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Synthesis and Biological Activity of Some 4-Aryl-Substituted 4-Oxazolin-2-onest

Francesco Bottari, Enrico Nannipieri, Marco F. Saettone,* Maria Francesca Serafini, Pharmaceutical Chemistry Institute, University of Pisa, Italy

and Natale Tellini

Guidotti C., S.p.A. Pharmaceutical Laboratories, Pisa, Italy. Received May 24, 1971

A series of 4-aryl-substituted 4-oxazolin-2-ones has been prepared by a method involving cyclization of carbamates of aryl hydroxymethyl ketones. On preliminary biological evaluation, some compounds produced myotonic symptoms and antagonized the barbiturate-induced sleep, while others showed mild to significant muscle relaxant and sedative activity. One of the "myotonic-analeptic" compounds, *viz.*, 4-phenyl-4-oxazolin-2-one, was obtained, through oxidation and cyclization, from the muscle relaxant drug, 2-hydroxy-2-phenylethyl carbamate (styramate).

During investigations on 5-unsubstituted 4-oxazolin-2ones,¹ we have described² the conversion of the muscle relaxant drug mephenesin carbamate (I) into one such oxazolinone, namely, 4-(o-toloxymethyl)-4-oxazolin-2-one (II). The significant sedative properties displayed by II prompted us to investigate the preparation of analogous 4-substituted 4-oxazolin-2-ones, with the aim of establishing structureactivity relationships for this class of compounds. Another mephenesin-like muscle relaxant 1,2-glycol monocarbamate, 2-hydroxy-2-phenylethyl carbamate (styramate, V) appeared as an interesting starting material for our study, since it might easily lend itself to cyclization.

The present paper is concerned with the synthesis and preliminary pharmacological evaluation of a series of 5-arylsubstituted 4-oxazolin-2-ones (VII, and Table I) whose simplest member, 4-phenyl-4-oxazolin-2-one (11) was obtained from styramate.



Chemistry. The synthesis of all 4-monosubstituted-4-oxazolin-2-ones was accomplished by our previously described method.^{1a}

The carbamates 1-10 were obtained on treatment with $COCl_2$ and NH_3 of the α -hydroxy ketones IV, which in turn were prepared from the aryl methyl ketones III by the procedure outlined in Scheme I. Phenacyl carbamate (1) was

either obtained from phenacyl alcohol (IV, R = Ph) or, in slightly better yield, by CrO_3 oxidation of styramate. All hydroxy ketones, with the exception of *p*-fluorophenacyl and 2,5-dimethoxyphenacyl alcohol (IV, R = *p*-FC₆H₄ and 2,5-(CH₃O)₂C₆H₃, respectively) were known.

Structure proof for 4-phenyl-4-oxazolin-2-one (11), taken as a model for the whole group, was obtained as indicated in the Experimental Section. The structure of all other

Scheme I



compounds rests on analogous ir and nmr data, and on the similarity of the preparative method.

Biological Evaluation. All compounds listed in Table I and the 4,5-dihydro derivative of 11, 4-phenyloxazolidin-2-one (VIII), for which pharmacological data were not found in the literature, were originally submitted for acute toxicity and behavioral studies in mice. This preliminary dose range testing evidenced two opposite types of activity: some of the compounds (11, 16, 17, and VIII) produced

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Table I.	4-Ar	yl-Substit	tuted 4-	Oxazol	in-2-ones
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R

No.

Yield, %	Recrystn solvent ^a	Mp, °C	Formula	Analysis ^b
	R — Ţ —			

			H			
				Ţ		
				0		
11	C ₆ H ₅	80	В	151-153	C ₉ H ₇ NO ₂	C, H, N
12	p-CH ₃ C ₆ H ₄	60	EA	197-200	C ₁₀ H ₉ NO ₂	C, H, N
13	o-ClC ₆ H ₄	10^{c}	E	207-209	C, H, ĆINO,	C, H, N, Cl
14	p-ClC ₆ H ₄	60	E	261-263	C ₂ H ₂ CINO ₂	C, H, N, Cl
15	p-BrC ₆ H ₄	90	А	248-250	C ₂ H ₆ BrNO ₂	C, H, N, Br
16	p-FC ₆ H ₄	55	В	210-212	C ₉ H ₆ FNO ₂	C, H, N, F
17	$2,5(CH_{3}O)_{2}C_{5}H_{3}$	50	E	218-220	$C_{11}H_{11}NO_4$	C, H, N
18	$p-C_{6}H_{5}C_{6}H_{4}$	70	E	220-222	$C_{15}H_{11}NO_2$	C, H, N
19	1-Naphthyl	60	E	181-183	$C_{13}H_{0}NO_{2}$	C, H, N
20	2-Naphthyl	78	В	202-204	C ₁₃ H ₉ NO ₂	C, H, N

 ${}^{a}B$ = benzene; EA = EtOAc; E = 95% EtOH; A = Me₂CO. ^bSatisfactory analytical results were obtained for the elements indicated. ^cYields was calcd from the amt of o-chlorophenacyl alcohol used in the reaction.

myotonic symptoms both on smooth and striated muscle, while others (12, 13, 14, 15, 18, and 20) behaved as CNS depressant and/or muscle relaxants. A summary of the dose range testing is presented in Table II.

The more active myotonic (11 and 16) and depressant (18 and 20) compounds were submitted to further screening. The ability of the former two compounds to increase the grip strength in mice was defined both in normal animals, and in animals pretreated with sodium pentobarbital, using a modification of the method described by Irwin.³ The modified test (see footnotes b and c, Table III) allowed a quantitative, rather than simply a qualitative evaluation of this parameter. The ability of the same compounds to antagonize the pentobarbital-induced sleep was assessed by a modification of the method of Roth, *et al.*⁴

Compounds 18 and 20 were tested "*in vitro*" for spasmolytic activity on guinea pig ileum, and their ability to pro-

Table II. Summary of Dose Range Testing in M	Table II.	Summary	of Dose	Range	Testing	in	Mic
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	$Dose,^a$	
No.	mg/kg ip	Observations ^b
VIII	100	↓SMA, ataxia, ↑ striated muscle tone
VIII	300	Loss of righting reflex, convulsions
11	30	Slight \downarrow SMA, \uparrow striated muscle tone
11	100	Slight ↓SMA, ↑ pain threshold, ataxia, strongly ↑ general body tone, bradycardia
11	300	Cyanosis, ridigity, tremors, loss of righting re- flex
12	300	Bradypnea, slight cyanosis, ↓SMA, hypotonia
13	100	Bradypnea, ↓SMA, ataxia, hypotonia, slight ptosis
14	300	Bradypnea, strongly ↓SMA, ataxia, brady- cardia, hypotonia
15	300	Strongly ↓SMA, ataxia, bradypnea, mydriasis, hypotonia, depression
16	30	Slight \downarrow SMA, strongly \uparrow general body tone
16	100	Ataxia, slight \downarrow SMA, strongly \uparrow body tone
16	300	Loss of righting reflex, mydriasis, clonic con- vulsions
17	300	Tachycardia, peripheral vasodilation
18	100	Slight ↓SMA, hypotonia, ptosis, ataxia
19	300	↓SMA, slight CNS depression
20	30	Hypotonia, bradypnea, ataxia
20	100	Ataxia, slight cyanosis, strongly \downarrow general body tone, tremors, strongly \downarrow SMA
20	300	Loss of righting reflex, tremors, bradypnea

^dThe test was carried out according to the procedure described in reference 3. The compds were administered as suspensions in 0.9% NaCl contg 1% GITEN-O (polyoxyethylene sorbitan monooleate, A. & D. Treves, Inc., New York, N. Y.). Ten male albino mice (Swiss SM) were used at each dose level. ^bSMA = spontaneous motor activity. duce neurological deficit in mice was determined using the accelerated rotarod test described by Jones and Roberts.⁵

The compounds under investigation were compared, pharmacologically, to a few relevant substances possessing analogous types of activity, in an attempt to obtain an approximate understanding of their mode of action. The results of the tests are presented in Table III.

Compd 16 [4-(*p*-fluorophenyl)-4-oxazolin-2-one] was very active in increasing the grip strength of normal animals and of animals pretreated with barbiturate.

The nonfluorinated homolog of 16, 11, obtained from styramate, had a similar type of activity, but to a much lower degree. Both compounds, at toxic doses, caused severe clonic convulsions, a typical effect of brain stem stimulants such as pentylenetetrazole or bemegride. Compound 16 also reduced significantly, at very low doses, the sleep time by barbiturates. In all the tests, it was significantly more active than the reference drugs, viz., pentylenetetrazole, physostigmine, and guanidine.

4-(2-Naphthyl)-4-oxazolin-2-one (20) exhibited spasmolytic activity to a moderate degree, and caused sedation and muscle relaxation. It was slightly more active than either mephenesin carbamate or styramate in the accelerated rotarod test. A more detailed study (see Table IV) showed that 20 potentiated subthreshold doses of EtOH, therefore its main activity appears to be of sedative rather than of muscle relaxant type.

Experimental Section

Melting points were determined on a Kofler hot stage and are uncor. Ir spectra were recorded in Nujol on a Perkin-Elmer infracord 137 spectrophotometer, nmr spectra on a Varian A60 spectrometer (TMS, CDCl₃ as solvent). Where analyses are indicated only by the symbols of the elements, analytical results obtained for those elements were within $\pm 0.3\%$ of the theoretical values.

Starting Materials and Intermediates. The α -hydroxy ketones IV were prepd from the corresponding bromo ketones (either obtained from commercial sources or prepd by known procedures^{7,8}) by the potassium formate method of Julian, *et al.* ⁹ *p*-Fluorophenacyl alcohol, obtained in 90% yield from the corresponding bromo ketone, melted at 109-111° after crystn from EtOH. *Anal.* (C₈H₂FO₂) C, H, F. **2,5-Dimethoxyphenacyl alcohol**, similarly obtained in 92% yield, melted at 95-97° after crystn from EtOH. *Anal.* (C₁₀H₁₂O₄), C. H. All other hydroxy ketones were known. The carbamates 1-10 were prepd by reaction of the hydroxy ketones V with COCl₂ and NH₃, using a modification of the procedure described in a previous paper.¹⁰ Their physical properties are listed in Table V. As an example, we report the following prepn.

Phenacyl Carbamate (1). To a soln of phenacyl alcohol (10 g, 73 mmoles) in a mixt of anhyd PhH (100 ml) and freshly distd

		Grip strength ^b			Reduction of sleep time by barbiturate ^e		Guinea pig ileum spasmolytic	Accelerating rota- rod, ^g ED _{co} , mg/kg <i>ip</i> (95%
Compd	mg/kg ip	mg/kg po	Eff % ± SE ^c	Eff %/PNa ± SEd	mg/kg po	R'	effect f	confidence limits)
11	750	20.0	96 ± 23	Ns	10.0	Ns		
		50.0	94 ± 37	Ns	30.0	Ns		
		100.0	124 ± 44	Ns	100.0	Ns		
16	900	0.05	117 ± 27	Ns	0.05	70 ± 7*		
		0.1	110 ± 30	Ns	0.1	63 ± 8		
		1.0	115 ± 22	Ns	1.0	63 ± 6		
		3.0	109 ± 31	76 ± 20	10.0	51 ± 6		
		10.0		132 ± 32				
18	>1000						200	>700
20	750						40	112 (97-141)
Pentvler	netetrazole	0.3	62 ± 23	Ns	0.3	Ns		
		1.0	119 ± 19	Ns	30.0	Ns		
		3.0	117 ± 32	Ns				
Physost	igmine salveilat	te 0.3	68 ± 29	54 ± 33	0.3	70 ± 9*		
Guanidi	ne	7.0	72 ± 31	47 ± 11	3.0	71 ± 7*		
Panaver	ine · HCl						1.3	
Mephen Styrama	esin carbamate							164 (117-230) 148 (125-178)

^aApprox values of acute toxicity in mice. ^bModified method of reference 3, in which animals (12 per dose) hand-held by the hind paws, were made to maintain themselves in an horizontal position by grasping a weighted (30 g) hinged bar with the front paws. ^cAverage per cent increase in performance time, respect to untreated controls. All tests were carried out 90 min following oral administration of the examined compounds. All results, unless marked Ns (not significant) were significant at the 0.01% probability level (analysis of variance test). ^dTest performed as described under b and c, on animals pretreated with sodium pentobarbital (50 mg/kg, sc). ^eModification of method described in reference 4, 10 animals/dose. R' = (drug + sodium pentobarbital sleep time/sodium pentobarbital sleep time) × 100, ± SE. Sodium pentobarbital dose, 50 mg/kg, sc. Data marked with an asterisk are significant only at the 0.05% probability level, all others at the 0.01% probability level (analysis of variance test). ^fApproximated ED₅₀ values in µg/ml, against BaCl₂, 300 µg/ml. ^gMethod of reference 5, 10 animals/dose.

 Table IV. Compound 20, Potentiation of the Sedative

 Effect of Ethanol

Expt ^a	Alcohol ^b plus placebo	Placebo and 20 ^c	Alcohol ^b plus 20 ^c
A	-18.25	-13.52	-59.39
В	-16.60	-14.15	-58.70
С	-17.10	-13.18	-59.06
Average	-17.31 (Ns) ^d	$-13.61 (Ns)^d$	$-59.06 ({ m S})^d$

^aTen mice/group. ^b8.3 ml/kg po, 10%. ^c50 mg/kg ip. Data refer to % reduction of performance time on rotating rod⁶ with respect to controls treated with placebos. ^dNs = not significant; S = significant, P < 0.02. procedure. To a soln of styramate \ddagger (V, 1.81 g, 10 mmoles) in Me₂CO (20 ml, freshly distd over KMnO₄) was slowly added, while stirring and cooling at 0-5°, a 25% soln of CrO₃ in H₂SO₄ (4.0 ml, 10 mmoles, stoichiometrical amount, 6.66 mmoles). After the addn, the mixt was dild with cold H₂O; the white solid which sepd was collected and crystd from PhH to afford pure 1 in 66% yield.

4-Aryl-4-oxazolin-2-ones (Table I). The title compds were obtd from the corresponding carbamates by the following general procedure. A soln of the carbamate (2.0 g) in glac AcOH (15 ml) was refluxed 4 hr. Evapn of the solvent under reduced pressure, followed by crystn of the residue from the appropriate solvent afforded the cyclic derivative. Yields and melting points are reported in Table I; ir and nmr spectra of the compds were consistent with their structure.

Table V. Aryl Hydromethyl Ketone Carbamates

No.	R	Yield, %	Recrystn solvent ^a	Mp, °C	Formula	Analysis ^b
			RCOCH2OCON	H ₂		
1	C ₆ H ₅	57 (66) ^c	В	150-152	C _o H _o NO ₃	C, H, N
2	p-ČH ₃ C ₆ H₄	75	Е	183-185	C ₁₀ H ₁₁ NO ₃	C, H, N
3	o-ClC,H,	d			C,H,CINO,	
4	$p-ClC_{6}H_{4}$	80	Е	197-200	C ₆ H ₈ ClNO ₃	C, H, N, Cl
5	p-BrC ₆ H ₄	87	Е	196-198	C ₉ H ₈ BrNO ₃	C, H, N, Br
6	p-FC,H	40	В	166-168	C ₆ H ₈ FNO ₃	C, H, N, F
7	2,5(CH ₃ O) ₂ C ₅ H ₃	40	В	140–142 ^e	C ₁₁ H ₁₃ NO ₅	C, H, N
8	p-C ₆ H ₅ C ₆ H ₄	70	EA	200-205 subl	C ₁ ,H ₁ ,NO ₃	C, H, N
9	1-Naphthyl	40	В	180-183	C ₁₃ H ₁ ,NO ₃	C, H, N
10	2-Naphthyl	60	В	165-167	C ₁₃ H ₁₁ NO ₃	C, H, N

 ${}^{a}B$ = benzene; E = 95% EtOH; EA = EtOAc. ^bSatisfactory analytical results were obtained for the elements indicated. ^cThe yield in parentheses refers to the prepn of 1 for styramate (Cf. Experimental Section). ^dThis carbamate could not be isolated: it underwent cyclization to the oxazolone 13 in the reaction medium. ^eAt temp above 142° the compd solidified, to melt again at 198-200°.

PhNMe₂ (20 ml) was added slowly, while stirring and cooling at 0°, a 20% soln of COCl₂ in PhMe (40 ml, *ca.* 80 mmoles). Stirring was contd 30 min after the addn, then the soln was satd with dry NH₃. The solid which sepd was collected, washed with H₂O, and crystd (PhH) to afford pure 1 (7.55 g, 57%). The same compd was alternatively obtd by oxidn of styramate, according to the following Treatment of o-chlorophenacyl alcohol, with COCl₂ and NH₃ led directly to the oxazolinone 13, the corresponding carbamate 3 being probably unstable under the reaction condns.

‡Lot F21403, kindly supplied by Armour Pharmaceutical Co., Chicago, Ill. 60690.

4-Phenyl-4-oxazolin-2-one (11), Structure Proof. § A. The nmr spectrum (CDCl₃) showed singlet at δ 7.05 (1 H), complex multiplet centered at 7.36 (6 H), broad singlet at 10.94 (1 H, N-bond proton); Ir spectrum showed 3.15 μ (NH group), 5.73 (=C=O in 5-membered ring).

B. NaBH₄ Reduction. To a soln of 11 (500 mg) in 95% EtOH (10 ml), cooled at $0-5^{\circ}$, was added a soln of NaBH₄ (250 mg) in H₂O (2.0 ml). The mixt was allowed to stand 1 hr at room temp, then was dild with H₂O, made slightly acidic with 10% H₂SO₄, and extd with Et₂O. Evapn of the dried (MgSO₄) ext gave a residue which was crystd from PhH to afford 4-phenyloxazolidin-2-one (VIII, 200 mg, 40%), identical with an authentic sample.¹¹

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§A literature reference¹⁰ indicated for a compd, mp 175-177° either structure 11 or the isomeric structure of 5-phenyl-4-oxazolin-2-one. The hypothesis was also advanced that the compd might be a constant-melting mixt of the two isomers. A sample of the product, kindly supplied by Professor Huisgen, gave on tlc a single spot and did not show in its ir spectrum some absorption bands peculiar to 11. On this evidence, the compd melting at 175-177°, for whose prepn we refer to Professor Huisgen's paper, should be assigned the structure of 5-phenyl-4-oxazolin-2-one.

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Derivatives of 4,5-Dihydro-1,3,dimethyl-1*H*-pyrazolo[3,4-*b*][1,4]benzoxazepine with Antiinflammatory Activity

Leo R. Swett,* Robert G. Stein, and Eugene T. Kimura

Experimental Therapy Division, Abbott Laboratories, North Chicago, Illinois. Received May 1, 1971

A new heterocyclic system, 4,5-dihydro-1,3-dimethyl-1H-pyrazolo[3,4-b][1,4]benzoxazepine, was synthesized, and a number of derivatives were screened for antiinflammatory action. Two members of the series are compared to phenylbutazone in test models.

During the past several years, tricyclic systems containing the oxazepine ring have been reported to have antipyretic and antiphlogistic activity. Coyne and Cusic¹ ascribed these properties to a number of dialkylaminoalkylurea derivatives of 10,11-dihydrodibenz [b, f] [1,4] oxazepine (Ia). Derivatives of 10,11-dihydrodibenz [b,f] [1,4] oxazepin-11(10H)-one (Ib), are the subject of a patent² with antiphlogistic claims. The 5,6-dihydropyrido [2,3-b] [1,4] benzoxazepin-6(5H)-one ring system $(II)^3$ has also been reported to possess this type of pharmacological activity.

In an attempt to enhance this activity, we prepared the title compounds (III) incorporating the pyrazole nucleus, since the latter is present in many drugs used to treat arthritic conditions. Compd 30, Table III, is of sufficient interest to warrant clinical evaluation. These compounds



were easily prepared following analogous procedures once an adequate supply of 5-chloro-1,3-dimethyl-4-nitropyrazole was available.

This chemical was first described by Musante,⁴ but the method was impractical for the preparation of large quantities, and the product was thought to be contaminated with an isomer. A more convenient method was described by Geiszler⁵ through low temperature nitration of 5-chloro-1,3-dimethylpyrazole.

Scheme I

