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Research Article

SYNTHESIS AND ANALGESIC ACTIVITY OF SOME OXAZOLIDINE DIONE DERIVATIVES

[1]V. Shankarananth*
Associate Professor, Dept. of Pharmaceutical Chemistry, Sri Padmavathi School of Pharmacy, Tiruchanoor-517503, Andhra Pradesh

[2]Dr. D. Ranganayakulu
Principal, Sri Padmavathi School of Pharmacy, Tiruchanoor-517503, Andhra Pradesh

[3]Dr. C. Sridhar
Director, C. E. S. College of Pharmacy, NH-7, Chinnatekur, Kurnool-518218, Andhra Pradesh

[4]Dr. K. K. Rajasekhar
H. O. D, Dept. of Pharmaceutical Chemistry, Sri Padmavathi School of Pharmacy, Tiruchanoor-517503, Andhra Pradesh

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ABSTRACT

A Convenient high yield one pot methodology for the synthesis of pharmaceutically interesting oxazolidine-2, 4-dione derivatives from α-hydroxy esters is described. The structures of compounds were established on the basis of IR and NMR spectral data. The title compounds were investigated for analgesic activity. The tested compounds exhibited good analgesic activity as compared to standard drug. The oxazolidine-2, 4 dione was generated from the condensation between α-hydroxy ester and guanidine and then converted to the desired derivatives via aqueous acid hydrolysis, alkylation with different alkyl halides.

Key words: *Synthesis, α-hydroxy ester, guanidine, oxazolidine-2, 4 dione, analgesic activity.*

INTRODUCTION

A number of oxazolidine-2,4diones and its derivatives have been associated with significant biological activities like aldose reductase inhibitors[1], hypoglycaemic and hypolipidemic agents[2], muscarinic agonists[3], anticonvulsants[4] and insulin sensitizers with antidiabetic activities[5]. Furthermore spirooxazolidine diones were found to be aldose reductase inhibitors[6].In addition, 5, 5-dimethyloxazolidine-2, 4 dione (DMO) was described as an indicator of intracellular pH due to its weak acidic properties[7]. It also have herbicidal activity[8] and antiulcer activity[9].Because of the importance of oxazolidine-2, 4 dione and its derivatives, a number of synthetic methods have been reported in the literature. However, upon closer inspection, it became apparent to us that among these synthetic methods, the following method (SCHEME-I) were typically used.

A few 5, 5-substituted-1, 3-oxazolidine-2, 4 dione and its derivatives have already been known, but their analgesic activity have not been reported so far. Therefore, a large number of 5, 5-disubstituted-1, 3-oxazolidine-2, 4 dione derivatives carrying various substituents were synthesized and their analgesic activity were evaluated.

MATERIALS AND METHODS

Chemicals and equipments:
α-hydroxy ester(ethyl lactate), Guanidine, concentrated hydrochloric acid, n-propyl iodide, Isopropyl iodide, n-butyl bromide, Isobutyl bromide, ethyl iodide, n-pentyl bromide, 2°-pentyl bromide, 3°-pentyl bromide, Reflux condenser, Heating mantle, Hot plate, Dimethyl Sulfoxide, Saline, Acetic acid and Aspirin.

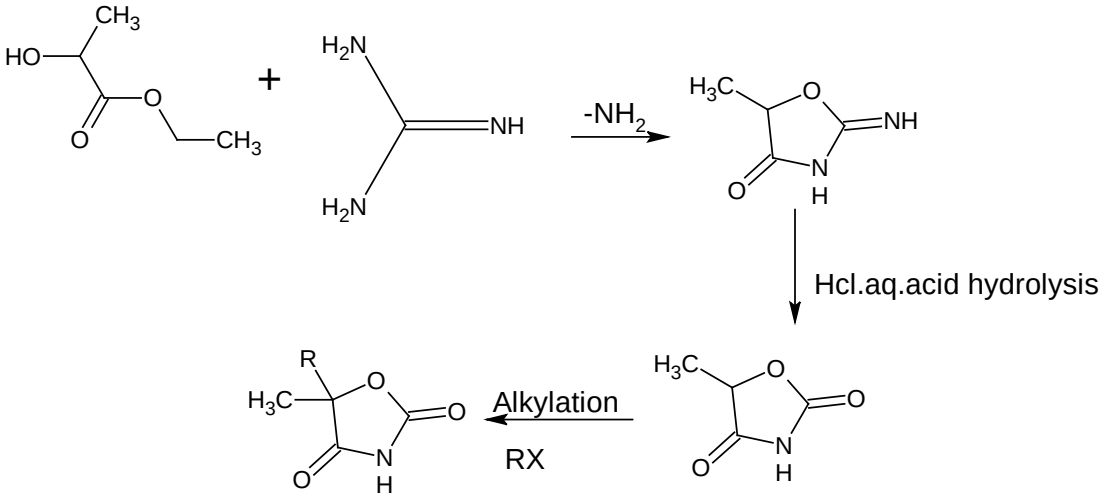
Corresponding author: *[1]V. Shankarananth**
Associate Professor, Dept. of Pharmaceutical Chemistry, Sri Padmavathi School of Pharmacy, Tiruchanoor-517503, Andhra Pradesh

METHODS

Synthesis of 5-methyl-1, 3-oxazolidine-2, 4- dione:
0.01M of α-hydroxy ester (ethyl lactate) and 0.01M of guanidine was reflux condensed for 12 hours. Then the mixture was subjected to acid hydrolysis and then it was kept in a refrigerator for formation of product and the product was filtered and kept for drying. Then it was used further without recrystallization.

Synthesis of 5-methyl-5-substituted-1, 3-oxazolidine-2, 4-dione derivatives:
0.01M of 5-methyl-1,3-oxazolidine-2,4-dione was taken and placed in a beaker, then it was subjected to alkylation by stirring for 2 hours with different alkylating reagents such as n-propyl iodide, isopropyl iodide, n-butyl bromide, isobutyl bromide, ethyl iodide, n-pentyl bromide, 2°pentyl bromide and 3° pentyl bromide to yield desired derivatives (Ia-Ih).

SCHEME-I:



(Ia-Ih)

Ia R- $CH_3CH_2CH_2$

Ib R- $-CH(CH_3)_2$

Ic R- $-CH_2CH_2CH_2CH_3$

Id R- $-CH\ CH_3CH_2\ CH_3$

Ie R- $-CH_2CH_3$

If R- $-(CH_2)_4-CH_3$

Ig R- $-CH(CH_3)-(CH_2)_3-CH_3$

Ih R- $-CH(CH_2-CH_3)_2$

Evaluation of Analgesic activity[10]:

All the title compounds were tested for analgesic activity using eddy's hot plate and acetic acid induced writhing method.

In the Hot plate (Eddy's Hot Plate; Techno, India) test animals were orally administered 30 mg/Kg of the Compound, saline (control) or 100 mg/Kg Aspirin(Reference drug). The animals were each placed on a hot plate (maintained at 55 ± 1°C) after 60 min of the administration of the Compound, drug or Saline and the time (Reaction time) it takes each of the animals to jump off the hot plate was noted and cut off period of 15 sec. The mean of the responses for the animals (2 per group) administered each compound was compared with the control group.

In writhing method, Swiss albino mice of either sex weighing between 25-30 gm were randomly distributed in forty two groups of two mice each.

The first group served as control and the animals of that group were administered 1% v/v acetic acid (1 ml/100 g) intraperitoneally. The onset and the number of writhing were recorded for a period of 10 min for each animal of the group. The second group of animals administered aspirin (50 mg/kg, i.p.) and 30 min later, acetic acid was administered to the animals of that group. The onset and the frequency of writhing response were observed7. The animals of remaining groups were treated with drug in DMSO 30 mg/kg and the acetic acid-induced writhing were recorded as described for group 1 and 2. Percent protection against acetic acid induced writhing was calculated using the formula:

$$\% \text{ protection} = (Nc - Nt / Nc) \times 100$$

where Nt and Nc are the mean values of number of writhing in the test and control group, respectively.

RESULTS AND DISCUSSION

The main aim of the present work was to synthesize some oxazolidine dione derivatives. They were confirmed by IR (KBr) and ^{1}HNMR spectra. Subsequent purification of crude compounds yielded pure compounds in moderate to high yields. Some of these compounds such as I_d and I_g exhibited significant analgesic activity in Eddy's hot plate method when compared to that of standard, whereas I_b and I_f showed moderate analgesic activity in Eddy's hot plate method when compared to that of standard.

Compounds such as I_d and I_e exhibited significant analgesic activity in Acetic acid induced writhing method when compared to that of standard, whereas I_c,I_f and I_h showed moderate analgesic activity in Acetic acid induced writhing method when compared to that of standard.

Table: 1
Characterisation of new substituted Oxazolidine diones [11]:

Physical Characterisation data of 5-methyl-5'substituted-1, 3 –oxazolidine-2, 4-dione derivatives (1_{a-h})

Compound	R	Molecular Formula	Molecular weight	Melting Point (°C)	Yield %	R_f value
1_a	$-CH_2CH_2CH_3$	$C_7H_{11}NO_3$	157.16714	152- 154°C	75	0.78
1_b	$-CH-(CH_3)_2$	$C_7H_{11}NO_3$	157.16714	165-168°C	77	0.70
1_c	$-(CH_2)_3-CH_3$	$C_8H_{13}NO_3$	171.19372	134-136°C	72	0.85
1_d	$-CH_2-CH(CH_3)-CH_3$	$C_8H_{13}NO_3$	171.19372	145-147°C	94	0.88
1_e	$-CH_2-CH_3$	$C_6H_9NO_3$	143.14056	125-128°C	87	0.90
1_f	$-(CH_2)_4-CH_3$	$C_9H_{15}NO_3$	185.2203	168-170°C	86	0.76
1_g	$-CH_3-(CH_2)_6-CH_2$	$C_{12}H_{21}NO_3$	227.30004	143-148°C	80	0.62
1_h	$-CH_2-CH=CH_2$	$C_7H_9NO_3$	155.15126	84-90 °C	65	0.66

Table: 2
Mass and IR spectral data of 5-methyl-5'substituted-1, 3–oxazolidine-2, 4-diones (1_{a-h})

Compound	Mass spectra (m/z)	Position of absoption band (cm^{-1})
1_a	143.1405	1085(C-O stretching),1725,1620(C=O stretching, α diketones, β diketones), 3384(N-H stretching),1635(N-H def), 2960(C-H stretching),1450(C-H def)2852(-CH_2; C-H stretching),1465(-CH_2;C-H def)
1_b	143.1405	1086(C-O stretching),1724, 1610(C=O stretching, α diketones, β diketones),3392(N-H stretching), 1620(N-H def), 2955(C-H stretching),1460(C-H def)2862(-CH_2; C-H stretching), 1480(-CH_2;C-H def)
1_c	171.1937	1088(C-O stretching),1715, 1590(C=O stretching, α diketones, β diketones), 3390(N-H stretching),1645(N-H def),2958(C-H stretching),1440(C-H def)2848(-CH_2; C-H stretching), 1468(-CH_2; C-H def)
1_d	171.1937	1084(C-O stretching),1722,1600(C=O stretching, α diketones, β diketones), 3391(N-H stretching), 1640(N-H def),2957(C-H stretching),1462(C-H def)2852(-CH_2; C-H stretching), 1470(-CH_2;C-H def)
1_e	129.1139	1087(C-O stretching), 1714,1597(C=O stretching, α diketones, β diketones), 3389(N-H stretching),1625(N-H def),2957 (C-H stretching),1461(C-H def)2852(-CH_2;C-H stretching),1480(-CH_2;C-H def)
1_f	185.2203	1083(C-O stretching),1724, 1610(C=O stretching, α diketones, β diketones), 3390(N-H stretching),1646(N-H def), 2965 (C-H stretching),1462 (C-H def)2860 (-CH_2;C-H stretching),1472(-CH_2;C-H def)
1_g	227.3000	1089.91(C-Ostretching), 833.35,856.50(C-N stretching),1458.36(CH_2:C-H def),1628.12 (C=O stretching),1643.55(N-H def), 2953.38 (C-H stretching), 2841.49, 2893.58 (CH_2; C-H stretching), 3393.21(N-H stretching)
1_h	155.1512	1080.27(C-O stretching),835.28,846.85(C-N stretching), 1464.15(CH_2;C-H def), 1643.55 (N-H def), 1610.76,1560.60(C=O stretching), 2849.21,2889.72(CH_2; C-H stretching),2949.52 (C-H stretching), 3397.06(N-H stretching), 3032.47(C-H stretching, R-CH=CH_2)

Table: 3
^{1}H NMR spectral data (400MHz) of 5-methyl-5'substituted-1, 3 –oxazolidine-2, 4-diones (1_{a-h})

Compound	Chemical Shift (δ) in ppm
1_a	1.654(CH_3, methyl), 1.259(CH_3, methyl), 1.340(CH_2, methylene), 1.763(CH_2, methylene), 8.765(NH,imide).
1_b	1.620(CH_3, methyl), 1.276(CH_3, methyl), 1.282 (CH_3, methyl), 2.2(CH, methine), 6.706(NH, imide).
1_c	0.903, 0.907(CH_3, methyl), 1.644, 1.658(CH_3, methyl), 1.215 (CH_2, methylene) 1.275(CH_2, methylene) 1.996 (CH_2, methylene) 8.819(NH, imide).
1_d	1.387(CH_3, methyl), 1.206(CH_3, methyl), 1.220(CH_3, methyl), 1.402 (CH_2, methylene), 2.1(CH,methine),11.850(NH, imide).
1_e	1.379(CH_3, methyl), 1.190(CH_3, methyl), 2.5(CH_2, methylene), 7.157(NH, imide).
1_f	1.618(CH_3, methyl), 1.197(CH_3, methyl), 1.733(CH_2, methylene), 1.210(CH_2, methylene), 1.407(CH_2, methylene), 1.459 (CH_2, methylene), 7.014(NH, imide).
1_g	0.910(CH_3, methyl), 1.27(CH_2, methylene),1.607(CH_2, methylene), 1.621(CH_2, methylene), 1.848(CH_3, methyl), 1.862(CH_2, methylene), 1.974(CH_2, methylene), 1.988(CH_2, methylene), 2.007 (CH_2, methylene), 8.602(NH, imide).
1_h	1.611(CH_3, methyl),1.490(CH_3, methyl),1.639(CH_2, methylene), 1.499(CH_2, methylene), 6.447(NH, imide).

Table: 4
Evaluation of Analgesic activity of synthesised compounds (1_{a-h}) by hot plate test in rats

S. No	Compound	Dose mg/kg	Reaction time in seconds (Mean ± S.D)	% increase in pain threshold
1.	Control	--------	3.82 ± 0.159	-------
2.	Standard(Aspirin)	100	9.45 ± 0.245	147.38
3.	1_a	30	7.95 ±0.156	108.98
4.	1_b	30	9.13 ± 0.212	125.98
5.	1_c	30	8.56 ± 0.165	112.24
6.	1_d	30	8.64 ± 0.234	148.98
7.	1_e	30	7.97 ± 0.228	101.24
8.	1_f	30	8.46 ± 0.126	121.34
9.	1_g	30	9.14 ± 0.222	150.24
10.	1_h	30	7.85 ± 0.211	100.26

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