, 3-CH_2, and 5-CH_2 groups of the pyrrolidine ring at 2.02 (m), 2.28 (m), and 3.49 (t) ppm, respectively.

Amidines of a different type were synthesized from 1-cyanomethyl-2-pyrrolidone (V), obtained by reacting (I) with the Vilsmeier reagent [2]. Heating the nitrile (V) with dimethylformamide acetal in an autoclave at high temperature gave the dimethylaminomethylene deriv-

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ative (IV), and treatment of (V) with hydrogen chloride in alcohol afforded the iminoether hydrochloride, from which was obtained the unsubstituted (VII) and N-(β-3,4-dimethoxyphenyl)-ethyl-substituted (VIII) amidines.

It was of interest to use N-(β-aminoethyl)-2-pyrrolidone (IX) as another starting material. The desirability of using this amine (IX) was dictated by the consideration that the distance between the basic (i.e., largely positively charged at pH 7.0) amino group and the partially negatively charged oxygen atom of the lactam carbonyl group in (IX) is approximately the same as that between the N^+H_3 and COO^- groups in γ-aminobutyric acid, thus rendering it possible for (IX) and its derivatives to interact with GABA-ergic systems. The amine (IX) was synthesized in high yields by a method described previously for the reduction of other nitriles [3], by the simultaneous use of sodium borohydride and Raney nickel. Acylation of the amine (IX) gave the N-acetyl (X) and N-benzoyl derivatives (XI), and reaction with acrylonitrile and acrylamide afforded N-(β-cyanoethyl)-(XII) and N-(β-carbamoylethyl)-(XIII) derivatives, isolated as their hydrochlorides.

Reaction of the aminolactam (IX) with N,N-dimethylformamide diethyl acetal gave the N-dimethylaminomethylene derivative (XIV). Interestingly, this formamidine (XIV), on treatment with hydrogen chloride solution, crystallized with two molecules of HCl, rather than one molecule (typical of amidines, which are monoacid bases), i.e., in addition to the salt, there is also apparently formed a molecular compound with hydrogen chloride. Microanalysis showed that the total chlorine content of this compound corresponded to the ionic chlorine, in agreement with the proposed structure. The mass spectrum of (XIV) conforms to the proposed formamidine structure: $M^{+\cdot}$ 183, 184. The most favored decomposition pathway is via $[M-N=CH-N(CH_3)_2]^+$112, followed by cleavage of the CH_2 groups of the pyrrolidine ring. The mass spectrum also showed the liberation of large amounts of hydrogen chloride.

EXPERIMENTAL CHEMISTRY

IR spectra were obtained on a Perkin-Elmer 457 (Sweden) as a paste in vaseline oil, and UV spectra on a Hitachi EPS-3T (Japan) in ethanol or methanol. The PMR spectra of (II) and (III) were obtained on a JMN-4H-100 spectrometer, internal standard tetramethylsilane, solvent deuterochloroform.

The analytical figures for the compounds obtained are given in Table 1, and the IR and UV spectra in Table 2.

N,N-Dimethyl-N'-(pyrrolidon-2-yl-1-acetyl)formamidine (II). A mixture of 16.8 g (118.0 mmole) of (I) and 16.0 g (109.0 mmole) of N,N-dimethylformamide diethyl acetal in 90 ml of dry xylene was heated at 100°C for 4 h, then 8.0 g (54.5 mmole) of N,N-dimethylformamide diethyl acetal was added, and heating continued for a further 3 h. The reaction mixture was cooled, and the precipitate of (II) which separated was filtered off. The xylene mother liquors were evaporated *in vacuo*, and the residue triturated with ether to give a further quantity of (II).

N,N-Dimethyl-N'-(pyrrolidon-2-yl-1-acetyl)acetamidine (III). A mixture of 2.8 g (20.0 mmole) of (I) and 4.8 g (30.0 mmole) of N,N-dimethylacetamide diethyl acetal in 15 ml of dry xylene was boiled for 3 h, 2.4 g (15.0 mmole) of N,N-dimethylacetamide diethyl acetal added, and boiling continued for a further 3 h. The reaction mixture was evaporated *in vacuo*, and the residue triturated with ether to give (III).

N-(1-Methyl-2-pyrrolidinylidene)-α-(pyrrolid-2-on-1-yl)acetamidine (IV). Obtained as for (III), from (I) and N-methyl-2-pyrrolidone diethyl acetal.

α-(Pyrrolid-2-on-1-yl)-β-dimethylaminoacrylonitrile (VI). A mixture of 8.3 g (67.0 mmole) of (V) and 15.0 ml of N,N-dimethylformamide diethyl acetal was heated in an autoclave of 50 ml capacity for 5.5 h at 200°C. The reaction mixture was evaporated *in vacuo*, and the residue distilled, the fraction boiling at 310-315°C (3 mm Hg) being collected. The distilled product was triturated with dry ether to give (VI).

2-(Pyrrolid-2-on-1-yl)acetamidine Hydrochloride (VII). Dry hydrogen chloride was passed through a solution of 5.0 g (40.0 mmole) of (V) in 25 ml of absolute alcohol at 0-5°C for 5 h. The mixture was filtered and evaporated *in vacuo*, and the residue washed with dry ether to give 5.5 g (67%) of the iminoester hydrochloride, decomp. 114-116°C. Gaseous ammonia was passed through a solution of 2.8 g (13.8 mmole) of this compound in 65 ml of absolute alcohol

TABLE 1. Physicochemical Properties of Compounds Obtained

Compound	Yield, %	mp, °C bp, °C /mm Hg	Found, %				Empirical formula	Calculated, %			
			C	H	N	Cl		C	H	N	Cl
II	93	98—102	54,80	8,07	21,57	—	$C_9H_{15}N_3O_2$	54,80	7,67	21,31	—
III	86	81—4	56,78	8,14	20,08	—	$C_{10}H_{17}N_3O_2$	56,85	8,11	19,89	—
IV	53	71—4	59,14	7,42	19,09	—	$C_{11}H_{17}N_3O_2$	59,17	7,67	18,82	—
VI	57	92—5	60,56	7,26	23,87	—	$C_9H_{13}N_3O$	60,31	7,31	23,45	—
VII*	76	108—11	36,80	7,46	21,75	18,35	$C_6H_{14}N_3O_2Cl$	36,83	7,21	21,48	18,12
VIII	47	184—7	56,13	7,26	12,18	10,60	$C_{16}H_{24}N_3O_3Cl$	56,22	7,08	12,29	10,37
IX·HCl	61†	128—131	43,79	8,03	17,41	21,28	$C_6H_{13}N_2OCl$	43,77	7,96	17,02	21,53
X	41	185—8/2	56,40	8,37	16,54	—	$C_8H_{14}N_2O_2$	56,45	8,29	16,46	—
XI	85	117—20	67,23	6,92	12,19	—	$C_{13}H_{16}N_2O_2$	67,22	6,94	12,06	—
XII	87	120—2	49,83	7,50	19,55	16,29	$C_9H_{16}N_3OCl$	49,65	7,41	19,30	16,29
XIII	74	182—5	45,77	7,50	17,95	15,31	$C_9H_{18}N_3O_2Cl$	45,86	7,70	17,83	15,04
XIV	92	162—5	42,11	7,86	16,56	27,38	$C_9H_{19}N_3OCl_2$	42,19	7,48	16,40	27,68

*Found, %: H_2O 8.59. Calculated, %: H_2O 9.2.
†Calculated on (IX). Compounds (III) and (IV) were crystallized from ether, (II) and (VI) from butyl acetate, (VII), (IX·HCl), (XI), (XII), and (XIV) from isopropyl alcohol, (VIII) from a mixture of N,N-dimethylformamide and ethyl acetate (2:1), and (XIII) from methanol.

TABLE 2. Spectral Properties of Compounds Obtained

Compound	IR spectrum, ν, cm^{-1}			UV spectrum, λ_{max}, nm (log ε)
	C=O	C=N	NH, NH_2	
II	1680, 1655	1610		206 (3,78), 262 (3,89)
III	1680, 1635	1570		207 (3,75), 262 (4,23)
IV	1675, 1645	1570		205 (3,70), 257 (4,33)
VI*	1690			203 (4,19), 270 (4,28)
VII	1675 (br.)		3340, 3460	205 (4,10)
VIII	1695	1655	3260	213 (4,18), 231 (4,01), 280 (3,50)
IX	1665		3400 (br.)	
X	1655 (br.)		3260, 3400	
XI	1675, 1640		3320	

*2185 (C≡N).

at 5-10°C for 1.5 h. The reaction mixture was evaporated *in vacuo*, and the residue triturated with dry ether followed by ethyl acetate to give (VII).

N-(3,4-Dimethoxyphenylethyl)-α-(pyrrolid-2-on-1-yl)acetamidine Hydrochloride (VIII). A mixture of 2.1 g (10.0 mmole) of the above iminoether and 2.0 g (11.0 mmole) of homoveratrylamine was stirred at ambient temperature for 4 h, evaporated *in vacuo*, the solid triturated with acetone, and filtered. On cooling the acetone mother liquors, (III) was obtained.

1-(2-Aminoethyl)-2-oxopyrrolidine (IX). To a mixture of 30.0 g (242.0 mmole) of (V) and 19.2 g of Raney nickel in 120 ml of methanol was added dropwise a solution of 15.6 g (413.0 mmole) of sodium borohydride in 48 ml of 8 N NaOH. The mixture was stirred at ambient temperature for 40 min, filtered, and evaporated *in vacuo*. The residue was distilled to give 20.0 g (65%) of (IX), bp 119-121°C/2 mm Hg. Dissolution of (IX) in ether followed by addition of alcoholic hydrogen chloride to pH 5.0 gave the hydrochloride (IX·HCl).

1-[2-(N-Acetyl)aminoethyl]-2-oxopyrrolidine (X). To a solution of 3.1 g (24.3 mmole) of (IX) in 25 ml of acetic acid was added dropwise 2.4 ml (26.0 mmole) of acetic anhydride. The mixture was stirred at ambient temperature for 2 h, then heated to 80°C for 45 min. The mixture was evaporated *in vacuo*, and the residue distilled to give (X).

1-[2-(N-Benzoyl)aminoethyl]-2-oxopyrrolidine (XI). To 2.6 g (20.0 mmole) of (IX) in 20 ml of water was added a solution of 1.5 g (38.0 mmole) of sodium hydroxide in 6 ml of water, followed by dropwise addition of 2.8 ml (24.2 mmole) of benzoyl chloride at 0-5°C. The reaction mixture was stirred at ambient temperature for 2.5 h, acidified with 18% HCl to pH 7.0, and extracted with chloroform. The chloroform extract was dried over calcined sodium sulfate, evaporated *in vacuo*, and the residue was triturated with ether to give (XI).

N-[N-(2-cyanoethyl)-2-aminoethyl]-2-pyrrolidone Hydrochloride (XII). A mixture of 1.9 g (15.0 mmole) of (IX) and 1.1 ml (17.0 mmole) of acrylonitrile in 15 ml of absolute alcohol was stirred at ambient temperature for 2.5 h, 0.5 ml (7.7 mmole) of acrylonitrile added, and stirring continued for a further 20 h. The mixture was evaporated *in vacuo*, the residue dissolved in 2-propanol (60 ml), and alcoholic hydrogen chloride added to give (XII).

N-[N-(2-carbamoylethyl)-2-aminoethyl]-2-pyrrolidone Hydrochloride (XIII). To a solution of 1.9 g (15 mmole) of (IX) in 8 ml of absolute alcohol was added dropwise a solution of 1.1 g (15.0 mmole) of acrylamide in 8 ml of absolute alcohol. The mixture was stirred at 60°C for 2 h, then boiled for 4 h. The mixture was evaporated *in vacuo*, the residue triturated with dry ether, and alcoholic hydrogen chloride added to give (XIII).

N,N-Dimethyl-N'-(2-pyrrolidon-1-ylethyl)formamidine Dihydrochloride (XIV). To a solution of 2.6 g (20 mmole) of (IX) in 15 ml of dry benzene was added dropwise a solution of 3.7 g (25.0 mmole) of N,N-dimethylformamide diethyl acetal in 5 ml of dry benzene. The mixture was stirred at ambient temperature for 2 h, and evaporated *in vacuo*. The residue was dissolved in 50 ml of dry ether, and alcoholic hydrogen chloride added to give (XIV).

EXPERIMENTAL PHARMACOLOGY

Compounds II, III, IV, VII, IX–XIV were examined pharmacologically.

In experiments on mice, in a model of acute hypoxic hypoxia (each mouse was placed in a hermetially sealed vessel of 250-ml capacity), it was found that (VI), (IX), and (XI-XIV) had a protective effect against the symptoms of oxygen deficiency, extending the lifespan in the enclosed space by 30, 50, and 100% as compared with the control group of animals, which received sodium chloride. The most active compound was (VI), which in doses of 500 and 1000 mg/kg increased the lifespan of mice to 44.2 (34.7-53.7) and 60.8 (52.2-69.4) min, respectively, this value in the controls (receiving sodium chloride) being 26.7 (23.1-30.9) min. In its level of antihypoxic activity, (VI) was superior to pyracetam by a factor of approximately two.

None of the test compounds, like pyracetam itself, had any protectant effect against hypoxia, induced in mice by treatment with sodium nitrite (200 mg/kg subcutaneously).

In mouse experiments using a convulsion model induced by thiosemicarbazide, (II), (VI), and (X) were found to extend the latent period of the convulsions, and the time of death of the animals. The greatest activity was shown by (VI), which in a dose of 1000 mg/kg intraperitoneally increased the latent period of convulsions from 57.4 (51.4-63.4) min to 81.7 (75.4-88.0) min, and the time of death from 62.8 (55.6-70.0) to 83.3 (72.6-90.0) min; in the

same dose, (II) increased the latent period of convulsions and the time of death to 77.0 min, and (X) changed these parameters by 15-25%, whereas pyracetam showed experimentally only weak anticonvulsive activity.

The test compounds displayed no ability to modify the pain threshold in mice, using the hot-plate method.

The LD_{50} values in white mice by the intraperitoneal route were 557 mg/kg for (XIV), and 1500-2000 mg/kg for the remaining compounds.

In electroencephalographic studies on cats and rabbits, (VI), (XII), and (XIV) (which had the greatest antihypoxemic effect) in intravenous doses of 100-200 mg/kg had no effect on spontaneous bioelectrical activity in various regions of the cerebral cortex. Reactions to the application of functional loading were also absent.

Like its derivatives, pyracetam had no effect on cerebral bioelectric activity. In experiments with the conditioned flight reflex in rats, (VI), (XII), and (XIV), like pyracetam, in an intraperitoneal dose of 500 mg/kg had no effect on the conditioned response.

Thus, six out of the 10 pyracetam derivatives tested increase the resistance of mice to acute hypoxic hypoxia. The greatest antihypoxic activity was shown by (VI). In this test, (VI) was approximately twice as active as pyracetam. Compound (VI) also displayed anticonvulsive activity in a model of convulsions induced the GABA antagonist thiosemicarbazide, suggesting the possible involvement of GABA-ergic structures in the mode of action of this compound. Antagonism to thiosemicarbazide, albeit less pronounced, was also shown by (II) and (X).

Like pyracetam itself, the test compounds had no analgesic activity.

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SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF DIACETYLENE ESTERS OF FATTY ACIDS

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Some symmetrical and unsymmetrical diacetylene have shown fairly high bactericidal properties [2-4].

In the course of directed synthesis with the aim of obtaining highly active bactericides, we have prepared some unsymmetrical diacetylenic esters of fatty acids, containing biologically active groupings. They were obtained by reacting the propargyl esters of lauric, margaric, and stearic acids with 1-bromophenylacetylene, 1-bromopropargyl alcohol, and the 1-bromopropargyl ether of m-nitrophenol in the presence of catalytic amounts of cuprous chloride and n-butylamine in an organic solvent, as follows:

$$RCOOCH_2C{\equiv}CH+BrC{\equiv}CR' \rightarrow RCOOCH_2C{\equiv}CC{\equiv}CR'+HBR;$$

I: $R = CH_3(CH_2)_{10}$, $R' = C_6H_5$; II: $R = CH_3(CH_2)_{15}$, $R' = C_6H_5$; III: $R = CH_3(CH_2)_{16}$, $R' = CH_2OC_6H_4NO_2$ = m; IV: $R = CH_3(CH_2)_{16}$, $R' = CH_2OH$; V: $R = CH_3(CH_2)_{15}$, $R' = CH_2OH$.

The diacetylene esters (I-V) (Table 1) are crystalline solids which are stable under normal conditions, and are readily soluble in alcohol, chloroform, ether, and acetone, but insoluble in water.

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