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α-Methoxy-*O*-(*N*-arylcarbamoyl)oximes: synthesis and pharmacological activities

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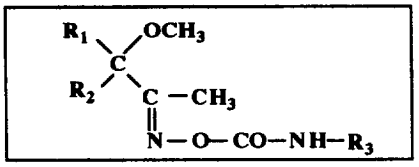
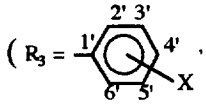
Introduction

In our previous studies [1, 2], we reported antiinflammatory and CNS activities (notably anticonvulsant properties) for some α-hydroxy *O*-alkyl ether–oxime compounds. A number of molecules with an ester carbamic function have CNS activity [3–6] and so we wanted to substitute the alkyl group on the *O*-alkyl-ether function of previously described compounds [1, 2] by a carbamoyl group. In this new series, a methoxy group also takes the place of the tertiary alcohol function. Indeed, for this new series, we only wanted monocarbamates and so we transformed the tertiary alcohol function of the previously described prototype series into an ether.



($R_1 = CH_3, C_3H_7$)
($R_2 = C_2H_5, C_3H_7$)
($R_1, R_2 = -(CH_2)_5-$)



(R_3 = , X = H, 3'- Cl, 4'- Cl, 4'- F, 6' - OCH_3)

In this study, we report the synthesis, anticonvulsant and antiinflammatory properties of these new compounds, α-methoxy-*O*-(*N*-arylcarbamoyl)oximes.

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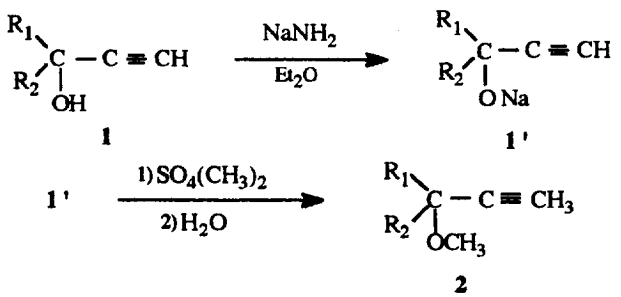
Chemistry

Ten new carbamates of α-methoxyoxime were synthesized from α-acetylenic tertiary alcohols. Acetylenic alcohol **1** was dissolved in anhydrous diethyloxide ether and was treated with commercial sodium amide in ether suspension under a nitrogen atmosphere. After evaporation of NH_3, acetylenic alcoholate **1'** was treated with methylsulfate, also under nitrogen [7].



Excess methylsulfate was removed by refluxing with sodium hydroxide [2, 7]. The α-acetylenic alcohols **1** used were purchased from Aldrich (France), except for 3-propylhex-1-yn-3-ol, which was obtained by treatment of heptan-4-one with sodium acetylide in liquid ammonia [8].

The synthesis of α-methoxyketones **3** was carried out by mercuric hydration of acetylenic methylethers, using mercuric oxide in aqueous sulfuric solution [9, 10]. The physical and chemical characteristics of **2** and **3** were in accordance with the literature.

The new methoxyoximes **4** were prepared by condensation of α-methoxyketone **3** with hydroxylamine hydrochloride in absolute alcohol, using

pyridine as a catalyst [10]. The physical properties of compounds **2–4** are shown in table I. The new α-methoxy-*O*-(*N*-arylcarbamoyl)oximes **5** were obtained by condensation of α-methoxyoximes **4** with the corresponding arylisocyanic derivatives and triethylamine as a catalyst, in an anhydrous ether mixture (scheme 1) [11].

The *E* configuration was found for compounds **5** from a crystallographic analysis for **5b** using interatomic distances (Å) and bond angles (°) [2]. The pure products **5** were characterized by their IR, ^1H and ^{13}C-NMR spectra (tables II and III) and elemental analysis.

Pharmacology and discussion

The pharmacological results are presented in table IV (for compounds **5**).

Acute toxicity

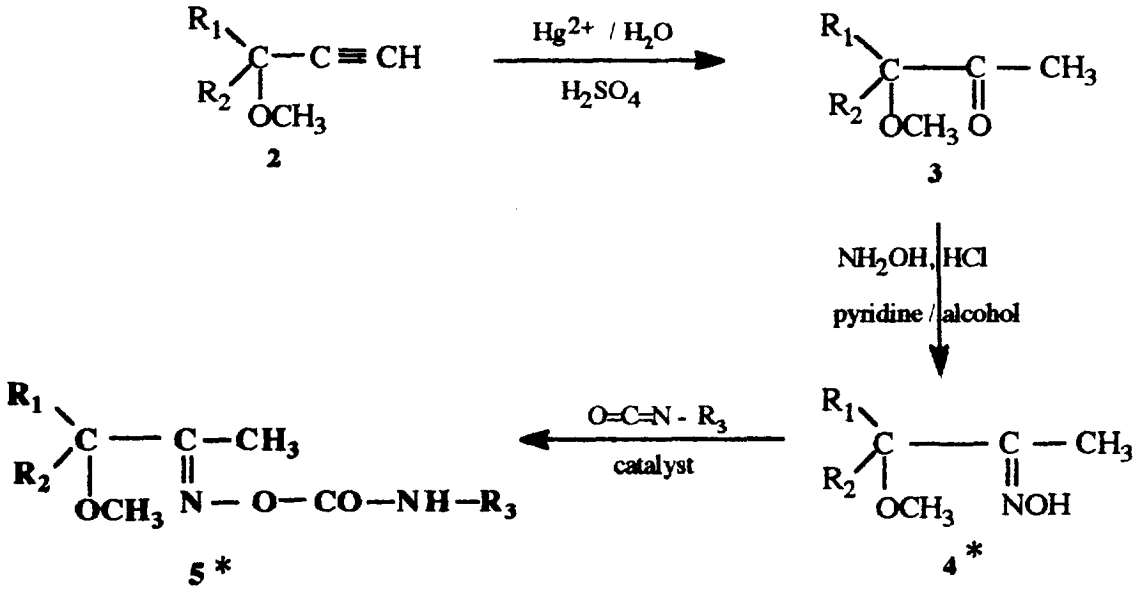
Under our experimental conditions, all the tested compounds were found to be atoxic orally (level 1 in Lorke's classification) [12] and no signs of intoxication were observed. By the intraperitoneal route, the dose of 1000 mg/kg induced 10% lethality only with **5b** and **5g** but no lethality for the other compounds. The main symptoms observed were sedation, decreased locomotor activity and ataxic gait (especially for **5a**, **5b**, **5e** and **5h**) and nociception (**5b**); these symptoms were not observed at 10 mg/kg.

Anti-oedematous activity

The results are expressed as a percentage of oedematous podal reduction with regard to control animals which only received 1% carrageenan. Dunnett's test

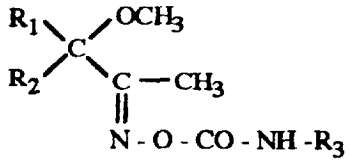
Table I. Physical properties of intermediate compounds **2–4**.

	R_1	R_2	2		3		4	
			Yield (%)	*Bp (°C/mmHg)*	*Yield (%)*	*Bp (°C/mmHg)*	*Yield (%)*	*Bp (°C/mmHg)*
α	CH_3	C_2H_5	25	103/760	50	42–45/760	92	30–40/0.4
β	-$(CH_2)_5$-		62	62/25	74	45–55/0.5	12	(Mp = 80 °C)
γ	C_3H_7	C_3H_7	65	70/25	58	125–130/760	90	112/0.3



Scheme 1.

Table II. Physical properties and IR spectra of compounds **5a–j**.



Compound	R_1	R_2	R_3	*Mp (°C)*	*Yield (%)*	*IR ν (cm^{-1})*
5a	CH_3	C_2H_5	C_6H_5	63	15	3280 (NH), 2820 (OCH_3), 1720 (CO), 1600 (CN)
5b	CH_3	C_2H_5	4'-ClC_6H_4	100	82	3280 (NH), 2820 (OCH_3), 1730 (CO), 1600 (CN)
5c	CH_3	C_2H_5	4'-FC_6H_4	73	36	3280 (NH), 2820 (OCH_3), 1730 (CO), 1620 (CN)
5d	CH_3	C_2H_5	3'-ClC_6H_4	115	87	3280 (NH), 2820 (OCH_3), 1725 (CO), 1630 (CN)
5e	CH_3	C_2H_5	6'-$CH_3OC_6H_4$	105	55	3280 (NH), 2820 (OCH_3), 1750 (CO), 1600 (CN)
5f	CH_3	C_2H_5	C_6H_{11}	62	62	3260 (NH), 2820 (OCH_3), 1730 (CO), 1630 (CN)
5g	-$(CH_2)_5$-		C_6H_5	85	15	3280 (NH), 2820 (OCH_3), 1730 (CO), 1600 (CN)
5h	-$(CH_2)_5$-		4'-FC_6H_4	72	19	3260 (NH), 2820 (OCH_3), 1730 (CO), 1620 (CN)
5i	-$(CH_2)_5$-		4'-ClC_6H_4	75	23	3260 (NH), 2820 (OCH_3), 1720 (CO), 1600 (CN)
5j	C_3H_7	C_3H_7	4'-ClC_6H_4	100	15	3280 (NH), 2820 (OCH_3), 1720 (CO), 1600 (CN)

[13] applied to the whole assay showed significant activity ($P \leq 0.01$) for acetylsalicylic acid (ASA); compounds **5a**, **5b**, **5f**, **5g** and **5i** with 65, 55, 56, 49 and 71% activity, respectively, were significantly active ($P \leq 0.01$), and the magnitudes of their effects were of the same order as that of ASA (no significant differences with Kruskall and Wallis test [15, 16]; 55% decrease in oedema).

Anticonvulsant activity

The results are expressed as percentage increase (+) or decrease (–) of one parameter (time delay of appearance of clonic seizures) with respect to the control animals which received only the convulsant agent (pentetrazol). The number of tonic seizures and deaths was expressed as a percentage. These results were analyzed by the Student's test for the latency period before clonic seizures. It showed a significant increase ($P \leq 0.01$) of the latency period before clonic seizures with compounds **5b**, **5i** and diazepam, in line with anticonvulsive effects [14]. This protective effect was also found upon the percentage of tonic seizures and deaths, but only for **5i**.

Antinociceptive activity: Koster test

The results are expressed as percentage of protection (decrease in painful writhes), evaluated over 10 min, with regard to standard animals which received only ASA. They were analyzed by the Kruskal and Wallis test [15, 16] and Mann–Whitney *U* test [17], which showed a significant protective activity for compound **5b**, with a 69% reduction in nociception ($P \leq 0.01$) and compounds **5a**, **5c** and **5h** with 46, 29 and 38% decrease, respectively ($P \leq 0.05$).

Conclusion

This study showed that two products displayed a real anticonvulsant activity: compounds **5b** and **5i**, whose nitrogen of the carbamoyl function had the same *para*-chlorophenyl substituent. Furthermore, five compounds (**5a**, **5b**, **5f**, **5g** and **5i**) showed an antiinflammatory activity (revealed by the Dunnett's test), with higher or similar activity as the standard (ASA). We have compared pharmacological activities of previously described α-hydroxy-*O*-alkyletheroximes [1], with

Table III. ^{1}H and ^{13}C-NMR spectra of compounds **5a–j**.

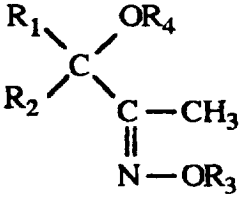
Compound	*^{1}H-NMR ($CDCl_3$): δ (ppm), J (Hz)*	*^{13}C-NMR ($CDCl_3$): δ (ppm), J (Hz)*
5a	0.89 (t, 3H, CH_3 ethyl) J = 7.5; 1.39 (s, 3H, CH_3), 1.77 (q, H_1, CH_2) J_1 = 7.5; 1.75 (q, H_2, CH_2) J = 7.5; 2.1 (s, 3H, =CCH_3), 3.14 (s, 3H, OCH_3), 7.13 (tt, $H_{4'}$) J_O = 7.3, J_m = 1.2; 7.36 (t, $H_{3'5'}$) J = 7.9; 7.49 (dd, $H_{2'6'}$) J_O = 8.8, J_m = 0.9; 8.21 (NH)	7.9 (CH_3CH_2); 11.5 (C*CH_3); 19.1 (=CCH_3); 30.2 (CH_3CH_2); 51.2 (OCH_3); 80.5 (C*); 152.2 (CO); 167.0 (CN); 119.6 ($C_{2'6'}$); 124.3 ($C_{4'}$); 129.1 ($C_{3'5'}$); 137.0 ($C_{1'}$)
5b	0.88 (t, 3H, CH_3 ethyl) J = 7.5; 1.39 (s, 3H, CH_3), 1.77 (q, H_1, CH_2) J_1 = 7.5; 1.74 (q, H_2, CH_2) J = 7.5; 2.07 (s, 3H, =CCH_3), 3.14 (s, 3H, OCH_3), 7.31 (t, $H_{3'5'}$) J = 8.9; 7.44 (dd, $H_{2'6'}$) J_O = 8.9; 8.21 (NH)	7.9 (CH_3CH_2); 11.4 (C*CH_3); 19.1 (=CCH_3); 30.2 (CH_3CH_2); 51.1 (OCH_3); 80.4 (C*); 152.0 (CO); 167.4 (CN); 120.7 ($C_{2'6'}$); 129.3 ($C_{4'}$); 129.1 ($C_{3'5'}$); 135.6 ($C_{1'}$)
5c	0.88 (t, 3H, CH_3 ethyl) J = 7.5; 1.39 (s, 3H, CH_3), 1.77 (q, H_1, CH_2) J_1 = 7.5; 1.74 (q, H_2, CH_2) J = 7.5; 2.07 (s, 3H, =CCH_3), 3.14 (s, 3H, OCH_3), 7.05 (t, $H_{3'5'}$) J_O = $J_{O\text{-}F}$ = 8.7; 7.45 (dd, $H_{2'6'}$) J_O = 9.1, $J_{m\text{-}F}$ = 4.7; 8.17 (NH)	7.9 (CH_3CH_2); 11.5 (C*CH_3); 19.1 (=CCH_3); 30.2 (CH_3CH_2); 51.1 (OCH_3); 80.4 (C*); 161.9 (CO); 167.2 (CN); 115.8 (d, $C_{2'6'}$) $J_{C\text{-}F}$ = 22.3; 121.5 (d, $C_{3'5'}$), $^{2}J_{C\text{-}F}$ = 8.0; 133.0 ($C_{1'}$); 154.7 (d, $C_{4'}$) $^{1}J_{C\text{-}F}$ = 23.43
5d	0.91 (t, 3H, CH_3 ethyl) J = 7.5; 1.39 (s, 3H, CH_3), 1.77 (q, H_1, CH_2) J_1 = 7.5; 1.74 (q, H_2, CH_2) J = 7.5; 2.07 (s, 3H, =CCH_3), 3.14 (s, 3H, OCH_3), 7.11 (td, $H_{4'}$) J_O = 7.8, J_m = 1.5; 7.27 (t, $H_{5'}$) J_O = 7.9; 7.38 (td, $H_{6'}$) J_O = 8.2, J_m = 1.6; 7.56 (t, $H_{2'}$) J_m = 1.9; 8.24 (NH)	7.9 (CH_3CH_2); 11.5 (C*CH_3); 19.1 (=CCH_3); 30.2 (CH_3CH_2); 51.2 (OCH_3); 80.4 (C*); 151.9 (CO); 167.5 (CN); 117.6 ($C_{2'}$); 124.3 ($C_{4'}$); 130.1 ($C_{5'}$); 134.8 ($C_{3'}$); 138.2 (C_1)
5e	0.90 (t, 3H, CH_3 ethyl) J = 7.5; 1.41 (s, 3H, CH_3), 1.78 (q, H_1, CH_2) J_1 = 7.5; 1.77 (q, H_2, CH_2) J = 7.5; 2.07 (s, 3H, =CCH_3), 3.15 (s, 3H, OCH_3), 3.68 (s, 3H, OCH_3), 6.89 (dd, $H_{5'}$) J_O = 7.6, J_m = 2.0; 6.97–7.10 (m, $H_{3'4'}$); 8.22 (dd, $H_{2'}$) J_O = 7.3, J_m = 2.3; 9.04 (NH)	7.9 (CH_3CH_2); 11.2 (C*CH_3); 18.8 (=CCH_3); 30.2 (CH_3CH_2); 51.1 (OCH_3); 55.8 (6'-OCH_3); 80.5 (C*); 152.0 (CO); 166.2 (CN); 110.0 ($C_{5'}$); 118.5 ($C_{2'}$); 121.2 ($C_{3'}$); 122.6 ($C_{1'}$); 123.4 ($C_{4'}$); 148.1 ($C_{6'}$)
5f	0.85 (t, 3H, CH_3 ethyl) J = 7.5; 1.32 (s, 3H, CH_3), 1.71 (q, H_1, CH_2) J_1 = 7.5; 1.69 (q, H_2, CH_2) J = 7.5; 2.00 (s, 3H, =CCH_3), 3.11 (s, 3H, OCH_3), 3.60–3.70 (m); 6.15 (NH)	7.6 (CH_3CH_2); 11.2 (C*CH_3); 19.0 (=CCH_3); 30.1 (CH_3CH_2); 51.0 (OCH_3); 80.3 (C*); 154.6 (CO); 165.8 (CN); 24.6 ($C_{3'5'}$); 25.5 ($C_{4'}$); 33.0 ($C_{2'6'}$); 49.7 ($C_{1'}$)
5g	1.60–1.63 (m, 10H, cyclohexyl), 2.06 (s, 3H, CH_3), 3.11 (s, 3H, OCH_3), 7.13 (tt, 2H, $H_{4'}$), J_O = 3.6, J_m = 7.3; 7.36 (t, $H_{3'5'}$) J_O = 3.7, J_m = 7.9; 7.49 (dd, $H_{2'6'}$) J_O = 0.6, J_m = 4.3; 8.21 (NH)	11.2 ($C_{4''}$); 24.4 ($C_{3''5''}$); 31.8 ($C_{2''6''}$); 78.5 ($C_{1''}$); 25.5 (=CCH_3); 50.6 (OCH_3); 119.6 ($C_{2'6'}$); 124.1 ($C_{4'}$); 129.1 ($C_{3'5'}$); 133.5 ($C_{1'}$); 161.0 (CO)
5h	1.58–1.62 (m, 10H, cyclohexyl), 2.06 (s, 3H, CH_3), 3.11 (s, 3H, OCH_3), 7.05 (t, $H_{3'5'}$) J_O = $J_{O\text{-}F}$ = 8.65; 7.45 (dd, $H_{2'6'}$) J_O = 9.1, $J_{m\text{-}F}$ = 4.7; 8.20 (NH)	11.2 ($C_{4''}$); 21.4 ($C_{3''5''}$); 31.8 ($C_{2''6''}$); 78.5 ($C_{1''}$); 25.4 (=CCH_3); 50.5 (OCH_3); 115.7 (d, $C_{2'6'}$) $^{3}J_{C\text{-}F}$ = 22.9; 121.5 (d, $C_{3'5'}$) $^{2}J_{C\text{-}F}$ = 8.25; 154.7 (d, $C_{4'}$) $^{1}J_{C\text{-}F}$ = 22.93; 133.0 ($C_{1'}$); 161.9 (CO); 167.5 (C=N)
5i	1.58–1.62 (m, 10H, cyclohexyl), 2.06 (s, 3H, CH_3), 3.11 (s, 3H, OCH_3), 7.31 (d, $H_{3'5'}$) J_O = 9.0; 7.45 (d, $H_{2'6'}$) J_O = 9; 8.25 (NH)	11.2 ($C_{4''}$); 21.4 ($C_{3''5''}$); 31.8 ($C_{2''6''}$); 78.5 ($C_{1''}$); 25.5 (=CCH_3); 50.5 (OCH_3); 120.8 ($C_{2'6'}$); 129.1 (d, $C_{3'5'}$); 129.3 ($C_{4'}$); 135.7 ($C_{1'}$); 167.6 (C=N)
5j	0.96 (t, 3H, CH_3 propyl) J = 7.2; 1.45–1.77 (m, 2H, CH_2 propyl); 2.06 (s, 3H, CCH_3); 3.10 (s, 3H, OCH_3); 7.31 (d, $H_{3'5'}$, Ph) J_O = 9.0; 7.44 (d, $H_{2'6'}$, Ph) J_O = 9.0; 8.20 (s, NH)	14.5 (CH_3 propyl); 16.4 ($CH_3CH_2CH_2$); 34.4 (CH_3-CH_2CH_2); 29.1 (=CCH_3); 50.6 (OCH_3); 82.3 ($C_3H_7)_2$ *C*; 120.8 ($C_{2'6'}$); 129.1 ($C_{3'5'}$); 129.3 ($C_{4'}$); 133.2 ($C_{1'}$); 152.1 (CO); 167.4 (C=N)

Table IV. Pharmacological results.

Compound	*Antioedematous activity (% of variation/ control)*	*Anticonvulsant activity*			*Antinociceptive activity Koster (% of variation/ control)*
		Latency period before clonic seizures (% of variation/ control)	*Tonic seizures (% of presence)*	*Lethality (% of presence)*	
Control	–	–	30	20	–
5a	65**	+ 20	20	20	46*
5b	55**	+ 94*	30	30	69**
5c	–33	+ 33	50	10	29*
5d	6	–	50	20	20
5e	–58**	+ 50	60	40	0
5f	56**	–30	30	20	5
5g	49**	+30	60	20	0
5h	29	–57	40	40	38*
5i	71**	+ 253*	10	10	4
5j	20	+ 50	10	30	13
ASA[a]	55**	–	–	–	72**
Diazepam[b]	–	+ 300*	0	0	

[a]250 mg/kg po, antioedematous activity and 50 mg/kg po, antinociceptive activity; [b]2.5 mg/kg po, anticonvulsant activity; $*P \leq 0.05$; $**P \leq 0.01$, with respect to respective controls, Dunnett, Kruskal and Wallis and Mann–Whitney *U* tests.

those described in this report. The two series corresponded to the following general structure:



Compounds **3**: R_3 = alkyl, R_4 = H; compounds **5**: R_3 = phenylcarbamoyl, $R_4 = CH_3$.

The two series were very different as regards of the nature of the R_3 group, but they did show some similar pharmacological properties. First, antiinflammatory activity was present in both series. It was moderate for most of the compounds of the first series, but definitely improved for **5** (except for **5c** and **5e**). Three molecules **5** (**5a**, **5f** and **5i**) showed a higher activity than the standard (ASA); **5b** was similar. Second, anticonvulsant activity was found in both series and was greater in the first series when R_3 was an alkyl group (for example, if $R_3 = CH_3$, C_2H_5), and in **5** (for example, if R_3 was 4-chlorophenyl, like **5b**, **5i**). Finally, antinociceptive activity seemed to be increased in **5** with respect to **3**, because there was a greater number of statistically active compounds in the former (4:10 and 1:11, respectively).

Experimental protocols

Chemistry

Infrared spectra were obtained using KBr pellets (2%) on a Perkin–Elmer 1310 spectrophotometer. ^1H and ^{13}C-NMR spectra were recorded on a Bruker AC 200 spectrometer using $CDCl_3$ as solvent. Elemental analyses were performed by the Service Central d'Analyses du CNRS and were within 0.4% of the theoretical values. Thin layer chromatography (TLC) was carried out on Merck precoated 0.25 mm analytical silica-gel plates 60 F_{254} using the solvent system chloroform/methanol (90:10, v/v) with ultraviolet detection.

Synthesis of O-(N-aryl)carbamates of α-methoxyoximes
The synthesis of compound **5b** will be described as an example.

Preparation of 3-methoxy-3-methylpent-1-yne 2α [2, 8]. The entire reaction was carried out under a nitrogen atmosphere. A suspension of commercial sodium amide (0.5 mol) in anhydrous diethyloxide ether was prepared under magnetic stirring. An ether solution of commercial 3-methylpent-1-yne-3-ol (0.35 mol) was added dropwise, first cold and then under 1 h reflux. After evaporation to remove NH_3, residual acetylenic alcoholate was treated with methylsulfate (0.5 mol) in ether solution under 1 h refluxing. Aqueous hydrolysis, ether extraction, and evaporation in vacuo under reduced pressure gave the crude product, which was purified by distillation [bp (°C/mmHg) = 103/760]. Excess methylsulfate was removed by refluxing with sodium hydroxide (15%).

Preparation of 3-methoxy-3-methylpentan-2-one 3α [2, 9, 10]. A mixture of 3-methoxy-3-methylpent-1-yne **2α** (0.2 mol) and mercuric oxide (2 g), in aqueous sulfuric solution (20%, w/v)

was refluxed for 2 h. After evaporation, the organic layer was neutralized with sodium bicarbonate, dried over anhydrous sodium sulfate and evaporated. Crude ketone was purified by normal pressure distillation [bp (°C/mmHg) = 45/760].

Preparation of 3-methoxy-3-methylpentan-2-one-oxime ***4α.*** A mixture of **3α** (0.05 mol) and hydroxylamine hydrochloride (0.05 mol) was refluxed for 2 h in absolute alcohol (75 mL) with pyridine (7.5 mL) as a catalyst. Solvent was evaporated and oily residue was treated by water (75 mL) in an ice-bath and then extracted with diethylether. The organic layer was dried over Na_2SO_4 and evaporated in vacuo to give crude original compound **4α**, purified by distillation [yield = 92%; bp (°C/mmHg) = 35/0.4].

Preparation of 3-methoxy-3-methylpentan-2-one-O-[N-(p-chlorophenyl)carbamoyl]oxime ***5b*** *[2, 11].* A mixture of 3-methoxy-3-methylpentan-2-one-oxime (0.025 mol) **4α**, 4-chlorophenyl isocyanate (0.025 mL) and triethylamine (10 drops) in anhydrous diethylether was stirred under reflux in a nitrogen atmosphere for 18 h. The reaction was controlled by TLC using chloroform/methyl alcohol (9:1) as eluent. As soon as a white crystallization appeared, the reactional mixture was evaporated and the crude resulting compound **5b** was purified by recrystallization in hexane (yield = 82%; mp = 100 °C).

Pharmacology

Synthesized compounds (**5a–j**) were tested for their antiinflammatory and CNS activities as well as for their acute toxicity. All experiments were performed in male Swiss mice EOPS purchased from IFFA CREDO (L'Arbresle, France), which were acclimatized to laboratory conditions for 1 week. The animals weighed about 20 g and were deprived of food for 12 h prior to the experiment, but water was available ad libitum.

For antioedematous, anticonvulsant and antinociceptive activities testing, the studied compounds were administered per os in suspension in a 0.1% aqueous solution of carboxymethylcellulose under 0.5 mL/20 g body weight constant volume administration. For acute toxicity, compounds were administered both per os in the same conditions as above and by the intraperitoneal route in the same volume of vehicle.

Acute toxicity

Acute toxicity was studied according to the method described by Lorke [12] in which the tested compounds were administered at doses of 10, 100 or 1000 mg/kg in three groups of three mice. Animals were kept under observation during the 15 days following the treatment. The purpose of this study was to define the lethality of the molecules according to ten levels: the first level (no lethality for the three tested doses) corresponded to the lowest acute toxicity, and the tenth level to the maximal acute toxicity (100% of lethality for the three tested doses).

Antioedematous activity

The method of Levy [18] was used on mice randomly divided into various groups, each group including ten treated animals or 20 control animals. Thirty minutes after administration of the tested compound or ASA (250 mg/kg po) or vehicle, the mouse was injected 0.025 mL of a freshly prepared suspension of carrageenan in water (1%) under the planter aponeurosis of the right hind paw. Four hours after the beginning of the experiment, all the animals were sacrificed and the hind paws were cut at the tarsocrural articulation level and weighed.

Anticonvulsant activity

The method described by Krall [19] and modified by Kupferberg [20] was applied to groups of ten mice (treated or controls). Treated animals received 250 mg/kg po of each of the tested compounds (except the reference diazepam which was studied at 2.5 mg/kg po) 13 min before the subcutaneous injection of pentetrazol (100 mg/kg) in the scruff of the neck. The measured parameters were as follows: apparition delay of clonic and tonic seizures and percentage of tonic seizures and death.

Peripheral antinociceptive activity

According to the method described by Koster [21] within the study of 'peripheral analgesic' properties, this test was applied to groups of ten treated or control mice. Treated animals received 50 mg/kg po of ASA or each tested compound 30 min before the ip injection of an acetic acid solution (0.5 mL per mouse of 0.5% aqueous solution). Analgesic activity was evaluated by the number of writhes during 10 min.

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