Pyrrylphenylethanones Related to Cathinone and Lefetamine: Synthesis and Pharmacological Activities[1)]

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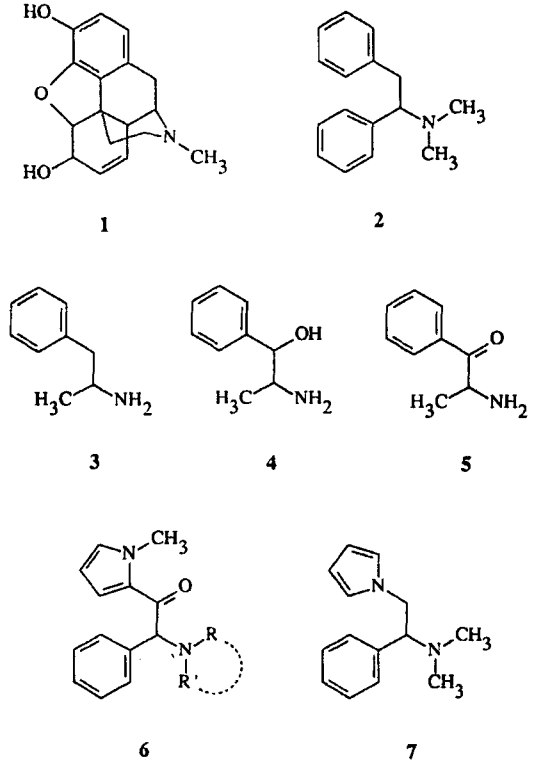
The synthesis of various pyrrylphenylethanones resembling cathinone and lefetamine is described starting from 2-chloro-1-(1-methyl-1*H*-pyrrol-2-yl)-2-phenylethan-1-one. Some derivatives showed good antinociceptic activity, comparable to that of morphine. The neuropsychopharmacological profile of title compounds has been also studied to explore their action on C.N.S.

Mit Cathinon und Lefetamin verwandte Pyrrylphenylethanone: Synthese und pharmakologische Wirkungen

Die Synthese der Titelverbindungen, ausgehend von 2-Chlor-1-(1-methyl-1*H*-pyrrol-2-yl)-2-phenyl-ethan-1-on, wird beschrieben. Einige dieser Derivate zeigen gute antinociceptive Eigenschaften, vergleichbar mit denen des Morphins. Das neuropsychopharmakologische Profil der Titelverbindungen wurde untersucht, um entspr. ZNS-Wirkungen zu studieren.

Research on simpler analogues of morphine **1** led to the discovery of lefetamine **2**, a potent drug used as analgesic in clinical practice[2)].

Lefetamine belongs to the class of phenethylamines which include among others amphetamine **3** and two natural products, cathine (**4**) and cathinone (**5**), found in khat extracts. Due to their structural similarity with amphetamine, the khatamines are miming the pharmacological profile of amphetamine producing similar central and peripheral effects. In particular cathinone (**5**), the major component of khat, increases the reaction time in the hot-plate and in the writhing tests. Amphetamine also has analgesic effects as shown in various experimental models[3)].



Scheme 1

These interesting data led us to synthesize various substituted aminopyrrylphenylethanones **6** as an attempt to acquire new potential analgesic agents.

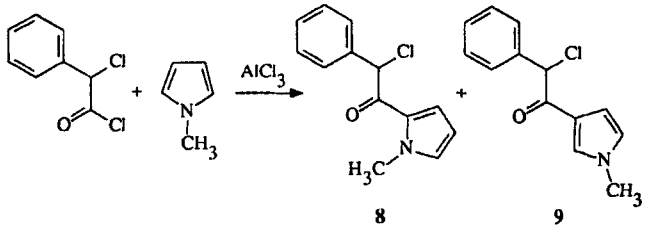
This work is a part of our running program on lefetamine derivatives bearing a pyrrole moiety, one of which, *N,N*-dimethyl-1-phenyl-2-(1*H*-pyrrol-1-yl)ethylamine (**7**), showed analgesic effects comparable to those of lefetamine, but devoid of its neurotoxic effects[4)] (Scheme 1).

All new derivatives here reported have been subjected to pharmacological screening for analgesic activity and neuropsychopharmacological effects. We tested also our compounds *in vivo* in the phenylquinone-induced writhing assay for evaluating their interaction with central α_2-receptors.

Chemistry

Friedel-Crafts aroylation of 1-methyl-1*H*-pyrrole with α-chlorophenacetyl chloride/$AlCl_3$ afforded the expected 2- and 3-substituted pyrrylketones **8** and **9** (Scheme 2)[5)].

Reaction of 2-chloro-1-(1-methyl-1*H*-pyrrol-2-yl)-2-phenylethan-1-one (**8**) with potassium phthalimide furnished the phthalimidoketone **10**, which led to 2-amino-1-(1-methyl-1*H*-pyrrol-2-yl)-2-phenylethan-1-one **11** on treatment with hydrazine hydrate (Scheme 3).



Scheme 2

Compound **8** was also reacted with various amines to give aminoketones **12**, **13**, and **14** (Scheme 4).

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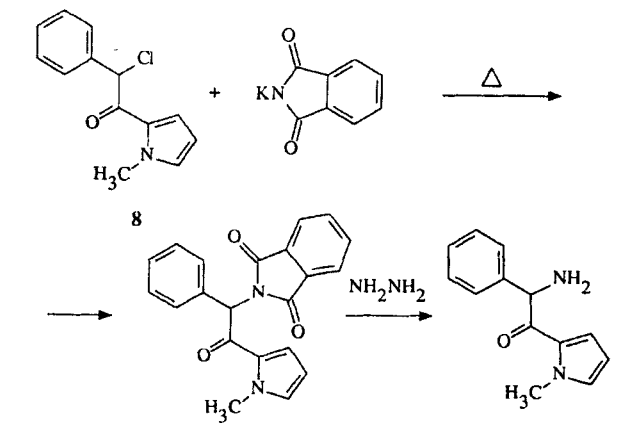
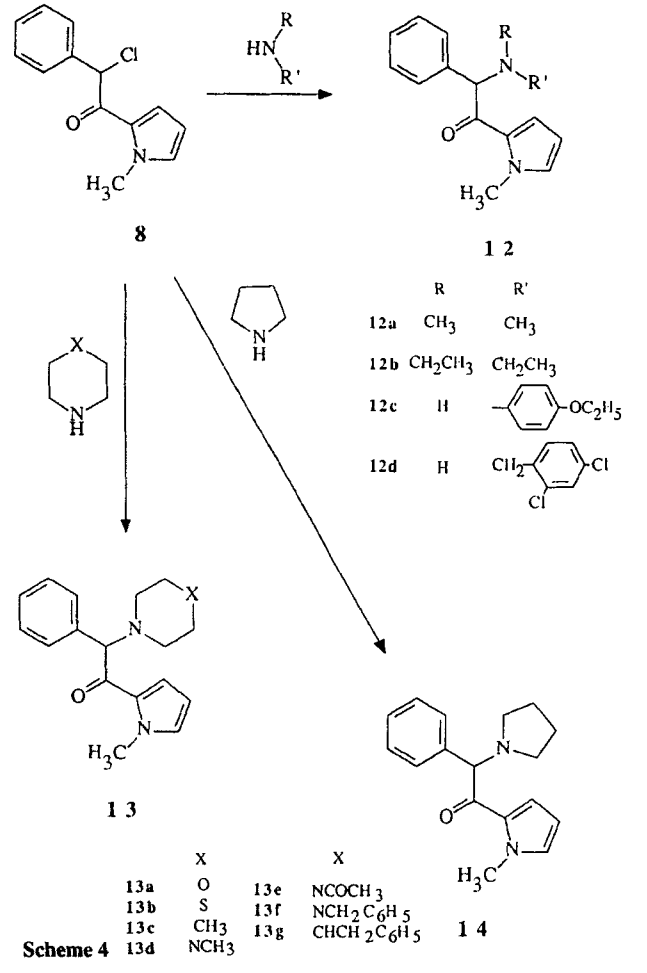
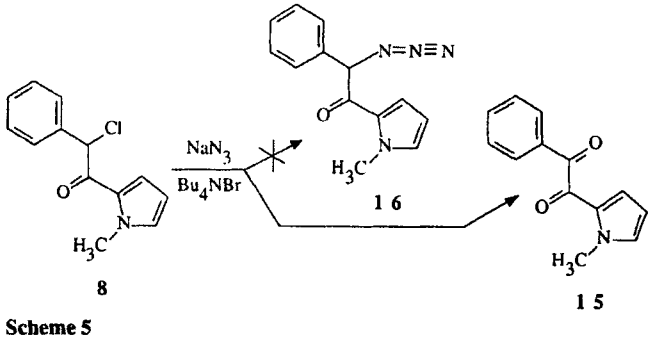


Scheme 3



Scheme 4



Scheme 5

In an attempt to prepare the aminoderivative **11** by reductive cleavage of the corresponding azide[6], we reacted chloroketone **8** with NaN_3 (Scheme 5). However, the expected azido-derivative **16** was not formed, the only product isolated being the diketone **15**, probably formed by loss of N_2 and ammonia. The structure of **15** has been confirmed by IR-, NMR-, and GC-MS-spectra.

Pharmacological Evaluation

Derivatives **10-14** were pharmacologically tested in mice in order to explore their neuropsychopharmacological effects (Table 1), their antinociceptic activity (Table 2), and their interaction with central α_2-receptors (Table 3).

Neuropsychopharmacological Effects

All test derivatives, with the exception of compounds **10**, **12b**, **13c**, and **14**, decreased spontaneous motor activity in mice without affecting other neuropsychobehavioural activities. Derivatives **11**, **12a**, and **13f** exhibited the highest significance ($p < 0.001$) like morphine. On the contrary, amphetamine increased strongly the spontaneous motor activity.

A significant decrease of the exploratory activity on the hole-board test was observed in the subsequent order morphine and amphetamine > **12b** and **13c** > **14**. With our substances animals behaved as disinterested rather than sedate, with an amphetamine-like pharmacological profile.

As regards to myorelaxant action all test derivatives were devoid of myorelaxant and ataxic action, with only few exceptions (compound **13g** and, at minor extent, compound **13d**).

Significative low effects at the Rota-Rod test (action on motor coordination) were observed with derivatives **13c** and **13g**.

With regard to the anticonvulsant activity, none of test compounds determined any protection from seizures. All compounds showed only a partial protection with particular reference (100% PP) to derivatives **10**, **13c**, and **13f**. This behaviour was similar to those of morphine (100% PP) and amphetamine (80% PP).

In conclusion, from data on neuropsychobehavioural screening we can observe that all test products did not show any exciting effect at the dose of 20 mg/kg i.p. In general they produced light sedation (decreasing of spontaneous motor activity) without alteration of exploratory activity on the hole-board. These effects can be correlated with a specific antiphobic-anxiolytic activity, which needs to be confirmed by further pharmacological studies with proper tests. It is interesting to note that these low sedative-anxiolytic effects are not accompanied by myorelaxation and ataxia.

Antinociceptive Action. Hot-Plate Test

Data of essay on antinociceptic activity (hot-plate test) are recorded in Table 2. Two derivatives, **10** and **12d**, showed high antinociceptic activity with the same significance ($p < 0.001$) of both morphine and amphetamine. Good activity,

Table 1: Neurobehavioural effects of derivatives **10-14** (dose: 20 mg/kg *i.p.*) on mice

Compd or Controls	A[a] $\bar{X} \pm$ S.D.[f]	B[b] $\bar{X} \pm$ S.D.	C_1[c] $\bar{X} \pm$ S.D.	C_2[c'] $\bar{X} \pm$ S.D.	D[d] $\bar{X} \pm$ S.D.	E[e] %
Controls	464.2±106.4	25.6±7.56	1.2±0.44	106.0±31.3	1.6±1.8	40 PP
	***[g]	***				60 NP
morphine	240.0±80.37	11.0±6.0	2.0±1.41	120.0±0	1.0±1.22	100 PP
	°°	***				
amphetamine	648.0±129.83	10.4±6.0	1.4±0.54	120.0±0 (40%)	1.2±1.64	80 PP
						20 NP
10	425.2±103.9	24.8±11.36	2.0 ±1.22	106.0±31.3	1.0±1.22	100 PP
	***					
11	250.0±85.9	30.0±5.19	1.2±0.44	110.0±22.3	0.4±0.89	40 PP
	***					60 NP
12a	259.8±107.3	20.2±12.75	1.8±0.83	97.6±25.0	7.0±9.87	40 PP
		**				60 NP
12b	409.0±105.1	14.2±4.86	1.2±0.44	111.2±19.67	2.8±1.48	40 PP
	°					60 NP
12c	336.0±91.50	23.2±6.26	1.2±0.44	112.0±17.8	3.8±3.1	20 PP
	*					80 NP
12d	355.8±55.43	27.2±3.56	2.4±2.6	120.0±0	1.8±2.4	60 PP
	**					40 NP
13a	306.8±107.33	17.4±15.0	1.6±0.89	108.0±26. 83	1.0±1.73	40 PP
	**					60 NP
13b	320.2±98.31	23.2±3.27	1.0±0	114.0±13.4	0.6±0.54	100 NP
		**			•	
13c	406.6±265.3	14.6±5.85	1.8±0.83	72.6±44.8	3.4±1.34	100 PP
	**		*			
13d	311.2±50.91	23.8±4.14	5.8±5.71	107.6±27.7	3.4±3.9	20 PP
	*					80 NP
13e	350.6±57.1	27.6±5.54	2.0±1.41	120.0±0	2.4±1.5	20 PP
	***					80 NP
13f	252.6±120.8	20.8±4.96	1.8±0.83	116.0±8.94	1.4±2.0	80 PP
	*	*	**		*	20 NP
13g	307.4±153.0	18.0±7.0	3.4±1.8	116.2±5.21	4.2±2.38	20 PP
		•				80 NP
14	378.6±244.7	15.2±11.34	1.4±0.54	99.2±29.7	2.6±2.79	100 NP

[a] Spontaneous motor activity in the open field (total number of movements in 5 min). [b] Exploratory activity on the hole-board (total number of holes in 5 min). [c] Myorelaxant action (traction test: time in sec on the horizontal wire for fore-legs). [c'] Myorelaxant action (traction test: how long the animals stayed on wire). [d] Motor coordination at Rota-Rod (total number of falls in 3 min). [e] Maximal electroshock seizures: PP = % of survival of animals with seizures (partially protected); NP = % of deaths of animals with seizures (non-protected). [f] Average ± standard deviation. [g] Significance: (*) or (°) $0.05 > p > 0.02$; (**) or (°°) $0.02 > p > 0.001$; (***) or (°°°) $p < 0.001$.

although with minor significance, was exerted by derivatives **12a** ($0.02 > p > 0.01$) and **11** ($0.05 > p > 0.02$). All other test derivatives did not show statistically significant activity at the hot-plate test.

Derivatives **11**, **12a**, and **12d** exhibit some sedative effects, whereas derivative **10** is devoid of any effects on the behavioural profile. For the latter compound positive effects were observed on the phenylquinone-induced writhing test (antidepressant effect) and against electroshock (partial protection from seizures).

As regard to the antinociceptic activity, the *N,N*-dimethyl-derivative **12a** is highly active, whereas the corresponding *N,N*-diethyl-derivative **12b** did not show any significant activity. Replacing of *N,N*-dimethylamino group with nitrogen-containing alicyclic moieties containing or not additional heteroatoms (**13a-g** and **14**) always abated dramatically the antinocicepic activity. Among the derivatives with *N,N*-disubstituted cyclic moieties, only the imidoderivative **10** is active, showing the best significance. The antinociceptic activity was also retained significantly by the *N*-monosubstituted derivative **12d**. The interesting pharmacological profile of phthalimidoderivative **10** encourages further research on the synthesis and pharmacological screening of mono- and disubstituted amides of **11** in order to obtain new analgesic agents of potential clinical usefulness.

Phenylquinone-Induced Writhing Assay

With exception of derivative **10**, all other compounds are inactive as regard to their ability to antagonize *in vivo* the α_2-adrenoceptors. For this reason we decided to assay some of them in animals treated with phenylquinone only with the aim to explore their potential α_2-adrenoceptors agonist properties. Derivatives **12a** and **13b** are capable to contrast partially the nociceptic effects produced by administration of phenylquinone.

Table 2: Analgesic activity of derivatives **10-14** by Hot-plate test in mice

Compd[a] or controls	30 sec. $\bar{X} \pm$ S.D.[b]
Controls	4.6 ± 1.31
morphine	12.2 ± 1.6***[c]
amphetamine	12.2 ± 2.59***
10	9.65 ± 3.6***
11	5.75 ± 0.4*
12a	6.72 ± 1.4**
12b	5.86 ± 2.4
12c	5.42 ± 2.39
12d	7.11 ± 0.8***
13a	4.62 ± 1.38
13b	5.84 ± 1.73
13c	5.14 ± 1.65
13d	5.14 ± 1.89
13e	5.82 ± 2.31
13f	4.62 ± 1.57
13g	4.7 ± 1.24
14	7.5 ± 4.3

[a] Administered at 20 mg/kg dose. [b] Average ± standard deviation. [c] Significance: (*) $0.05 > p > 0.02$; (**) $0.02 > p > 0.001$; (***) $p < 0.001$.

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Experimental Part

Chemistry

M.p.: Electrothermal IA6304 (uncorr.).- IR-spectra (nujol mulls): Perkin Elmer 297.- ^{1}H-NMR-spectra: Varian EM-390 (90 MHz, TMS).- GC-MS: Hewlett-Packard hp 5890 A.- Column chromatography: silica gel Merck (70-230 mesh) and alumina Merck (70-230 mesh).- TLC: Stratocrom SIF Carlo Erba (silica gel precoated plates with fluorescent indicator) and Stratocrom ALF Carlo Erba (aluminium oxide precoated plates with fluorescent indicator).- Microanalyses: Laboratories of Prof. A. Pietrogrande, University of Padova (Italy). Organic extracts were dried over anhydrous Na_2SO_4.- Evaporation of solvents under reduced pressure.- Chemical and physical data of compounds **8-15**: Table 4 and Table 5.

Friedel-Crafts reaction of α-chlorophenacetyl chloride with 1-methylpyrrole

$AlCl_3$ (1.41 g, 0.0106 mole) was added in small portions during 30 min to a well stirred mixture of 1-methylpyrrole (0.86 g, 0.0106 mole) and α-chlorophenylacetylchloride (1.00 g, 0.0053 mole) in CH_2Cl_2 (30 ml) cooled at -20°C. After adding, the mixture was stirred at -20°C for 20 min more. Treatment with crushed ice (100 g) and concentrated HCl (2 ml) followed by extraction with $CHCl_3$ (2 x 50 ml) furnished an org. solution which was sequentially washed with brine (3 x 100 ml), $NaHCO_3$ saturated solution (3 x 100 ml), brine again (3 x 100 ml), and then dried. Removal of solvent afforded a crude mixture of 2-chloro-1-(1-methyl-1*H*-pyrrol-2-yl)-2-phenylethan-1-one (**8**) and 2-chloro-1-(1-methyl-1*H*-pyrrol-3-yl)-2-phenylethan-1-one (**9**). The isomers were separated by column chromatography. Elution furnished sequentially **8** and **9**.

1-(1-Methyl-1H-pyrrol-2-yl)-2-phenyl-2-phthalimidoethan-1-one (**10**)

Potassium phthalimide (25.70 g, 0.139 mole) was added to a well stirred solution of **8** (12.26 g, 0.0553 mole) and $Bu_4N \cdot HSO_4$ (1.88 g, 0.0055 mole) in toluene (300 ml). The mixture was refluxed for 24 h. After cooling the precipitate was removed by filtration and the solvent was evaporated. The residue was treated with ethyl acetate (100 ml), stirred and filtered to give 7.8 g of **10**. The solution was washed with brine, dried, and then evaporated to afford 11.2 g of crude product, which after chromatographic purification afforded additional 9 g of **10**.

2-Amino-1-(1-methyl-1H-pyrrol-2-yl)-2-phenylethan-2-one (**11**)

Hydrazine hydrate (2.65 ml, 0.051 mole) was added to a suspension of **10** (8.75 g, 0.0254 mole) in boiling 95% ethanol (120 ml). The mixture was vigorously stirred while refluxing for 50 min more. After cooling the precipitate was removed by filtration and the solution was evaporated. The crude aminoethanone **11** was purified by chromatography.

Derivatives **12, 13,** *and* **14**: *general procedure*

A solution of chloroethanone **9** in acetone was added dropwise to a well stirred suspension of the proper amine and K_2CO_3 in the same solvent (Table 4). The mixture was refluxed under stirring. When the reaction stopped the inorganic salt was removed by filtration and the solvent was evaporated. The residue was dissolved in $CHCl_3$ and the org. solution was washed with brine. Evaporation of the dried solution furnished crude products which were purified by chromatography or by recrystallization.

2-(1-Methyl-1H-pyrrol-2-yl)-1-phenylethan-1,2-dione (**15**)

NaN_3 (0.58 g, 0.009 mole) was added to a well stirred suspension of **8** and Bu_4NBr (0.145 g, 0.00045 mole) in dry benzene (12 ml). The mixture was refluxed for 1 h while stirring. After cooling the mixture was filtered and then evaporated to an oily residue (1.29 g), which was chromatographed to afford 0.86 g of pure **15**.

Pharmacology

Male and female Swiss inbred mice (Charles River Italia) weighing 25 ± 3 g were used. Animals were housed in standardized environmental conditions: temp. 22 ± 1°C, humidity 60-65%, light period 5 a.m. - 9 p.m. Morphine and amphetamine were used as standard controls.

Neuropsychopharmacological effects

Every single dose (20 mg/kg) of test compound, dissolved in 1% Tween 80, was administered i.p. to each group of 10 mice (5 male and 5 female). A group of mice was treated only with vehicle (treated controls - T.C.), a second group with morphine (20 mg/kg, i.p.) and a third group of animals with amphetamine (20 mg/kg, i.p.). Each single dose was dissolved in 10 ml/kg of vehicle. Results of experiments were statistically drawn up by the "Dunnet t" test[7] and percent controls were calculated using the "Fisher exact probability test". In all methods the significance against controls was estimated as follows: (*) or (°) $0.05 > p > 0.02$; (**) or (°°) $0.02 > p > 0.001$; (***) or (°°°) $p < 0.001$. Comparison was performed according to the two-tailed Student's "t" test.

Tests were performed on each animal according to the following schedule[8]:

time 0 min = supply of substance
time 15 min = spontaneous activity in an open field (A)
time 20 min = exploratory activity: hole-board (B)
time 25 min = traction test (C)
time 30 min = motor coordination in Rota-Rod test (D)
time 60 min = maximal electroshock seizures (E)

A) *Spontaneous Motor Activity*

Mice were placed individually in standard polypropylene mouse cages (19 x 25 cm). Each cage was placed on the top of a Small Animal Activities Monitor Platform (Coulbourn Instruments, Leigh Valley, U.S.A).

Table 3: *In vivo* determination of central pre-synaptic interaction with α_2-receptors

Effect of test compound and reference drugs in the phenylquinone writhing test of clonidine-induced analgesia		Effect of test compounds and reference drugs against phenylquinone-induced writhings	
Compd or Controls	n° of Contractions $\bar{X} \pm$ S.D.	Compd or Controls	n° of Contractions $\bar{X} \pm$ S.D.
T.C. 1[a]	19.0±9.21	T.C. 1[a]	19.0±5.02
T.C.2 [b]	0±0^{***c}	-	-
morphine	0±0***	-	-
amphetamine	0±0***	amphetamine	16.90±7.15
10	12.6±2.6	-	-
11	0±0***	11	18.60±7.90
12a	0±0***	12a	10.25±7.57**
12b	0±0***	-	-
12c	0±0***	-	-
12d	0.2±0.44***	-	-
13a	0.2±0.44***	13a	14.12±11.90
13b	0±0***	13b	14.25±5.20*
13c	0±0***	-	-
13d	2.2±2.28***	13d	16.25±7.28
13e	0±0***	-	-
13f	0±0***	13f	14.0±16.0
13g	0±0***	-	-
14	0±0***	-	-
-	-	clonidine	0±0***

[a] Animals treated with phenylquinone only. [b] Animals treated with clonidine and then with phenylquinone. [c] Significance: (*) or (°) $0.05 > p > 0.02$; (**) or (°°) $0.02 > p > 0.001$; (***) or (°°°) $p < 0.001$.

The sensitivity setting on each platform was adjusted to a level (10.00) producing a significant number of counts in absence of any toxin or drug, increased counts after low doses of (+)-amphetamine and decreased counts after high doses of (+)-amphetamine.

The activity of each mouse was continuously monitored for 5 min.

B) *Exploratory Activity on the Hole-Board*

This test was performed using *Boissier* and *Simon's* technique[9]. The number of explorations was recorded automatically by an infrared device placed below the four hole lines. The total number of holes explored by each animal during 5 min was recorded.

C) *Myorelaxant Action*

This action was analyzed either by the *Boissier* and *Simon's* "traction test"[10] [time employed by animals to place their hind legs on an horizontal wire (wire reflex) (C^1)] or by determining how long the animals stayed on wire (C^2) (cut-off 120 sec).

D) *Action on Motor Coordination*

This action was examined using the Rota-Rod test[11]. The number of fallings of the animals during an observation period of 180 sec was determined.

E) *Anticonvulsant Activity*

This activity was tested determining the protection from seizures and from death caused by the electroshock intensity produced by the U. Basile ECT-Unit 7800 apparatus adjusted as follows: 200 mA frequency pulses/sec; 60 mA current intensity; 0.4 sec shock duration; 0.6 msec pulse width. The animals were considered "protected" (P) when they did not show seizures, "non-protected" (NP) when animals died in consequence of seizures and "partially protected" (PP) when they show seizures without death.

Table 4: Preparative and analytical data

Nr	Yield (%)	Formula (MW)	Reagents ratio [a] A	B	C	Reaction Time (h)	Chrom. system [b]	MP (°C) solvent [c]	Analysis (%) Found / Calcd C	H	N	Cl	S
10	48.9	$C_{21}H_{16}N_2O_3$ 344.35	-	-	-	-	D	176-177 H	73.29 / 73.24	4.73 / 4.68	8.15 / 8.14		
11	94.6	$C_{13}H_{14}N_2O_3$ 214.26	-	-	-	-	E	71-72 H	72.71 / 72.87	6.71 / 6.59	13.09 / 13.08		
12a	15.2	$C_{15}H_{18}N_2O$ 242.31	2	2	3	168	D	82-83 I	74.40 / 74.35	7.42 / 7.49	11.40 / 11.56		
12b	39.8	$C_{17}H_{22}N_2O_3$ 270.36	4	4	2	144	D	-	-	-	-		
12c	43.7	$C_{21}H_{22}N_2O_3$ 334.40	4	4	3	216	-	127-128 L	75.34 / 75.42	6.71 / 6.63	8.34 / 8.38		
12d	60.0	$C_{20}H_{18}Cl_2N_2O$ 373.27	6	6	9	240	F	75-76 M	64.07 / 64.35	5.02 / 4.86	7.38 / 7.51	19.19 / 19.00	
13a	65.4	$C_{17}H_{20}N_2O_2$ 284.35	2	2	2	12	G	97-98 L	71.61 / 71.80	7.16 / 7.09	10.01 / 9.85		
13b	37.4	$C_{17}H_{20}N_2SO$ 300.41	2	2	2	72	D	128-129 I	68.25 / 67.96	6.90 / 6.71	9.45 / 9.33		10.45 / 10.67
13c	97.3	$C_{18}H_{22}N_2O$ 282.37	2	2	2	48	G	87-88 I	76.60 / 76.56	8.08 / 7.85	9.84 / 9.92		
13d	100	$C_{18}H_{23}N_3O$ 297.39	2	2	2	72	-	131-132 L	72.46 / 72.69	7.86 / 7.80	14.26 / 14.13		
13e	77.6	$C_{19}H_{23}N_3O_2$ 325.40	2	2	3	144	G	87-88 I	-	-	-		
13f	75.2	$C_{24}H_{27}N_3O$ 373.48	2	2	3	120	-	111-112 M	77.35 / 77.18	7.34 / 7.29	11.14 / 11.25		
13g	91.6	$C_{25}H_{28}N_2O$ 372.49	2	2	3	24	D	-	-	-	-		
14	53.4	$C_{17}H_{20}N_2O$ 268.35	2	2	2	96	D	62-63 L	75.94 / 76.08	7.54 / 7.51	10.28 / 10.44		
15	-	$C_{13}H_{11}NO_2$ 213.23	-	-	-	-	-	83-84 L	73.28 / 73.22	5.14 / 5.20	6.61 / 6.57		

[a] A: chloroethanone **8**; B: amine; C: K_2CO_3. [b] D: $Al_2O_3/CHCl_3$:petroleum ether (1:1); E: Al_2O_3/ethyl acetate; F: SiO_2/ethyl ether: n-hexane (1:1); G: $Al_2O_3/CHCl_3$. [c] H: benzene:cyclohexane; I: cyclohexane: n-hexane; L: cyclohexane; M: n-hexane.

Antinociceptive Action. Hot-Plate Test

30 min after administration of test compounds, the animals were gently placed on the surface of the plate maintained at 55.5 ± 0.5°C. When the animal was licking its paw, latency (cut-off 15 sec) was measured.

Phenylquinone-Induced Writhing Assay

This test was used to evaluate *in vivo* the interaction of test compounds with central α_2-receptors. In this test the substances were administered i.p. to mice (20 mg/kg) and their ability to antagonize analgesic effects of clonidine was determined by the *Fielding* method[12]. 30 min after i.p. injection of test substance, mice were treated *per os* with clonidine (0.1 mg/kg). 20 min later, phenylquinone was injected i.p., and the number of writhings was counted 5 min after injection.

A group of animals was treated in the same manner without administration of clonidine. This modification of *Fielding* test was made to evaluate the agonist ability of the test substance against α_2-adrenoceptors.

References

1 An account of the present work has been presented at CISCI 90 (Congresso Interdivisionale della Società Chimica Italiana), San Benedetto del Tronto, Sept. 30 - Oct. 5, 1990.

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Table 5: Spectroscopic data of derivatives **8-15**

Nr	IR cm^{-1}	^{1}H-NMR[a] δ
8	1630 (CO)	3.90 (s, 3H, CH_3), 6.07-6.18 (m, 2H, overlapped CH and H-4 pyrrole), 6.85 (m, 1H, H-5 pyrrole), 7.08 (m, 1H, H-3 pyrrole), 7.30-7.68 ppm (m, 5H, benzene H).
9	1640 (CO)	3.57 (s, 3H, CH_3), 5.93 (s, 1H, CH), 6.53 (m, 2H, H-4 and H-5 pyrrole), 7.27-7.62 ppm (m, 6H, H-3 pyrrole and benzene H).
10	1655 - 1710 (CO imide and ketone)	3.95 (s, 3H, CH_3), 5.95 (m, 1H, H-4 pyrrole), 6.63-6.77 (4 m, 2H, overlapped CH and H-5 pyrrole), 6.83 (m, 1H, H-3 pyrrole), 7.25-7.93 ppm (m, 9H, benzene H).
11	3280, 3350 (NH_2) 1635 (CO)	3.90 (s, 3H, CH_3), 5.48 (bs, m, NH_2), 5.68 (s, 1H, CH), 6.08 (m, 1H, H-4 pyrrole), 7.32(m, 1H, H-5 pyrrole), 7.25-7.68 ppm (m, 6H, H-3 pyrrole and benzene H).
12a	1640 (CO)	2.23 (s, 6H, $N(CH_3)_2$) , 3.87 (s, 3H, CH_3), 4.50 (s, 1H, CH), 6.06 (m, 1H, H-4 pyrrole), 6.80(m, 1H, H-5 pyrrole), 7.17-7.65 ppm (m, 6H, H-3 pyrrole and benzene H).
12b	1635 (CO)	0.97 (t, 6H, J=7.5 Hz, CH_2CH_3 , 2.70(q, 4H, J=7.5 Hz, CH_2CH_3), 3.90 (s, 3H, NCH_3), 5.13 (s, 1H, CH), 6.07 (m,1H, H-4 pyrrole), 6.77(m, 1H, H-5 pyrrole), 7.13--7.43(m,4H, H-3 pyrrole and *meta* and *para* benzene H), 7.43-7.63 ppm (m, 2H, *ortho* benzene H).
12c	3390 (NH), 1630 (CO)	1.28 (t, 3H, J= 6 Hz, CH_3), 3.83 (s, 3H, NCH_3), 3.88 (q, 2H, J= 6 Hz, CH_2), 4.97 (bs, 1H, NH), 5.68 (s, 1H, CH), 6.10 (m, 1H, H-4 pyrrole), 6.53--=6.75 (m, 4H, *para*-phenetidine H), 6.80 (m,1H, H-5 pyrrole), 7.18-7.60 ppm (m, 6H, H-3 pyrrole and benzene H).
12d	3300 (NH), 1625 (CO)	2.58 (bs, 1H, NH), 3.77 (s, 2H, CH_2), 3.88 (s, 3H,CH_3), 5.03 (s,1H, CH), 6.07 (m, 1H, H-4 pyrrole), 6.78 (m, 1H, H-5 pyrrole), 6.98 (m, 1H, H-3 pyrrole), 7.17-7.52 ppm (m, 8H, benzene H).
13a	1630 (CO)	2.47 (m, 4H, H-2; H-6 morpholine), 3.72 (m, 4H, H-3; H-5 morpholine), 3.85 (s, 3H, CH_3), 4.58 (s, 1H, CH), 6.08 (m, 1H, H-4 pyrrole), 6.80 (m, 1H, H-5 pyrrole), 7.22--7.40 (m, 4H, H-3 pyrrole and *meta* and *para* benzene H), 7.48-7.60 ppm (m, 2H, *ortho* benzene H).
13b	1640 (CO)	2.57-2.90 (m, 8H, CH_2), 3.85 (s, 3H, CH_3), 4.75 (s, 1H, CH), 6.07 (m, 1H, H-4 pyrrole), 6.78 (m, 1H, H-5 pyrrole), 7.13-7.62 ppm (m, 6H, H-3 pyrrole and benzene H).
13c	1640 (CO)	1.50 (m, 6H, H-3; H-4; H-5 piperidine), 2.40 (m, 4H, H-2; H-6 piperidine), 3.85 (s,3H, CH_3), 4.57 (s, 1H, CH), 6.07 (m,1H, H-4 pyrrole), 6.85 (m, 1H, H-5 pyrrole), 7.18--7.35 (m, 4H, H-3 pyrrole and *meta* and *para* benzene H), 7.40-7.57 ppm (m, 2H, *ortho* benzene H).
13d	1630 (CO)	2.23 (s, 3H, NCH_3 piperazine), 2.47 (m, 8H, CH_2), 3.87 (s, 3H, NCH_3 pyrrole), 4.58 (s, 1H, CH), 6.08 (m, 1H, H-4 pyrrole), 6.75 (m, 1H, H-5 pyrrole), 7.22-7.35 (m, 4H, H-5 pyrrole and *meta* and *para* benzene H), 7.45- 7.58 ppm (m, 2H, *ortho* benzene H).
13e	1610-1650 (CO imide and ketone)	1.98 (s, 3H, $COCH_3$), 2.35-2.61 (m, 4H, H-2; H-6 piperazine), 3.45-3.63 (2t, 4H, H-3; H-5 piperazine), 3.85 (s, 3H NCH_3), 4.65 (s, 1H, CH), 6.07 (m, 1H, H-4 pyrrole), 6.78 (m, 1H, H-5 pyrrole), 7.18 (m, 1H, H-3 pyrrole), 7.65-7.60 ppm (m, 5H, benzene H).
13f	1625 (CO)	2.48 (s, 8H, CH_2 piperazine), 3.48 (s, 2H, CH_2 benzile), 3.83 (s, 3H, CH_3), 4.58 (s, 1H, CH), 6.05 (m, 1H H-4 pyrrole), 6.77 (m, 1H, H-5 pyrrole), 7.22-7.65 ppm (m, 6H, H-3 pyrrole and benzene H).
13g	1630 (CO)	1.35-1.68 (m, 4H, H-3; H-5 piperidine), 1.71-2.18 (m, 1H, H-4 piperidine), 2.51 (d, 2H, CH_2 benzyle), 2.65-3.15 (m, 2H, H-2; H-6 piperidine), 3.83 (s, 3H, CH_3), 4.58 (s, 1H; COCH), 6.05 (m, 1H, H-4 pyrrole), 6.75 (m, 1H, H-5 pyrrole), 7.05-7.60 ppm (m, 11H, H-3 pyrrole and benzene H).
14	1630 (CO)	1.77 (m, 4H, H-3; H-4 pyrrolidine), 2.33-2.73 (m, 4H, H-2; H-5 pyrrolidine), 3.87 (s, 3H, CH_3), 4.60 (s, 1H, CH), 6.10 (m, 1H, H-4 pyrrole), 6.77 (m, 1H, H-5 pyrrole), 7.20-7.43 (m, 4H, H-3 pyrrole and *meta* and *para* benzene H), 7.50-7.70 ppm (m, 2H, *ortho* benzene H).
15[b]	1665, 1615 (CO)	4.03 (s, 3H, CH_3), 6.17 (m, 1H, H-4 pyrrole), 6.78-7.23 (m, 2H, H-3; H-5 pyrrole), 7.38-7.73 (m, 3H, *meta* and *para* benzene H), 7.90-8.20 ppm (m, 2H, *ortho* benzene H)

[a] Spectra were performed in $CDCl_3$ for all compounds, with exception of derivative **11** (DMF-d_7).

[b] MS: m/e 213 (M^+).

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