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

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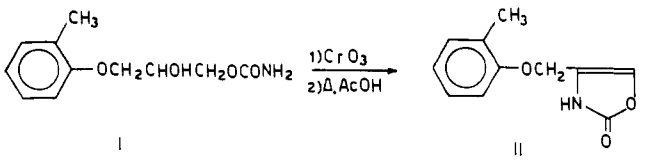
A series of 4-aryl-substituted 4-oxazolin-2-ones has been prepared by a method involving cyclization of carbamates of aryl hydroxymethyl ketones. On preliminary biological evaluation, some compounds produced myotonic symptoms and antagonized the barbiturate-induced sleep, while others showed mild to 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-2-ones,[1] we have described[2] 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 structure–activity 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-aryl-substituted 4-oxazolin-2-ones (VII, and Table I) whose simplest member, 4-phenyl-4-oxazolin-2-one (**11**) was obtained from styramate.



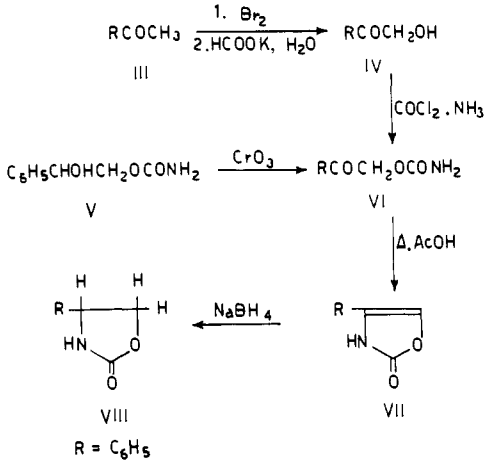
I II

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*-FC_6H_4 and 2,5-$(CH_3O)_2C_6H_3$, 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

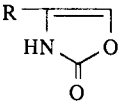


compounds rests on analogous ir and nmr data, and on the similarity of the preparative method.

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

†This work was supported in part by a grant from "Consiglio Nazionale delle Ricerche," and is dedicated to Professor Remo de Fazi on his 80th birthday.

Table I. 4-Aryl-Substituted 4-Oxazolin-2-ones

No.	R	Yield, %	Recrystn solvent[a]	Mp, °C	Formula	Analysis[b]
						
11	C_6H_5	80	B	151–153	$C_9H_7NO_2$	C, H, N
12	p-$CH_3C_6H_4$	60	EA	197–200	$C_{10}H_9NO_2$	C, H, N
13	o-ClC_6H_4	10[c]	E	207–209	$C_9H_6ClNO_2$	C, H, N, Cl
14	p-ClC_6H_4	60	E	261–263	$C_9H_6ClNO_2$	C, H, N, Cl
15	p-BrC_6H_4	90	A	248–250	$C_9H_6BrNO_2$	C, H, N, Br
16	p-FC_6H_4	55	B	210–212	$C_9H_6FNO_2$	C, H, N, F
17	2,5$(CH_3O)_2C_6H_3$	50	E	218–220	$C_{11}H_{11}NO_4$	C, H, N
18	p-$C_6H_5C_6H_4$	70	E	220–222	$C_{15}H_{11}NO_2$	C, H, N
19	1-Naphthyl	60	E	181–183	$C_{13}H_9NO_2$	C, H, N
20	2-Naphthyl	78	B	202–204	$C_{13}H_9NO_2$	C, H, N

[a] B = benzene; EA = EtOAc; E = 95% EtOH; A = Me_2CO. [b] Satisfactory analytical results were obtained for the elements indicated. [c] Yields 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 produce 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.

Table II. Summary of Dose Range Testing in Mice

No.	Dose,[a] mg/kg ip	Observations[b]
VIII	100	↓SMA, ataxia, ↑ striated muscle tone
VIII	300	Loss of righting reflex, convulsions
11	30	Slight ↓SMA, ↑ striated muscle tone
11	100	Slight ↓SMA, ↑ pain threshold, ataxia, strongly ↑ general body tone, bradycardia
11	300	Cyanosis, ridigity, tremors, loss of righting reflex
12	300	Bradypnea, slight cyanosis, ↓SMA, hypotonia
13	100	Bradypnea, ↓SMA, ataxia, hypotonia, slight ptosis
14	300	Bradypnea, strongly ↓SMA, ataxia, bradycardia, hypotonia
15	300	Strongly ↓SMA, ataxia, bradypnea, mydriasis, hypotonia, depression
16	30	Slight ↓SMA, strongly ↑ general body tone
16	100	Ataxia, slight ↓SMA, strongly ↑ body tone
16	300	Loss of righting reflex, mydriasis, clonic convulsions
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 ↓ general body tone, tremors, strongly ↓SMA
20	300	Loss of righting reflex, tremors, bradypnea

[a] The 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. [b] SMA = spontaneous motor activity.

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, $CDCl_3$ as solvent). Where analyses are indicated only by the symbols of the elements, analytical results obtained for those elements were within ±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.* ($C_8H_7FO_2$) C, H, F. **2,5-Dimethoxyphenacyl alcohol**, similarly obtained in 92% yield, melted at 95–97° after crystn from EtOH. *Anal.* ($C_{10}H_{12}O_4$), C. H. All other hydroxy ketones were known. The carbamates 1–10 were prepd by reaction of the hydroxy ketones V with $COCl_2$ and NH_3, using a modification of the procedure described in a previous paper.[1b] 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

Table III. Summary of Activity of Some 4-Aryl-4-oxazolin-2-ones

Compd	LD_{50},[a] mg/kg ip	Grip strength[b] mg/kg po	Grip strength[b] Eff % ± SE[c]	Grip strength[b] Eff %/PNa ± SE[d]	Reduction of sleep time by barbiturate[e] mg/kg po	Reduction of sleep time by barbiturate[e] R'	Guinea pig ileum spasmolytic effect[f]	Accelerating rotarod,[g] ED_{50}, mg/kg *ip* (95% 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)
Pentylenetetrazole		0.3	62 ± 23	Ns	0.3	Ns		
		1.0	119 ± 19	Ns	30.0	Ns		
		3.0	117 ± 32	Ns				
Physostigmine salycilate		0.3	68 ± 29	54 ± 33	0.3	70 ± 9*		
Guanidine		7.0	72 ± 31	47 ± 11	3.0	71 ± 7*		
Papaverine · HCl							1.3	
Mephenesin carbamate								164 (117-230)
Styramate								148 (125-178)

[a]Approx values of acute toxicity in mice. [b]Modified 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. [c]Average 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). [d]Test performed as described under *b* and *c*, on animals pretreated with sodium pentobarbital (50 mg/kg, sc). [e]Modification 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). [f]Approximated ED_{50} values in μg/ml, against $BaCl_2$, 300 μg/ml. [g]Method 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
B	−16.60	−14.15	−58.70
C	−17.10	−13.18	−59.06
Average	−17.31 (Ns)[d]	−13.61 (Ns)[d]	−59.06 (S)[d]

[a]Ten mice/group. [b]8.3 ml/kg po, 10%. [c]50 mg/kg ip. Data refer to % reduction of performance time on rotating rod[6] with respect to controls treated with placebos. [d]Ns = not significant; S = significant, $P < 0.02$.

Table V. Aryl Hydromethyl Ketone Carbamates

No.	R	Yield, %	Recrystn solvent[a]	Mp, °C	Formula	Analysis[b]
			$RCOCH_2OCONH_2$			
1	C_6H_5	57 (66)[c]	B	150-152	$C_9H_9NO_3$	C, H, N
2	*p*-$CH_3C_6H_4$	75	E	183-185	$C_{10}H_{11}NO_3$	C, H, N
3	*o*-ClC_6H_4	*d*			$C_9H_8ClNO_3$	
4	*p*-ClC_6H_4	80	E	197-200	$C_9H_8ClNO_3$	C, H, N, Cl
5	*p*-BrC_6H_4	87	E	196-198	$C_9H_8BrNO_3$	C, H, N, Br
6	*p*-FC_6H_4	40	B	166-168	$C_9H_8FNO_3$	C, H, N, F
7	2,5$(CH_3O)_2C_6H_3$	40	B	140-142[e]	$C_{11}H_{13}NO_5$	C, H, N
8	*p*-$C_6H_5C_6H_4$	70	EA	200-205 subl	$C_{15}H_{13}NO_3$	C, H, N
9	1-Naphthyl	40	B	180-183	$C_{13}H_{11}NO_3$	C, H, N
10	2-Naphthyl	60	B	165-167	$C_{13}H_{11}NO_3$	C, H, N

[a]B = benzene; E = 95% EtOH; EA = EtOAc. [b]Satisfactory analytical results were obtained for the elements indicated. [c]The yield in parentheses refers to the prepn of 1 for styramate (*Cf.* Experimental Section). [d]This carbamate could not be isolated: it underwent cyclization to the oxazolone **13** in the reaction medium. [e]At temp above 142° the compd solidified, to melt again at 198-200°.

$PhNMe_2$ (20 ml) was added slowly, while stirring and cooling at 0°, a 20% soln of $COCl_2$ in PhMe (40 ml, *ca.* 80 mmoles). Stirring was contd 30 min after the addn, then the soln was satd with dry NH_3. The solid which sepd was collected, washed with H_2O, 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 procedure. To a soln of styramate‡ (V, 1.81 g, 10 mmoles) in Me_2CO (20 ml, freshly distd over $KMnO_4$) was slowly added, while stirring and cooling at 0–5°, a 25% soln of CrO_3 in H_2SO_4 (4.0 ml, 10 mmoles, stoichiometrical amount, 6.66 mmoles). After the addn, the mixt was dild with cold H_2O; 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.

Treatment of *o*-chlorophenacyl alcohol, with $COCl_2$ and NH_3 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 ($CDCl_3$) 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. $NaBH_4$ Reduction. To a soln of 11 (500 mg) in 95% EtOH (10 ml), cooled at 0–5°, was added a soln of $NaBH_4$ (250 mg) in H_2O (2.0 ml). The mixt was allowed to stand 1 hr at room temp, then was dild with H_2O, made slightly acidic with 10% H_2SO_4, and extd with Et_2O. Evapn of the dried ($MgSO_4$) 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]

§ A literature reference[10] 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

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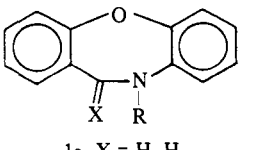
Received May 1, 1971

A new heterocyclic system, 4,5-dihydro-1,3-dimethyl-1*H*-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.

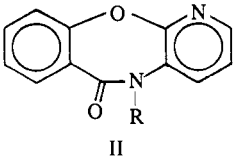
During the past several years, tricyclic systems containing the oxazepine ring have been reported to have antipyretic and antiphlogistic activity. Coyne and Cusic[1] ascribed these properties to a number of dialkylaminoalkylurea derivatives of 10,11-dihydrodibenz[*b,f*][1,4]oxazepine (Ia). Derivatives of 10,11-dihydrodibenz[*b,f*][1,4]oxazepin-11(10*H*)-one (Ib), are the subject of a patent[2] with antiphlogistic claims. The 5,6-dihydropyrido[2,3-*b*][1,4]benzoxazepin-6(5*H*)-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.

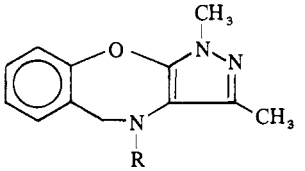
This chemical was first described by Musante,[4] but the method was impractical for the preparation of large quantities, and the product was thought to be contaminated with an isomer. A more convenient method was described by Geiszler[5] through low temperature nitration of 5-chloro-1,3-dimethylpyrazole.



Ia, X = H, H
b, X = O

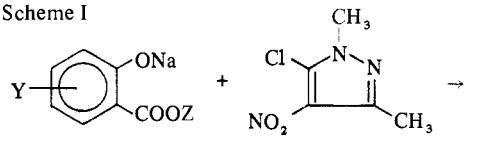


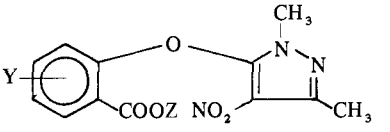
II



III

Scheme I





1. $Ni-H_2$
2. Δ, xylene