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5-substituted-3-phenacyl-2-iminooxazolidines as anti-arrhythmic and local anaesthetic agents

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Introduction

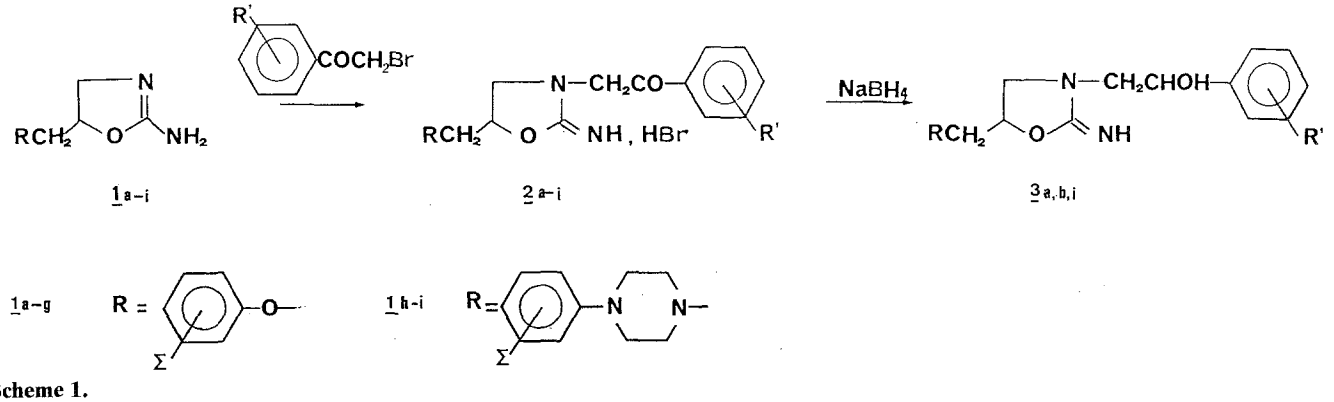
In previous papers we described the preparation of 5-aryloxymethyl and 5-dialkylaminomethyl-2-amino-2-oxazolines [1, 2]. This work has been extended to the synthesis of some 3-phenacyl-2-iminooxazolidines **2** by alkylation of 5-substituted-2-amino-2-oxazolines with α-bromocarbonyl reagents. Like other heterocyclic amines having an amino group at the α-position in relation to the ring nitrogen atom, the condensation was initiated by the endo nitrogen atom [3–8]. The 5-substituted-3-phenacyl-2-iminooxazolidines **2** were tested for their anti-arrhythmic and local anaesthetic activity.

Chemistry

The 2-iminooxazolidines **2** and **3** were synthesized as shown in scheme 1. The 5-aryloxymethyl **1(a–g)** and 5-(1-aryl-4-piperazinomethyl)-2-amino-2-oxazolines **1(h, i)** were obtained from phenols and amines in a two step reaction described previously [1, 2]. Treatment of **1** with 2-bromo or 2-bromo-4'-chloro-acetophenone gave compounds **2** which afforded **3** after reduction with sodium borohydride in methanol. The alkylation reaction is generally believed to proceed *via* the initial displacement of the bromine atom by the oxazoline ring nitrogen atom, followed by rearrangement of the resonance stabilized oxazolinium salt [7]. All new 2-iminooxazolidines were stable as hydrobromide salts or as bases and could not be converted to imidazo– or dihydroimidazo[2,1-*b*]oxazolidines, using experimental conditions from previously described methods [3, 6, 8].

The IR spectra of compounds **2** and **3** exhibited a characteristic C=N band around 1680 cm^{-1}. For **2** (as bases) and **3**, a sharp NH band was observed at 3200–3400 cm^{-1}. The CO band in compounds **2** appeared at about 1690 cm^{-1} and alcohols **3** showed an OH absorption band around 3150 cm^{-1}.

In the ^1H NMR spectra of compounds **2** and **3**, the protons on the C-4 and C-5 positions, and the CH_2 of the lateral chain, form an ABXMN system. The C-5



Scheme 1.

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methine proton was found at about 5 ppm. In compounds **2**, N–CH_2 of the 3-lateral chain appeared as a singlet at about 5.4 ppm. An exchangeable singlet assigned to the N^+H_2 protons was found near 8 ppm for **2** as hydrobromide salts. The exchangeable NH proton of **2h** (base) appeared with the C-5 methine proton. In alcohols **3**, OH and NH protons appeared as a large exchangeable peak at 5.6 ppm.

The ^1H NMR of compounds **3** showed evidence for the presence of 2 diastereoisomers. The C*H*OH appeared as 2 triplets at 4.85 and 5.25 ppm. The ratio of the integrals for these peaks is about 70:30. HPLC analysis on C-8 reversed phase column (mobile phase methanol/KH_2PO_4 50/50 v) was performed with compound **3b**. Two peaks appeared at retention times 6.73 and 10.56 min, with an integral ratio 73:27.

The study of a structurally related 3-substituted–2-iminooxazolidine hydrochloride was performed by X-ray crystallography [9]. The results showed that the protonation occurred on the exo-nitrogen atom and that the double bond was almost exocyclic. No hydrogen bond was observed between the carbonyl of the lateral chain and NH_2. Molecular modelling has been performed on compound **2a** in order to check the possibility of an intramolecular H-bond in the hypothetical enol or ketone forms. The structures depicted in figure 1 are the lowest energy conformations of the 2 forms generated by Concord [10] on a PS 330 terminal (Evans & Sutherland). In both cases, there was no possibility of H-bonding. The ketone form was found to be more stable than the enol one (ΔE_{MM} = 7.5 kcal). The distance between the ketone and the imino groups was quite large (3.705 Å). In addition,

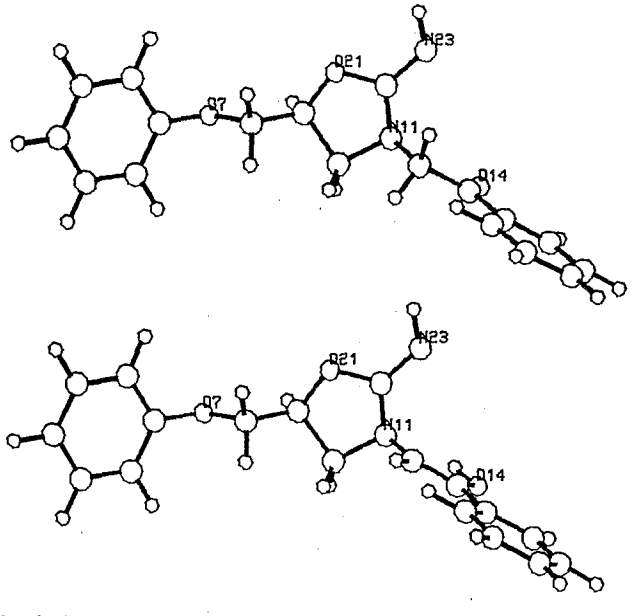

Fig 1. Low energy conformations of compound **2a**. Top: probable ketone form; bottom: hypothetical enol form.

the influence of the oxygen atom of the heterocyclic ring might explain the stability to ring closure of the 3-phenacyl-2-iminooxazolidines **2** which was not observed with corresponding 2-iminothiazolidines [5, 8, 11].

Pharmacology

Of the synthetized compounds, 7 were selected for pharmacological screening. Only the anti-arrhythmic activity in mice deserves attention (table II). Effective compounds in the first test were screened for their local anaesthetic activity in guinea pigs (table II).

In the anti-arrhythmic assay, **2b** did not present activity. Compound **2g** has only been tested at the dose level of 10 mg/kg since higher doses induced potent toxicity; this dose did not induce the anti-arrhythmic effect. **2d** and **2e** are borderline at 10 mg/kg and **2h** at 25 mg/kg, since 66% of mice are protected at these doses by intra peritoneal administration. Compound **2c** is only effective at 50 mg/kg. For **2i**, the anti-arrhythmic effect, found only at 25 mg/kg, may partially relate to an observed *in vitro* calcium antagonist activity. Under the same conditions, all mice were protected by the reference compound Lidocaine at the dose level of 50 mg/kg.

As reported in table II, all tested compounds, except **2i**, are effective in the local anaesthetic assay at the concentration of 5%. Derivatives **2c** and **2e** show a good activity at the concentration of 0.5%; nevertheless, this effect disappears 60 min after topical administration. Compound **2h** is not effective at this dose level and compound **2d** is only effective 5 min after administration. At the concentration of 5%, Lidocaine did not induce a blink response during the 60 min following the topical administration.

Conclusion

The restricted pharmacological data obtained with some 3-phenacyl-2-iminooxazolidines point only to a limited structure–activity relationship. The test results seem to indicate that 5-aryloxymethyl-3-phenacyl-2-iminooxazolidines are more potent than the corresponding 1-aryl-4-piperazinomethyl analogues. The introduction of a chlorine atom on the benzenic ring on phenacyl chain in **2b** leads to a compound which was inactive in all tests. However, the influence of the chlorine substituent could not be proved, as the corresponding non-chlorinated **2a** derivative was not tested. **2e** is the most effective compound thanks to its good anti-arrhythmic activity at 25 mg/kg ip and local anaesthetic effect at the concentration of 0.5%. A stabilizing membrane effect could be at the origin of the observed pharmacological results. Further biological studies are in progress in order to evaluate the electronic factors due to the influence of the carbonyl group on the 3-lateral chain.

Table I. Chemical characteristics of 5-aryloxymethyl-2-iminooxazolidines **2(a–g)**, **3(a–b)**, and 5-(1-aryl-4-piperazino)-methyl-2-iminooxazolidines **2(h–i)**, **3i**.

Compound	*Σ*	*R'*	*Formula*	*M*	*mp (°C) (free base solvent)*	*Yield %*	*IR cm⁻¹ CO*	*IR cm⁻¹ C=N*
2a	H	H	$C_{18}H_{19}BrN_2O_3$	390.9	194 (98-hept)	81	1705	1690
2b	H	Cl	$C_{18}H_{18}BrClN_2O_3$	425.4	206 (124-hept)	89	1690	1675
2c	4-CH_3	H	$C_{19}H_{21}BrN_2O_3$	404.9	194 (91-hept)	75	1695	1680
2d	4-$C_6H_5CH_2$	H	$C_{25}H_{25}BrN_2O_3$	480.9	189	76	1700	1680
2e	3-$N(CH_3)_2$	H	$C_{20}H_{24}BrN_3O_3$	433.9	195	62	1695	1680
2f	4-$(CH_3)_3C$	H	$C_{22}H_{27}BrN_2O_3$	446.9	187 (116-hept)	64	1695	1675
2g	4-morpholino	H	$C_{22}H_{26}BrN_3O_4$	475.9	145	93	1695	1685
3a	H	H	$C_{18}H_{20}N_2O_3$	312	(98-hept)	78	NH:	1665 3340
3b	H	Cl	$C_{18}H_{19}ClN_2O_3$	346.5	(110-hept)	84	NH:	1670 3320
2h	H	H	$C_{22}H_{26}N_4O_2$	378	(146-hept)	30	NH: 1695	3350 1680
2i	2,3-CH_3	H	$C_{24}H_{31}BrN_4O_2$	486.9	204	71	1710	1690
3i	2,3-CH_3	H	$C_{24}H_{32}N_4O_2$	408	(150-hept)	82	NH:	1650 3300

Experimental protocols

Chemistry

Satisfactory elemental analysis ±0.4% of calculated values were obtained for all new compounds. Melting points were determined with a Kofler hot-stage and were uncorrected. IR spectra were recorded on a Beckmann Acculab spectrometer as KBr disks. ^1H and ^{13}C NMR spectra were recorded on Bruker AM-80 and Bruker AC-200 instruments with tetramethylsilane as internal standard. The purity of synthesized compounds was checked by thin-layer chromatography on silica gel plates Kieselgel 60 F 254 (Merck). HPLC analysis was performed on a Hypersil C-8 column (5μ, 25 cm), using a Perkin–Elmer chromatograph equipped with a UV Perkin-Elmer LC 95 absorbance detector (λ = 225 nm).

General synthesis of 3-phenacyl-2-iminooxazolidines 2

The α-bromoacetophenone (0.02 mol) was added at 20°C to a stirred suspension of the 2-amino-2-oxazoline **1** (0.02 mol), in 200 ml of acetone. The reaction mixture was stirred for 24 h at room temperature and then filtered. The hydrobromide salt was washed with acetone (4 x 50 ml). The free base was liberated upon treatment with sodium carbonate and crystallized in heptane. The spectrometric data for **2h**, which is representative of the title compounds, are listed below.

3-phenacyl-5-(1-phenyl-4-piperazinomethyl)-2-iminooxazolidine **2h**. IR (KBr): 1690 (CO) and 1680 (C=N) cm^{-1}. ^1H NMR 200 MHz, $CDCl_3$, δ ppm: 2.6–2.9 (m, 6H, NCH_2); 3.2–3.3 (m, 4H, NCH_2); 3.7–3.77 (m, 1H, C4-H) and 3.47–3.95 (m, 1H, C4-H); 4.7–4.8 (m, 2H, C5-H and NH exchange with D_2O); 4.79 (s, 2H, CH_2CO); 6.6–7.6 (m, 10H, phenyl). ^{13}C NMR DMSO–D_6, δ ppm: C-4 51.07; NCH_2CO 51.6; NCH_2C-5 61; C-5 74.1; C-2 160.9; CO-Ar 194.7.

General synthesis of 3-(β-hydroxyphenethyl)-2-iminooxazolidines 3

0.02 mol of sodium borohydride was added portionwise to a stirred suspension of **2** (0.01 mol) in methanol (150 ml) at 5°C. After 48 h the reaction mixture was concentrated under reduced pressure and the residue crystallized after trituration with ether. Finally, the solid was recrystallized from heptane. The spectrometric data for **3a** which is representative of the title compounds are listed below.

3-(β-hydroxyphenetyl)-5-phenoxymethyl-2-iminooxazolidine **3a**. IR (KBr): 3340 (NH), 3150 (OH) and 1665 (C=N) cm^{-1}. ^1H NMR 80 MHz, DMSO D_6, δ ppm: 3.38 (d, 2H, CH_2CHOH);

Table II. Anti-arrhythmic and local anaesthetic activity.

	Anti-arrhythmic activity Dose (mg/kg ip)*				*Local anaesthetic activity** concentration (% = g/100 ml)*											
Compound					*5%*				*0.5%*				*0.05%*			
No	*50*	*25*	*10*	*5*	*5*	*15*	*30*	*60*	*5*	*15*	*30*	*60*	*5*	*15*	*30*	*60*
2b	0	–	–	–							▲					
2c	100	33	–	–	0	0	0	0	0	0	0	5	5	5	5	5
2d	–	66	66	33	0	0	0	0	4	1	0	1	5	5	4	4
2e	–	100	66	0	0	0	0	0	0	1	1	3	4	3	3	5
2g	–	–	33	–							▲					
2h	–	66	33	–	0	0	1	1	3	3	4	5	–	–	–	–
2i	–	100	0	–	5	5	5	5	–	–	–	–	–	–	–	–
lidocaine	100	–	–	–	0	0	0	0	–	–	–	–	–	–	–	–

*Percentage of mice per group which do not display cardiac arrhythmia 30 min after ip administration of the test compound. **Number of blink responses at different concentrations of the test compound. Local anesthetic activity was assessed at 5, 15, 30, 60 min after administration. ▲Not tested.

3.1–4.2 (m, 4H, OCH_2 and C4-H); 4.6–5 (m, 1H, C5-H); 4.85, 5.25 (2t, 1H, CHOH); 5.3–5.8 (m, 2H, NH and OH exchange with D_2O); 6.8–7.5 (m, 10H, phenyl).

Pharmacology

Test compounds were prepared as an aqueous solution. Small amounts of DMSO were used to increase solubility. At the concentration employed, DMSO did not produce any arrhythmic or anti-arrhythmic effect.

Anti-arrhythmic activity

Male Swiss mice (9) were intraperitoneally dosed with the test compounds. Thirty min later, they were submitted to deep chloroform anaesthesia which prolongs the refractory period and depresses myocardial excitability [12]. A compound is assessed as anti-arrhythmic if more than 66% of mice by group do not display cardiac arrhythmia and heart rate above 200 beats/mn (EKG).

Local anaesthetic activity

Surface anaesthesia was assessed on male Dunkan Hartley Guinea pigs according to the method of Regnier [13]. 0.1 ml of the test solution was instilled on the cornea. After 30 s the excess was allowed to trickle. The anaesthesia was checked by means of a nylon thread applied 5 times on the cornea 5, 15, 30 and 60 min after topical administration of the test compound. Local anaesthetic activity was assessed at 4 different times after administration and was judged as positive in the presence of a blink response in less than 3 of the 5 stimuli.

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