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Preliminary communication

Synthesis and psychotrope evaluation of new 3-ureidopropan-2-ols using the skin conductance reaction (SCR)-habituation test

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Summary — The syntheses of 1-substituted 3-ureidopropan-2-ols **2** and 3-acetyl-5-(1-phenyl-4-piperazinyl)methyl-2-oxazolidinones **5** from the corresponding 2-amino-2 oxazolines **1** are described. Some of these compounds have been investigated for psychotropic activity in mice using the skin conductance reaction (SCR)-habituation test. All the compounds produced a delay in habituation. The standard delaying dose (SDD 150) that delays SCR extinction until 150 100ths of an hour (+50% control time) was compared with that of the reference drug fenozolone for all the compounds.

3-ureidopropan-2-ol / 2,3-diacetyl-2-iminooxazolidine / 3-acetyl-2-oxazolidinone / skin conductance reaction (SCR)-habituation test / stimulant activity

Introduction

2-Amino-2-oxazolines are 5-membered heterocyclic compounds which have been widely investigated for pharmaceutical use [1]. The 2 nitrogen atoms of 2-amino-2-oxazolines are potent nucleophilic centers allowing substitution reactions. Depending on the experimental conditions, substitution reactions take place on the *endo* and/or the *exo* nitrogen atoms [2, 3]. It has also been suggested that oxazolines may be considered as potentially useful prodrug candidates for β-amino alcohols by opening the oxazoline ring [4]. 5-Aryloxymethyl-2-amino-2-oxazolines were shown to have potent anorectic [5] and central nervous system (CNS) stimulant activities [6]. Recently, some of us reported the synthesis and antidepressant activity of 2-amino-2-oxazolines bearing an arylpiperazine moiety on the oxazoline ring [7].

In a continuation of our work on the screening of new compounds with potential psychopharmacological activity, we report here the stimulating activity of some compounds derived from 2-amino-2-oxazolines in relation to a leader compound 4,5-dihydro-5-[(4-phenyl-1-piperazinyl)methyl]-2-oxazolamine (COR 3224) **1b**, which is presently under clinical trial [8]. This study was conducted by using the SCR (skin conductance reaction)-habituation test, an original method for psychopharmacological screening which detects a drug's ability to maintain arousal at a certain level during monotonous solicitations [9]. This tool was specially designed and adapted for use with mice by the authors [9], and proved to be very sensitive to very low doses (sometimes ≤ µg/kg) and allows the quantification of psychological activity, *ie* CNS sedative or stimulant action [9–11].

Chemistry

The substituted 3-ureidopropan-2-ols **2** were synthesized by hydrolytic ring opening of the corresponding 2-amino-2-oxazolines **1** in basic medium (scheme 1). The reaction, which probably proceeds through the attack of a hydroxide ion on the 2-carbon atom of the heterocyclic ring [12], was found to give the 3-ureidopropan-2-ols **2** accompanied by the corresponding 3-aminopropan-2-ols **3** [6, 13]. The structure of **2** was assigned by ^{1}H-NMR spectral analysis (table I). The OH proton was found as a doublet (J = 5.6 Hz) at about 5 ppm. For the urea moiety, the NH_2 appeared as a singlet near 5.5 ppm and the NH as a triplet (J = 6.7 Hz) at 6 ppm. 1-(1-Phenyl-4-piperazinyl)-3-aminopropan-2-ol **3b** was isolated by preparative HPLC for characterization purposes.

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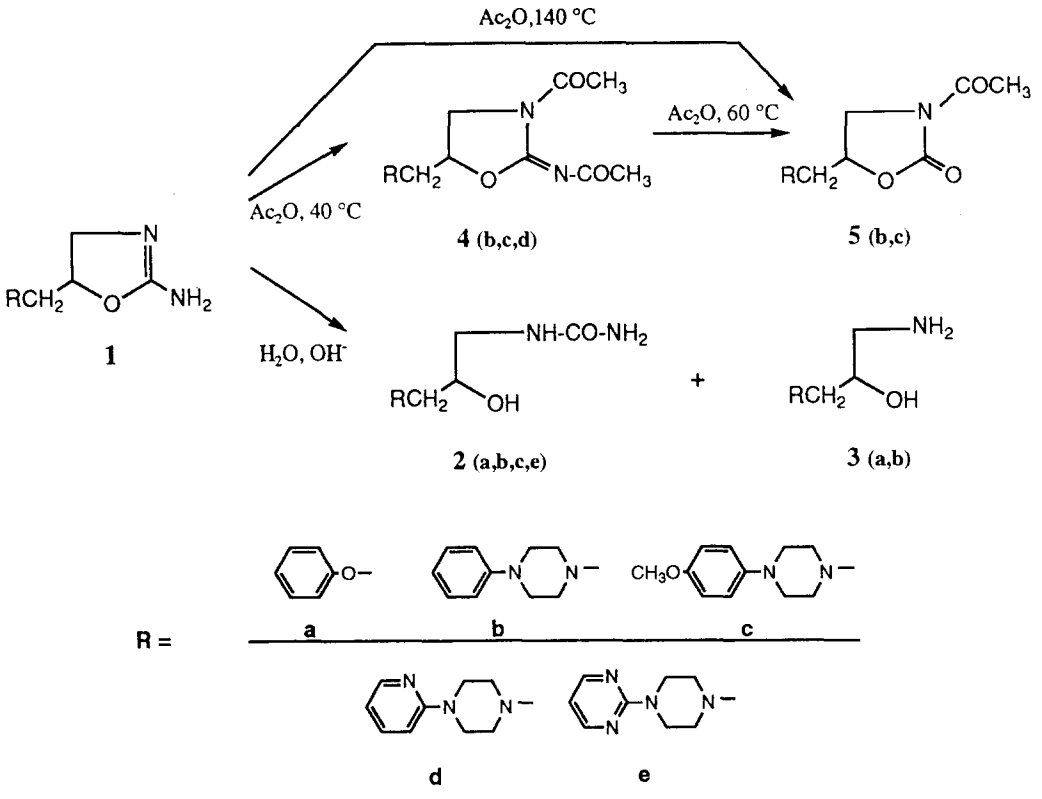

Scheme 1.

Table I. Physical data of synthesized compounds.

Compound	*Mp (°C) solvent*	*Yield (%)*	*IR (cm^{-1}) (KBr)*	*^{1}H-NMR (ppm/TMS) (DMSO d_6)*
2a	127, H_2O	48	1650 (CO), 3340, 3350 (OH, NH)	7.1 (m, 5H, arom); 6.2 (t, NH); 5.6 (NH_2); 5.3 (d, OH); 3.9 (m, 3H, OCH); 3.2 (m, 2H, NCH_2)
2c	217, EtOH	53	1655 (CO), 3340, 3350 (OH, NH)	6.9 (4H, arom); 5.8 (t, NH); 5.6 (s, NH_2); 4.7 (d, OH); 3.7 (s, OCH_3); 3.8–2.2 (m, 13H, CH_2N and CHO)
2e	198, toluene	28	1655 (CO), 3340, 3350 (OH, NH)	8.5–6.4 (m, 3H, arom); 6.0 (t, NH); 5.5 (s, NH_2); 4.8 (d, OH); 3.9–2.1 (m, 13H, CH_2N and CHO)
4c	121, EtOH	41	1600 (CN), 1660, 1730 (CO)	7.1 (m, arom); 5.0 (m, C5-H); 3.9 (m, 2H, C-4H); 3.65 (s, OCH_3); 3.6–2.6 (m, CH_2N); 2.1, 2.4 (2s, $COCH_3$)
4d	117, EtOH	39	1600 (CN), 1660, 1745 (CO)	8–6.6 (m, 4H, arom); 4.9 (m, C5-H); 3.9 (m, 2H, C-4H); 3.7–2.6 (m, CH_2N); 2.1, 2.4 (s, $COCH_3$)
5c	128, $CHClCCl_2$	58	1685, 1750 (CO)	4.8 (m, C5-H); 3.8 (m, 2H, C-4H); 3.6–2.6 (m, CH_2N); 2.4 (s, $COCH_3$)

Numerous reports deal with the acylation of 2-amino-2-oxazolines **1** [6, 13–16]. Depending upon the experimental conditions, this led to compounds with or without heterocyclic structure. The acetylation of 5-(1-aryl-4-piperazinyl)methyl-2-amino-2-oxazolines **1b–d** conducted in acetic anhydride at 40°C led to the corresponding 2,3-diacetyl-2-iminooxazolidines **4b–d**. According to our previous results on the different reactivity of the 2 nitrogen atoms in 2-amino-2-oxazolines [12], the reaction may be initiated by substitution on the endocyclic nitrogen atom leading to the delocalization of the double bond between N(3)-C(2)-N(exocyclic). A second substitution on the exocyclic nitrogen afforded the 2,3-diacetyl-5-substituted 2-iminooxazolidines **4**. The analytical data for the isolated 2,3-diacetyl-5-(1-aryl-4-piperazinyl)methyl-2-iminooxazolidines **4** are listed in table I. In the ^{1}H-NMR spectrum the protons on the C-4, C-5 and NCH_2-C-5 positions formed an ABXMN system comparable to that of an 2-iminooxazolidine, whose structure has been established by X-ray crystallography [3]. The singlet at 2.55 ppm assigned to the methyl protons of the 3-acetyl substituent in relation to that of **5b**; the other CH_3 was found at 2.25 ppm.

These 2,3-diacetyl-2-iminooxazolidines were slightly stable in aqueous solution [6, 14] which prevented their pharmacological evaluation. By heating in acetic anhydride at 60°C **4b** was converted into the stable 3-acetyl-5-(1-phenyl-4-piperazinyl)methyl-2-oxazolidinone **5b**. The other 3-acetyl-2-oxazolidinones **5a**, **c** were prepared in 1 step from the corresponding 2-amino-2-oxazolines by refluxing in acetic anhydride for 1 h. Compound **5a**, which is not listed in table I, was also prepared as a reference compound from 1-phenoxy-2,3-epoxypropane according to reference [17]. The IR spectra of 3-acetyl-2-oxazolidinones showed 2 strong absorptions at 1750 and 1685 cm^{-1}, which were assignable to the carbonyl groups of the cyclic urethane and the acetyl substituent, respectively. The characteristic ABX system of the ring protons was observed in the ^{1}H-NMR spectrum; the C-5 methine was found at about 4.7 ppm. The CH_3 protons appeared as a singlet at 2.55 ppm.

As an example of the influence of the *endo* or *exo* double bond position of the C=N, in the ^{13}C-NMR spectra of **4b** and **5b** we noticed a deshielding effect of the C-4 peak of about 10 ppm, in relation to the corresponding signal in the reference 2-amino-2-oxazoline **1b** with an endocyclic C=N double bond [18, 19].

Pharmacology

The psychogalvanic reaction or SCR is a neuro-humoral reaction with emotional origin. It is related to the activation of reticular formation [20]. It also constitutes an index of arousal performance and provides important information about the vigilance persistence. The SCR is due to an increase in the amount of sweat which causes an increase of the skin electrical conductivity. The investigation here was performed on palmar sides of aroused mice. The SCR was induced by a photostimulus (PS) and measured by means of a palmar-skin-conductance meter [21]. When the PS is repeated every 2 min, the SCR magnitude decreases in time to become useless. For the control mice, this habituation phenomenon, as it is called, appears after about 1 h. Following a previously described protocol [9], SCR was measured every 10 min until eventual extinction (*ie* habituation). For each animal, the habituation time (HT) was determined. HT is expressed in hundredths (100ths) of an hour, and was correlated with the doses (mg/kg) for each tested drug. For a compound, if a dose/effect ratio was found, the following parameters were determined: the standard delaying dose (SDD 150) delaying SCR extinction until 150 100ths of an hour (+50% control time); or the standard shortening dose (SSD 50) speeding up SCR extinction to 50 100ths of an hour (–50% control time).

In previous pharmacological studies, some of us demonstrated that the HT was delayed by psychoanaleptics [9], and accelerated by central depressants [10]. We noted that SDDs or SSDs were always lower than doses used in other psychopharmacological animal models, *ie* locomotor activity [9], confering on the SCR-habituation test an unusual sensitivity. Thus the SCR-habituation test was used as a tool to assess either the stimulant or the sedative activity of new compounds.

Results and discussion

Six compounds **2a–c**, **2e**, **5c**, and **1b** (COR 3224) were evaluated in mice using the SCR-habituation test and compared with 3 appropriate standards: fenozolone (an oxazolidinone psychostimulant); piracetam (a cerebral stimulant); and viloxazine (an antidepressant drug with a profile close to that of **1b**) [22]. The HT to iterative photostimulation in the palmar SCR of control mice was 96.40 100ths of an hour (± 17.21). All the studied compounds produced a delay of habituation in relation to control batch. This delaying effect was linearly proportional to the log-doses and reached a plateau with the higher doses. The SDD 150s expressed in mg/kg and calculated from the corresponding regression equations are reported in table II. Figure 1 shows some dose–effect curves with the statistical confidence limits and gives information about the relative activity of each compound.

It appeared that the parent 2-amino-2-oxazoline **1b** was the most potent compound (SDD 150:

Table II. Habituation times (HT) and standard delaying doses (SSD 150) of 3-ureidopropan-2-ols and reference drugs.

Compound	*Dose (mg/kg)*	*r*	*HT ± CL (1/100th)*	*SDD 150 (mg/kg)*
Control	–	–	96.40 ± 17.21	–
1b	0.00001	0.9556	123.0 ± 23.68	0.000047*
	0.0001		163.0 ± 17.06	
	0.001		203.0 ± 17.06	
	0.01		259.6 ± 23.46	
	(0.1)		259.6 ± 23.46	
	(1)		176.6 ± 31.35	
2a	0.0001	0.9812	106.4 ± 23.46	0.0015**
	0.001		139.6 ± 23.63	
	0.01		182.8 ± 25.34	
	0.1		223.0 ± 23.68	
	1		229.6 ± 33.92	
2b	0.0001	0.9409	109.8 ± 18.25	0.00032*
	0.001		193.2 ± 37.48	
	0.01		246.4 ± 17.21	
	(1)		246.2 ± 26.94	
2c	0.0001	0.8991	116.4 ± 25.34	0.00054*
	0.001		166.2 ± 25.34	
	0.01		193.0 ± 34.31	
	0.1		269.0 ± 72.48	
	1		292.0 ± 27.66	
2e	0.0001	0.9986	96.4 ± 30.84	0.00035***
	0.001		196.4 ± 39.59	
	0.01		279.6 ± 39.79	
	(1)		279.6 ± 17.65	
5c	0.00125	0.9915	113.0 ± 17.06	0.0062***
	0.01		163.0 ± 17.06	
	0.1		213.0 ± 22.43	
	1		243.0 ± 34.87	
Fenozolone	0.0312	0.9929	96.3 ± 12.29	0.144*
	0.0625		126.4 ± 14.05	
	0.125		128.0 ± 12.75	
	0.5		198.1 ± 11.83	
	1		228.0 ± 18.56	
	4		276.4 ± 14.05	
	8		287.9 ± 13.86	
Viloxazine	0.31	0.9823	99.8 ± 14.48	0.653***
	0.62		143.2 ± 11.55	
	1.25		183.0 ± 14.92	
	2.50		199.0 ± 14.48	
Piracetam	0.5	0.9869	87.9 ± 16.99	1.24***
	1		151.2 ± 16.34	
	4		221.3 ± 31.31	
	10		256.3 ± 12.77	

Doses not selected for calculations are written in brackets; r = correlation coefficient of linear regression; CL (confidence limits): $p = 0.05$; significance of the linear regression: $*p < 0.001$, $**p < 0.005$, $***p < 0.05$.

0.047 µg/kg). Nevertheless the other compounds revealed a significant activity with SDD 150s ranging from 0.35 to 6.2 µg/kg. In the SCR-habituation test, all compounds presented a similar increase in psychological activity, whatever the action mechanism involved. As regards the locomotor activity, 2 opposing data sets were observed. Compound **1b** [22] and viloxazine [23] decreased the locomotor activity whereas compounds **2a**, **2b**, **2e**, and **5c** (Quermonne, unpublished data) and fenozolone [9] increased it. Piracetam did not produce a locomotor stimulant effect [9, 24]. These results suggest an amphetamine-like action for compounds **2**, **5c** and fenozolone, while compound **1b**, viloxazine and piracetam can improve the attention without psychomotor stimulation.

The CNS-stimulant activity previously noted with some 2-amino-2-oxazolines [5] was found in the present study with the non-cyclic compounds **2**. Among them **2a–c**, and **2e** are structurally related to a 3-ureidopropanol moiety. The 1-aryl-4-piperazinyl substituted compounds **2b**, **2c**, and **2e** were found to be very potent and their SDD 150s were quite similar. The replacement of the 1-aryl-4-piperazinyl moiety by a phenoxy group resulted in a less potent compound (**2a**). Compared with the corresponding non-cyclic compound **2c**, we observed a decrease in activity for the 3-acetyl-2-oxazolidinone **5c**. There may be a relationship between the action mechanism of the two 5-membered heterocyclic compounds **5c** and fenozolone.

For all the tested compounds, the calculated octanol/water partition coefficients (log P_{calc}) were determined according to a fragment method [25]. The order of decreasing values was 0.88 (**5c**), –0.64 (**2a**), –1.17 (**2c**), –1.31 (**2b**) and –3.07 (**2e**) showing, surprisingly, that the least potent compound **5c** was the most lipophilic one; moreover the value for **1b** in its amino tautomeric form was 0.50. From these fragment results it is difficult to simply relate the observed pharmacological results to the lipophilic behavior of the title compounds.

Experimental protocols

Chemistry

Melting points were determined with a Kofler hot-stage and were uncorrected. Satisfactory elemental analysis (± 0.4% of calculated values) were obtained for all new compounds. IR spectra were recorded on a Beckman Acculab spectrometer as KBr discs. ^{1}H- and ^{13}C-NMR spectra were recorded on Bruker AM-80 and Bruker AC-200 instruments with tetramethylsilane as an internal standard. Analytical HPLC was performed on a µ Bondapack C-18 column (10 µm, 15 cm) using a Waters chromatograph equipped with a UV LC Waters absorbance detector (λ = 250 nm). The mobile phase was acetonitrile/phosphate buffer M/15 (50:50, v/v); the pH was adjusted to 7.8 at a flow rate 2 ml/min.

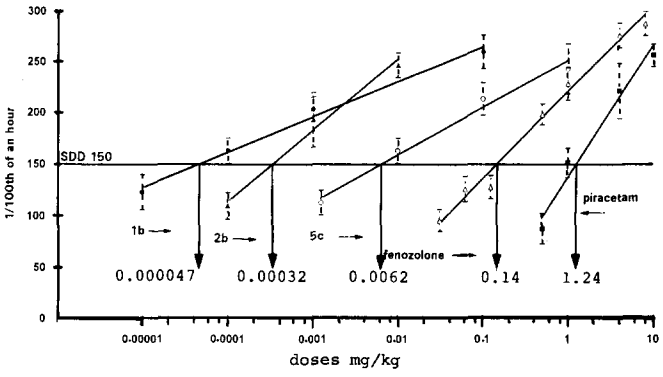

Fig 1. Dose-related delay of habituation to iterative photostimulus of some of the compounds.

Preparative HPLC was performed on a µ Bondapack C-18 column (15–20 µm, 40 x 100 µm) using a Waters chromatograph equipped with a refractive index detector ATT 128. The mobile phase was water adjusted to pH 2.8 with phosphoric acid and the flow rate was 27 ml/min.

Typical procedure for the preparation of 1-(1-phenyl-4-piperazinyl)-3-ureidopropan-2-ols ***2b***

A solution of 2-amino-2-oxazoline **1b** (0.02 mol, 5.2 g) and 0.02 mol of 1 N sodium hydroxide in 50 ml water was refluxed for 8 h. After cooling the crystals formed were filtered, washed with water, dried and recrystallized from ethanol. The yield was 47%. HPLC analysis of the aqueous phase showed the presence of a small amount of a soluble compound identified as 1-(1-phenyl-4-piperazinyl)-3-aminopropan-2-ol **3b**. A kinetic study of the hydrolysis reaction of **1a** was performed by HPLC in order to choose the heating duration and the concentration ratio 2-amino-2-oxazoline/OH^- allowing the optimization of the formation of the desired 3-ureidopropan-2-ol. The other 3-ureidopropan-2-ols (table I) were similarly prepared, except for **2c** which was isolated by extraction with chloroform.

1-(1-Phenyl-4-piperazinyl)-3-ureidopropan-2-ol **2b**: mp 212°C; IR (KBr) 3350, 3340, 1650 cm^{-1}; ^{1}H-NMR 200 MHz (DMSO-d_6) δ ppm: 7.25 and 6.65 (2m, 5H, phenyl); 6.0 (t, 1H, J = 6.7 Hz, NH); 5.55 (s, 2H, NH_2); 4.75 (d, 2H, J = 5.6 Hz, OH); 3.61 (m, 1H, C-2-H); 3.0 (m, 2H, C-1-H); 2.37 (dd, 2H, C-3-H); 3.1–2.55 (m, 8H, CH_2 piperazine). ^{13}C-NMR $CDCl_3$ δ ppm: 160.8 CO; 151.3, 129.3, 118.7, 114.4 C_{ar}; 77.9 CHOH; 62.2 C-1; 54.5 C-3; 53.1, 48.2 CH_2 piperazine.

Because of the difficulty encountered in purifying the 1-substituted 3-aminopropanols **3** by usual methods, these compounds were isolated by preparative HPLC. The separated chromatographic fractions were adjusted to pH 10 with ammonia, and extracted 6 times with dichloromethane. The solution was dried and evaporated to dryness. Compound **3a** was identified by its previously reported analytical data [26].

1-(1-Phenyl-4-piperazinyl)-aminopropan-2-ol **3b**: mp 134°C; IR (KBr) 3350 cm^{-1}; ^{1}H-NMR 80 MHz (DMSO-d_6) δ ppm: 6.9 (m, 5H, phenyl); 3.7 (m, 1H, OH); 3.5 (m, 3H, C-2-H and C-3-H); 3.2–2.3 (m, 12H, CH_2 piperazine and NH_2). ^{13}C-NMR $CDCl_3$ δ ppm: 149.0, 129.1, 120.6, 116.2 C_{ar}; 68.2 CHOH; 62.3 C-1; 53.2, 45.3 CH_2 piperazine; 46.1 C-3.

Typical procedure for the preparation of 2,3-diacetyl-5-(1-phenyl-4-piperazinyl)methyl-2-iminooxazolidine ***4b***

A solution of 2-amino-2-oxazoline **1b** (0.02 mol, 5.2 g) in 21.5 ml (0.2 mol) acetic anhydride was stirred for 2 h at 40°C. After cooling the mixture was triturated with 20 ml ether and the crystals formed were filtered, washed with ether, dried and recrystallized from ethanol (yield 41%). Mp 113°C; IR (KBr) 1730, 1670 cm^{-1}; ^{1}H-NMR 200 MHz ($CDCl_3$) 7.35 and 6.85 (2m, 2H and 3H, phenyl); 4.82 (m, 1H, C5-H); 4.15 and 3.80 (2 dd, 1H each; J = 11.2, 6.8 Hz, C4-H); 3.20 (d, 2H, J = 6.8 Hz, CH_2-C5); 3.15 and 2.75 (2m, 8H, CH_2 piperazine), 2.55 and 2.25 (2s, 3H each, $COCH_3$). ^{13}C-NMR $CDCl_3$ δ ppm: 181.2 and 169.7 CO; 146.9 C-2; 151.0, 129.0, 119.6, 115.9 C_{ar}; 75.4 C-5; 60.1 NCH_2-C-5; 54.0, 49.1 CH_2 piperazine; 46.9 C-4; 26.5, 24.2 CH_3.

Other 2,3-diacetyl-5-(1-aryl-4-piperazinyl)methyl-2-imino-oxazolidines **4c**, **4d** were similarly prepared and characterized by their elemental and spectral data (table I).

Using HPLC we observed a rapid hydrolytic opening of the heterocyclic ring of all 2,3-diacetyl-5-(1-aryl-4-piperazinyl)-methyl-2-iminooxazolidines in aqueous solution at 25°C. By heating **4b** in acetic anhydride at 60°C, it was converted in 3-acetyl-5-(1-phenyl-4-piperazinyl)methyl-2-oxazolidinone **5b**.

Typical procedure for the preparation of 3-acetyl-5-(1-phenyl-4-piperazinyl)methyl-2-oxazolidinone ***5b***

A solution of 2-amino-2-oxazoline **1b** (0.02 mol, 5.2 g) in 21.5 ml (0.2 mol) acetic anhydride was refluxed for 1 h at 140°C. The reaction mixture was evaporated to dryness and the residue was triturated twice with 25 ml ether. The insoluble part was filtered, washed with ether and recrystallized from trichloroethylene (yield 27%). Mp 146°C; IR (KBr) 1750, 1685 cm^{-1}; ^{1}H-NMR 200 MHz ($CDCl_3$) 7.32 and 6.87 (2m, 5H, phenyl); 4.73 (m, 1H, C5-H); 4.10 and 3.70 (2 dd, 1 H each, J = 10.3, 5.8 Hz, C4-H); 3.30 and 2.75 (2m, 10H, NCH_2); 2.55 (s, 3H, $COCH_3$). ^{13}C-NMR $CDCl_3$ δ ppm: 169.8 CO; 153.9 C-2; 151.0, 128.9, 119.6, 115.9 C_{ar}; 71.7 C-5; 60.0 NCH_2-C-5; 53.9, 49.0 CH_2 piperazine; 42.4 C-4; 26.7 CH_3.

The physical data of the 3-acetyl-5-[1-aryl-(4-piperazinyl)] methyl-2-oxazolidinones **5c** are listed in table I.

Pharmacology

Animals

For the pharmacological studies, female IOPS OF1 naive mice (18–25 g) were used. They were randomized into batches of 5 or 10.

Drugs

Hydrochloride salts of the compounds were used. They were dissolved in normal saline (0.9% NaCl) and administered intraperitoneally, the concentration level adjusted in order to administer 0.4 ml per 20 g body weight. Each animal in a given batch received an equal amount of the drug and from one batch to another the amount was usually increased in a logarithmic progression. Drugs were administered after the initial measurement of the SCR.

Apparatus

The palmar-skin-conductance meter used to evaluate the SCR consisted of resistances, a DC generator (a 4.5 V dry battery) and a galvanometer connected to 2 metallic electrodes. Their free ends were 2 mm apart, so that the circuit was open. A 100 W glow lamp was switched on and off with a timer, which could be disconnected and switched on manually allowing the non-automatic delivery of the PS. A wire cylinder, with one end closed, restrained the animals vertically with the head upward, the closed end and facing the glow lamp during the automatic delivery of PS.

Readings

The mouse, taken by its nuckal skin and placed in front of electrodes, immediately grasped them by reflex. In this manner, the circuit was completed and the intensity of current (μA), which was proportional to the animal skin conductance level (on palmar sides), was noted. The glow lamp located 10 cm above the mouse's head was switched on, which caused the skin conductance level to increase and the new value was noted. Each SCR recorder included 2 consecutive readings (r) of the skin conductance level, the first in the dark (r_d) and the second during the PS (r_p). The difference between the 2 readings (r_p–r_d) represented the SCR. The PSs were repeated every 2 min until reduction and extinction (*ie* habituation) of SCRs occurred. The SCRs were only recorded at the beginning of the test, and then every 10 min. The sequence of PSs and measurements was stopped when the SCR became extinct (*ie* r_p–r_d = 0 or SCR = 0).

Statistical analysis

For each batch of animals, the average HT at which SCR = 0 (expressed in 100ths of an hour) was calculated and compared with the average time of the control batch by means of Student's t-test. For each group (several doses), these times were computed against doses using the regression equations $y = a\log x + b$ where y was the HT, and x the dose. From these equations, the SDD 150 of each drug was determined.

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