2-Amino-2-oxazolines, III:

Synthesis, Structure, and Preliminary Pharmacological Evaluation of Cycloaddition Compounds with Unsaturated Carboxylic Esters

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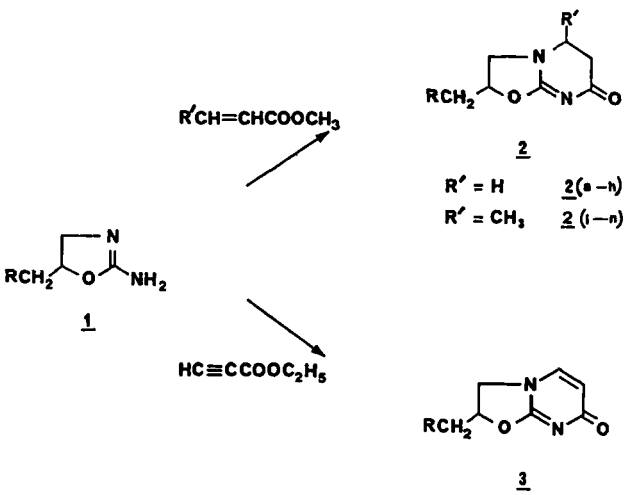
The reaction of 5-substituted 2-amino-2-oxazolines with unsaturated carboxylic esters yieded 2,3,5,6-tetrahydro- and 2,3-dihydro-7*H*-oxazolo[3,2-*a*]pyrimidin-7-ones. The structure of these compounds was established by IR- and NMR-spectra and by X-ray crystallography. They were tested for anti-arrhythmic and hypocholesterolemic activities.

2-Amino-2-oxazoline, 3. Mitt.: Synthese, Struktur und vorläufige pharmakologische Bewertung von Cycloadditionsverbindungen mit ungesättigten Estern

Aus 5-substituierten 2-Amino-2-oxazolinen entstehen mit ungesättigten Carbonsäureestern 2,3,5,6-Tetrahydro- und 2,3-Dihydro-7*H*-oxazolo[3,2-*a*]pyrimidin-7-one. Dir Struktur dieser Verbindungen wurde durch IR- und NMR-Spektren sowie durch Röntgenstrukturanalyse geklärt. Die Substanzen wurden auf antiarrhythmische und lipidsenkende Wirkung geprüft.

2,3-dihydrooxazolo[3,2-*a*]pyrimidines are substantially useful as intermediates for the synthesis of pyrimidines derivatives[1]. They were reported as cyclic derivatives of the pyrimidine bases and were related to the structure of potent carcinostatic cyclonucleosides[2,3].

In order to extend our research on 2-amino-2-oxazolines we synthesized derivatives of 2,3,5,6-tetrahydro- and 2,3-dihydro-7*H*-oxazolo[3,2-*a*]pyrimidin-7-ones corresponding to the general formulae **2** and **3** (Scheme 1), from the reaction of various 5-substituted 2-amino-2-oxazolines with unsaturated carboxylic esters. 2-Amino-2-oxazoline can react under this form or under its imino-2-oxazolidine tautomeric form[4]. In the first case we have shown that the endo nitrogen is more reactive than the exo one whereas in the second case the contrary occurs. Consequently two different series of cycloaddition compounds could a priori be expected. In our experimental conditions a single series of compounds was isolated and the structure was established by X-ray crystallography.



Scheme 1.

Synthesis

2-substituted-2,3,5,6-tetrahydro-7H-oxazolo[3,2-a]pyrimidin-7-ones **2**

Various 2-amino-2-oxazolines **1** were prepared according to [5,6]. Treatment of **1** with a slight excess of methyl acrylate or methyl crotonate in boiling dry toluene gave compounds **2** in good yields (Scheme 1). As early noticed[7,8] the two nitrogen atoms of 2-amino-2-oxazolines are potent nucleophilic centers. The cycloaddition of unsatured esters might occur on these centers leading to both pyrimidin-7-one and/or 5-one[9,10]. In our case the reaction led to a single derivative. Structure **2j** was established by X-ray crystallography.

The spectral data of 2,3,5,6-tetrahydro-7H-[3,2-a] pyrimidin-7-ones **2** are reported in Table 1. The IR spectra of **2** in the solid state show CO and CN absorptions at 1600 and 1670 cm^{-1} [1,8]. In the ^{1}H-NMR spectra the protons at the C-2 and C-3 form an ABX system, the C-2 methine H is found at about 5 ppm. In compounds **2i-2n** the methyl protons appear as a doublet near 1.3 ppm. The ^{13}C-NMR spectra of **2b** and **2j** are identical except for the C-6 and 5-CH_3 atoms. The ^{13}C-NMR spectrum of compound **2j** showed the presence of two diastereoisomers. Two peaks appeared for C-2, C-5, CH_2 of the lateral chain and CH_3 ($\Delta\delta$=0.55 ppm). HPLC analysis on a C-18 reversed phase column (mobile phase methanol/phosphate buffer pH 6.6, 45/55) was performed with the compound **2j**. Two peaks appeared at retention times 5.06 and 5.6 min with a ratio of about 1:1.

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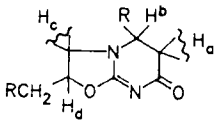
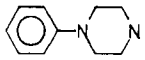
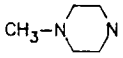


Table 1: Analytical and spectroscopic data of **2**

Cpd.	R	R'	Formula Mol.W.	F(°C)*	^{1}H-NMR ($CDCl_3$) H_A^d	H_B^d	H_C	H_D	Yield %
2a	CH_3O	H	$C_{18}H_{12}N_2O_3$	136[b]	2.64	3.55	3.88-3.37	5.1-4.8	
			184		t, 2H	t, 2H	m, 2H	m, 1H	69
2b		H	$C_{13}H_{14}N_2O_3$	95[b]	2.67	4-3.5		5.2-4.9	
			246		t, 2H	m, 4H		m, 1H	74
2c	$(C_2H_5)_2N$	H	$C_{11}H_{19}N_3O_2$	111[a]	2.70	4.1-3.4		5.2-4.8	
			225		t, 2H	m, 4H		m, 1H	63
2d		H	$C_{12}H_{19}N_3O_2$	147[a]	*2.73	4-3.5		5.3-4.8	
			237		t, 2H	m, 4H		m, 1H	66
2e		H	$C_{11}H_{17}N_3O_3$	132[c]	2.69	4.2-3.3		5.3-4.7	
			239		t, 2H	m, 4H		m, 1H	58
2f	$C_6H_5CH_2NCH_3$	H	$C_{15}H_{19}N_3O_2$	123[a]	2.66	3.8-3.3		5.1-4.7	
			273		t, 2H	m, 4H		m, 1H	52
2g		H	$C_{17}H_{22}N_4O_2$	163[b]		4.1-2.4		5.3-4.7	
			314			m, 6H		m, 1H	61
2h		H	$C_{12}H_{20}N_4O_2$	124[b]	2.9-2.4	4.1-3.3		5.3-4.7	
			252		m	m, 4H		m, 1H	53
2i	CH_3O	CH_3	$C_{19}H_{14}N_2O_3$	Oil	3.1-2.1	4.2-3.2		5.2-4.6	
			198		m, 2H	m, 3H		m, 1H	39
2j		CH_3	$C_{14}H_{16}N_2O_3$	150[a]	2.9-2.2	4.3-3.6		5.6-5.2	
			260		m, 2H	m, 3H		m, 1H	76
2k	$(C_2H_5)_2N$	CH_3	$C_{12}H_{21}N_3O_2$	107[a]	3-2.3	4.2-3.2		5.2-4.6	
			239		m, 2H	m, 3H		m, 1H	62
2l		CH_3	$C_{13}H_{21}N_3O_2$	134[a]	3-2.2	4.2-3.2		5.2-4.6	
			251		m, 2H	m, 3H		m, 1H	71
2m		CH_3	$C_{12}H_{19}N_3O_3$	120[c]	** 2.9-1.9	4.2-3.1		5.3-4.7	
			253		m, 2H	m, 3H		m, 1H	65
2n	$C_6H_5CH_2NCH_3$	CH_3	$C_{16}H_{21}N_3O_2$	108[a]	3-2.3	4.1-3.5		5.4-4.9	
			287		m, 2H	m, 3H		m, 1H	56

* Recryst. Solvent a:CCl_4 - b: $CHCl_3/CCl_4$ - c: Toluene - d: J between 7 and 8 Hz
** DMSO [D_6]

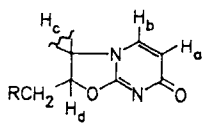
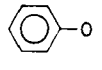
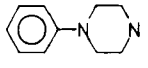


Table 2: Analytical and spectroscopic data of **3**

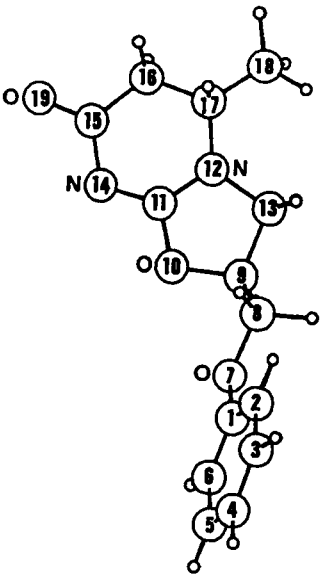
Cpd.	R	Formula Mol.W.	F(°C)*	^{1}H-NMR ($CDCl_3$) H_A^d	H_B^d	H_D^e	H_C^e	Yield %
3a	Cl	$C_7H_7ClN_2O_2$	189[a]	5.8**	7.7	5.6-5.1	4.6-3.9	76
		186.5		d, 1H	d, 1H	1H		
3b	CH_3O	$C_8H_{10}N_2O_3$	124[b]	6.05	7.35	5.2-4.9	4.6-3.95	59
		182		d, 1H	d, 1H	1H	2H	
3c	$(CH_3)_3C$-O	$C_{11}H_{16}N_2O_3$	173[b]	6	7.4	5.3-4.9	4.6-4.1	51
		224		d, 1H	d, 1H	1H	2H	
3d		$C_{13}H_{12}N_2O_3$	174[a]	**5.8	7.8	5.7-5.1	4.7-3.9	70
		244		d, 1H	d, 1H	1H		
3e	$(C_2H_5)_2N$	$C_{11}H_{17}N_3O_2$	190[c]	5.9	7.5	5.3-4.8	4.6-3.9	63
		223		d, 1H	d, 1H	1H	2H	
3f		$C_{12}H_{17}N_3O_2$	177[c]	6	7.4	5.4-4.8	4.7-3.9	67
		235		d, 1H	d, 1H	1H	2H	
3g		$C_{17}H_{20}N_4O_2$	175[c]	6	7.3	5.30-4.9	4.6-3.95	58
		312		d, 1H	d, 1H	1H	2H	

* Recryst. Solvent: a: EtOH - b: CCl_2CHCl - c: Toluene - d: In all cases H_B and H_B appear as doublets with J_{ortho} = 8 Hz - e: H_C and H_D always appear as unresolved multiplets
** DMSO [D_6]

2-substituted-2,3-dihydro-7H-oxazolo[3,2-a]pyrimidin-7-ones **3**

The reaction of heterocyclic nitrogen compounds carrying an α-amino group with acetylene caboxylates has been widely investigated. According to the heterocyclic nucleus it can generate both the isomeric pyrimidin-7-ones or 5-ones[10-14]. The treatment of various 5-substituted 2-amino-2-oxazolines with ethyl propiolate in boiling ethanol gave the corresponding 2,3-dihydro-7H-oxazolo[3,2-a]pyrimidin-7-ones **3**.

The structure of **3c** was identified by spectral data (Table 2). As already noticed[12,15] the IR-spectra of pyrimidin-7-ones and 5-ones are quite different. The amide bond of 7-ones appears below 1650 cm^{-1} while the same absorption for 5-ones is above 1680 cm^{-1}. The ^{1}H-NMR spectra of **3c** display two multiplets for the C-2 and C-3 protons at 5.3-4.9 and 4.6-4.1 ppm (ABX system). All components **3** show the olefinic C-5 and C-6 protons at 7.4 and 6 ppm. These data are similar to the findings of *Inaki* for cyclic compounds of uracil and thymine[1,3] and to those of *Kinoshita* for thiazolo[3,2-*a*]pyrimidin-7-ones[14]. The ^{13}C-NMR spectra of **3a** can be used for the establishment of the proposed structure. The most deshielded signal (171.3 ppm) is assigned to C-7 and is consistent with a pyrimidin-7-one structure. In the thiazolo[3,2-*a*]pyrimidin-5-ones the C=O-carbon is found at 161 ppm[16]. Similar values are reported for some tautomeric pyrimidines: 169.8 ppm for 1-methyl-4-oxo- and 161.4 ppm for 3-methyl-4-oxo-pyrimidines[17].



Projection of the molecule showing the numbering scheme

X-Ray Crystallography

Crystal data are presented in Table 3. The cell-dimensions and orientation matrix were calculated by least-squares method from the angular values of 25 reflections collected with an Enraf-Nonius CAD-4 diffractometer. The intensities were collected with ω / θ scan mode and graphite monochromated CuKα radiation ($\overline{\lambda}$ = 1.54178 Å). No appreciable drop in intensity of two standard reflections checked every 90 min was noticed. The data were corrected for *Lorentz*- and polarization effects but not for absorption.

The structure was solved by direct methods using the MULTAN 80 Program System and the statistically weighted tangent formula[18]. All remaining calculations based on the programs CRISTA, CRISAF, CRISEC, and UTIL from the Laboratory of Crystallography (Univ. of Bordeaux I, Talence) were carried out on a Mini 6-92 CII-Honeywell-Bull computer. Block-diagonal matrix least-squares refinements were performed for a scale factor, and positional, and anisotropic thermal parameters of the non-hydrogen atoms. The hydrogen atoms, located from difference *Fourier* maps, were included in the calculations and refined with isotropic thermal parameters. The function minimized was $\Sigma w \| Fo | - | Fc \|^2$ where $w = 1$ if $| Fo | < P$, $P = [Fo^2(max)/10]^{1/2}$, $w = (P/Fo)^2$ if $| Fo | > P$. The scattering factors for non-hydrogen atoms were those proposed by *Cromer* and *Waber*[19] and those for H atoms were from *Stewart*, *Davidson*, and *Simpson*[20].

The fractional atomic coordinates and Beq values of non-hydrogen atoms are presented in Table 4. Bond lengths and angles are presented in Tables 5 and 6. The conformation is shown in Fig. 1*.

Examination of the bond lengths and angles (Tables 5 and 6) shows a delocalization of the π electrons around C(11). The shortening of the C(11)-N(14) bond (1.299(7)Å) vs C(11)-N(12) (1.311(7)Å) would indicate that the double bond is better localized between the former. However the bond angles around N(12) would indicate that the hybridation state is close to sp^2. The observed bond lengths are comparable to those found in opened related imino-2-oxazolidines[4]. The oxazoline ring is almost flat with C(9) and C(13) slighty below the plane defined by O(10), C(11), N(12) and N(14) (-0.029(6) and -0.015(6)Å, respectively). The dihydropyrimidine ring is twisted with C(15), C(16) and C(17) at 0.076(6), 0.145(9) and -0.116(9)Å from the same plane.

The conformation of the chain is extended as indicated by the torsion angles C(6)-C(1)-O(7)-C(8)= -176(1)°, C(1)-O(7)-C(8)-C(9)= -174° and O(7)-C(8)-C(9)-C(13)= -178°.

Pharmacology

All new compounds were screened for anti-arrhythmic and hypocholesterolemic activities.

Anti-arrhythmic activity

Only compounds **2c** and **3c** show slight activity in this test. The percentages of mice which did not display cardiac arrhythmia 30 min after administration of the test compounds were 33% for **2c** (60 mg/kg i.p.) and 66% - 33% for **3c** (100, 50 mg/kg i.p.). In the same conditions the ED 100 for quinidine was found at 100 mg/kg.

Hypocholesterolemic activity

Reductions in serum cholesterol and heparin precipitating betalipoproteins concentrations were observed for some

* Weitere Einzelheiten zur Kristallstrukturuntersuchung können beim Fachinformationszentrum Energie, Physik, Mathematik D-7514 Eggenstein - Leopoldshafen 2, unter Angabe der Hinterlegungsnummer...., des Autors und des Zeitschriftenzitates angefordert werden.

Tab. 3: Crystal Data

Molecular formula	$C_{14}H_{16}N_2O_3$
Molecular weight	260.3
Symmetry	Monoclinic
Space group ; Z	$P2_1/c$; 4
Unit-cell parameters	a = 12.596(1) Å
	b = 9.428(1)
	c = 12.113(1)
	β = 111.83(1)°
Volume (Å^3)	1335.3(1)
Number of reflections used for the determination of unit-cell parameters; 2θ range (deg)	25 ; 14-32
Density (calcd)	1.295
Number of measured reflections	2378
Number of observed reflections $I \geq 3\sigma(I)$	1082
Number of refined parameters	236
2θ range scanned (deg)	1-130
μ(CuKα) (cm^{-1})	7.7
Crystal dimensions (mm)	0.57 x 0.30 x 0.10
Solvent of recrystallization	Ethanol
Final R	0.062

Table 4: Atomic coordinates (x 104) and equivalent isotropic temperature factors

$$B_{eq} = \frac{4}{3} \sum_i \sum_j \beta_{ij} \vec{a}_i . \vec{a}_j$$

	x	y	z	Beq(Å^2)
C(1)	2193(5)	3805(8)	4787(5)	6.1(3)
C(2)	2612(5)	3059(8)	4069(5)	6.0(3)
C(3)	1858(6)	2367(8)	3068(6)	7.2(3)
C(4)	690(7)	2466(10)	2815(6)	9.4(5)
C(5)	287(6)	3225(12)	3538(7)	10.1(5)
C(6)	1052(6)	3884(11)	4543(6)	9.2(4)
O(7)	2869(3)	4525(6)	5807(4)	7.2(2)
C(8)	4073(5)	4571(7)	6086(5)	5.6(3)
C(9)	4580(5)	5267(7)	7285(5)	5.5(3)
O(10)	4406(3)	4322(5)	8166(3)	5.9(2)
C(11)	5424(5)	3967(6)	8980(5)	4.7(2)
N(12)	6263(4)	4581(6)	8769(4)	5.2(2)
C(13)	5873(5)	5464(7)	7707(5)	5.7(3)
N(14)	5442(4)	3110(6)	9827(4)	5.7(2)
C(15)	6498(6)	2858(7)	10660(5)	6.0(3)
C(16)	7504(6)	3542(11)	10547(7)	10.5(5)
C(17)	7418(6)	4242(12)	9477(7)	10.8(5)
C(18)	8306(7)	4788(14)	9190(8)	11.7(6)
O(19)	6622(4)	2110(6)	11515(4)	8.6(3)

2,3,5,6-tetrahydro- and 2,3-dihydro-7H-oxazolo[3,2-a]pyrimidin-7-ones. For **2g** with a dose level of 400 and 200 mg p.o. the reductions in these two tests were 20% - 24% and 11% - 13% respectively. For bezafibrate the results were 33% - 38% at the dose level 200 mg p.o.. The activity of **2g** was not accompanied by a significant decrease in the HPL/cholesterol ratio. Following a dose of 100 mg/kg, no estrogenic activity was noted in conjunction with this hypocholesterolemic effect.

Conclusion

The pharmacological screening showed only little activity for these series of 2-substituted-2,3,5,6-tetrahydro- and 2,3-dihydro-7*H*-oxazolo[3,2-*a*]pyrimidin-7-ones. In particular the activity on the CNS which characterizes related opened series[6] (one molecule in clinical trials) disappeared. As we have shown non-substituted nitrogen atoms are certainly involved in the antidepressant activity, binding to the correspondant receptor. In the present case the loss of activity could be attributed to the enclosing of the two nitrogen atoms in the pyrimidine ring. The oxazolo[3,2-*a*]pyrimidin-7-ones being structuraly close to some potent carcinostatic cyclonucleosides will be tested for such activity.

Experimental Part

Chemistry

Satisfactory elemental analysis with deviations of ± 0.4% of the calculated values were obtained for all new compounds.- Uncorrected melting points: KOFLER hot-stage.- IR-spectra: Acculab, Beckman KBr discs.- ^{1}H- and ^{13}C-NMR spectra: Bruker WH 90 and Bruker WP 60, tetramethylsilane as int. standard.- Purity of synthesized compounds was checked by thin-layer chromatography, Kieselgel 60 F 254 (Merck).- HPLC analysis: Waters µBondapack C18 column (30 cm x 3.9 mm i.d. 10µ particle size), Waters chromatograph equipped with a LC Spectrophotometer.

General procedure for the synthesis of 2-substituted-2,3,5,6-tetrahydro-7H-oxazolo[3,2-a]pyrimidin-7-ones

30 mmol of **1** and 40 mmol of methyl acrylate or methyl crotonate were refluxed in 50 ml of dry toluene for 3 h. The mixture was concentrated under reduced pressure and the residue crystallized after trituration with ether. The solid was recrystallized from appropriate solvent. The NMR spectrometric data for **2b** and **2j** which are representative of the title compounds are listed below.

2-Phenoxymethyl-2,3,5,6-tetrahydro-7H-oxazolo[3,2-a]pyrimidin-7-one **(2b)**

^{1}H-NMR (90 MHz, $CDCl_3$); δ (ppm) = 2.67 (2H, C-6); 4-3.5 (m, 4H, C-5 and C-3); 4.2 (2H, OCH_2); 5.2-4.9 (m, 1H, C-2); 7.4-6.7 (m, 5H, phenyl).- ^{13}C-NMR (DMSO D_6); δ ppm = CO 178; C=N 167.5; phenyl

Table 5: Bond lengths (Å)

C(1)-C(2)	1.368(8)	O(10)-C(11)	1.337(6)
C(1)-C(6)	1.357(9)	C(11)-N(12)	1.311(7)
C(1)-O(7)	1.389(7)	C(11)-N(14)	1.299(7)
C(2)-C(3)	1.393(9)	N(12)-C(13)	1.456(7)
C(3)-C(4)	1.390(10)	N(12)-C(17)	1.423(9)
C(4)-C(5)	1.367(11)	N(14)-C(15)	1.359(7)
C(5)-C(6)	1.387(11)	C(15)-C(16)	1.473(10)
O(7)-C(8)	1.426(7)	C(15)-O(19)	1.214(7)
C(8)-C(9)	1.503(8)	C(16)-C(17)	1.422(11)
C(9)-O(10)	1.468(6)	C(17)-C(18)	1.388(12)
C(9)-C(13)	1.526(8)		

Table 6: Bond angles (°)

C(2)-C(1)-C(6)	121.2(6)	O(10)-C(11)-N(14)	117.9(5)
C(2)-C(1)-O(7)	124.3(5)	N(12)-C(11)-N(14)	130.5(5)
C(6)-C(1)-O(7)	114.6(5)	C(11)-N(12)-C(13)	113.2(4)
C(1)-C(2)-C(3)	119.7(5)	C(11)-N(12)-C(17)	120.1(5)
C(2)-C(3)-C(4)	118.9(6)	C(13)-N(12)-C(17)	126.5(5)
C(3)-C(4)-C(5)	120.6(7)	C(9)-C(13)-N(12)	101.2(4)
C(4)-C(5)-C(6)	119.6(7)	C(11)-N(14)-C(15)	114.8(5)
C(1)-C(6)-C(5)	120.0(7)	N(14)-C(15)-C(16)	119.5(5)
C(1)-O(7)-C(8)	118.1(4)	N(14)-C(15)-O(19)	121.0(5)
O(7)-C(8)-C(9)	105.9(4)	C(16)-C(15)-O(19)	119.4(6)
C(8)-C(9)-O(10)	108.2(4)	C(15)-C(16)-C(17)	120.7(7)
C(8)-C(9)-C(13)	113.2(4)	N(12)-C(17)-C(16)	111.6(6)
O(10)-C(9)-C(13)	105.0(4)	N(12)-C(17)-C(18)	120.3(7)
C(9)-O(10)-C(11)	109.1(4)	C(16)-C(17)-C(18)	127.2(8)
O(10)-C(11)-N(12)	111.5(4)		

158, 129.7, 121.3, 114.7; C-2 76.4; OCH_2 67.8; C-3 48.4; C-5 40.2; C-6 29.4.

2-Phenoxymethyl-5-methyl-2,3,5,6-tetrahydro-7H-oxazolo[3,2-a]pyrimidin-7-one (**2j**)

^{1}H-NMR (90 MHz, DMSO D_6); δ (ppm) = 1.4 (3H, CH_3); 2.9-2.2 (m, 2H, C-6); 4.3-3.6 (m, 3H, C-5 and C-3); 4.5 (m, 2H, OCH_2); 5.6-5.2 (m, 1H, C-2); 7.7-7 (m, 5H, phenyl).- ^{13}C-NMR (DMSO D_6); δ (ppm) = CO 177.9; C=N 167.1; phenyl 158.2, 129.7, 121.3, 114.7; C-2 76; OCH_2 67.8; C-5 47; C-3 45.9; C-6 37.5; CH_3 18.

General procedure for the synthesis of 2-substituted-2,3-dihydro-7H-oxazolo[3,2-a]pyrimidin-7-ones

10 mmol of **1** and 10 mmol of ethyl propiolate were refluxed in 80 ml of ethanol for 6 h. The mixture was concentrated under reduced pressure and the residue crystallized after trituration with ether. The final solids were recrystallized from appropriate solvents. The NMR spectrometric data for **3a**, representative of the title compounds, are listed below.

2-Chloromethyl-2,3-dihydro-7H-oxazolo[3,2-a]pyrimidin-7-one (**3a**)

^{1}H-NMR (90 MHz, DMSO D_6); δ (ppm) = 4.6-3.9 (m, 4H, C-3 and CH_2Cl); 5.6-5.1 (m, 1H, C-2); 5.8 (1H, C-6); 7.7 (1H, C-5).- ^{13}C-NMR (DMSO D_6); δ (ppm) = CO 171.3; C=N 160.3; C-5 138.3; C-6 107.9; C-2 77.3; CH_2Cl 48.6; C-3 45.5.

Pharmacology

Anti-arrhythmic activity

Male Swiss mice were intraperitonealy dosed with the test compounds. Thirty min later they were submitted to deep chloroform anaesthesia which prolongs the refractory period and depresses the myocardial excitability. 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). Test compounds were prepared as aqueous solutions. Small amounts of DMSO were used to increase the solubility. At the concentration employed, DMSO did not produce any arrhythmic or anti-arrhythmic effect.

Hypocholesterolemic activity

Male Swiss mice, made hypercholesterolemic by being fed a high cholesterol-cholic acid diet for seven days, were dosed on the sixth and seventh days p.o. (one half the total recorded dose was given on day 6 followed by the other half on day 7). After fasting overnight the reduction in serum cholesterol concentration was determined. The reduction of the serum heparin precipitating lipoprotein concentrations (corresponding to LDL and VLDL fractions) was assessed in the same hypercholesterolemic mice.

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