SYNTHESIS OF SOME NOVEL IMIDAZOLINONES

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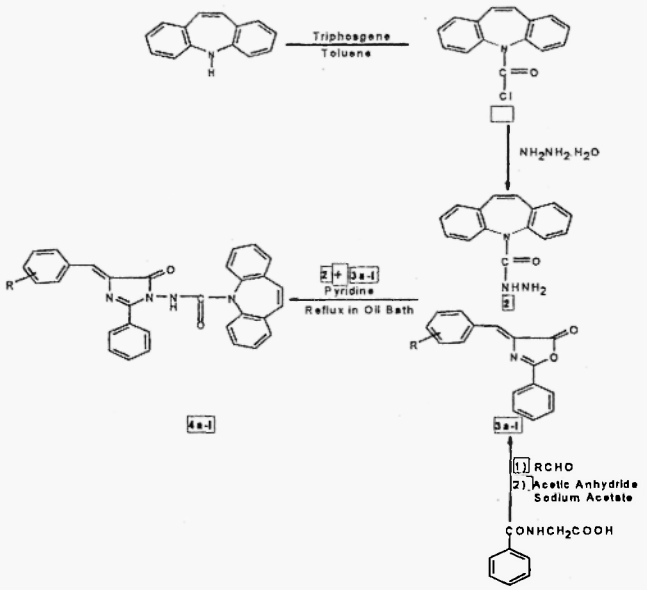
Abstract: Imidazolinone derivatives of **4a-l** have been prepared by the condensation of known heterocyclic drug derivative with 5-oxazolone derivatives, which were prepared by Erlenmeyer condensation of benzoyl glycine with different aldehydes in the presence of sodium acetate and acetic anhydride. The compounds **3a-l** were further reacted with 5*H*-dibenzo (*b,f*) azepine -5-acid hydrazide **2** to give 4**a-l** in basic condition . The constitution of the products has been supported by IR, ^{1}H-NMR, Mass spectra and elemental analysis data.

Introduction

Over the last ten years many synthetic efforts have been directed toward synthesis of benzazepines annelated to various rings (isoindole, pyrolidine, benzene..) because a number of natural prouducts (1, 2, 3) contains this moiety and present potential biological activities. Many analogues of dibenzo (*c,e*; *b,e*; *b,f*) azepines are known and exhibit biological activities (4, 5, 6).Several dibenzoazepine and its derivatives are shown to be affective ventricular defibrillatory drug agents (7). The dibenzo (*b,f*) azepine and its derivatives such as carbamazepine and oxcarbazepine have become established as an effective agents in the management of epilepsy and effective disorders (8). The 5*H*-dibenzo (*b,f*) azepine-5-acid hydrazide 2 are synthesized and have been used for the attachment to proteins for the preparation of the corresponding immunogens (9).

Oxazolone is a class of small heterocycles which are important intermediates in the synthesis of several small molecules, including amino acids, peptides, (10, 11, 12) antimicrobial or antitumor compounds, (13, 14) heterocyclic precursors (15, 16, 17) as well as biosensors coupling and photosensitive composition devices for proteins (18). Some oxazolones have shown a wide range of pharmaceutical properties (19). 5-oxazolones are synthesized by the Erylenmeyer condensation as reported in the literature (20).

Literature survey reveals that various imidazolinone derivatives possess a broad spectrum of activities which are reflected by their use as anticonvulsant (21) and anti-Parkinsonian agents (22). Some novel imidazolinones have been synthesized by using different oxazolones and condensing them with aliphatic and aromatic amines (23, 24) and with sulphonamide as anticonvulsant agents (25). Here we have shown the synthesis of 5*H*-dibenzo (*b,f*) azepine-5-acid hydrazide 2 and various 5-oxazolones 3a-l to give novel imidazolinones 4a-l (Scheme-1).



Experimental

All the recorded melting points were determined in open capillary tubes and are uncorrected. All the chemicals and solvents used are of Laboratory Grade and solvents were purified. Completion of the reaction was monitored by TLC (silica gel GF254 (E. Merck), Toluene: Methanol= 8:2). The final products were purified by column chromatography using silica gel in increasing percentage of ethyl acetate in carbon tetrachloride. I.R (Infrared Spectrum) (KBr, cm-1) were recorded on a Shimadzu-8400 FT-IR spectrometer, 1H NMR spectra on a Brucker spectrometer (300MHz) using TMS as a internal standard (chemical shift in δ, ppm) in $CDCl_3$ and DMSO d_6 and mass spectrum was recorded on Hewlett-Packard 5989, a Quadrapole Mass Spectrum and LC-MS on Perkin Elmer API 165. All the synthesized compounds gave satisfactory C, H, N analyses on Perkin Elmer (U.S.A) 2400 Series.

Preparation of 5*H*-dibenzo (*b,f*)azepine-5-acid hydrazide 2

A solution of 5*H*-dibenzo(*b,f*)azepine-5-carbonyl chloride 1 (0.01 mole) with hydrazine hydrate (0.01 mole,80%) in absolute ethanol (20ml) was stirred for 1 hour and then refluxed for half an hour in water bath. The contents were cooled to get white crystals, which were filtered and washed with cold ethanol, dried and recrystallized from methanol. Yield 63% m.p 178°C, Found: C, 71.52; H, 5.10; N, 16.60%. Calculated for $C_{15}H_{13}N_3O$: C, 71.71; H, 5.17; N, 16.73%, **IR:** 3326 (NH amine), 3276 (-NH_2), 2921 (Aromatic C-H stretch),1622 (N-C=O), **^{1}H NMR** ($CDCl_3$)**:** δ 6.90 to 7.42 (m, 8H, Ar-H), 6.87 (s, 2H, CH=CH), 5.85 (br, 1H, -NH), 3.41 (br, 2H, -NH_2), **MS:** (m/z)% : 252 (53, M+), 221 (20.2), 192 (100), 165 (14.6).

Preparation of 4-Arylidene-2-phenyl-5-(*4H*)-oxazolones 3a-l

4-Arylidene-2-phenyl-5-(*4H*)-oxazolones were prepared according to the reported method [20].

General procedure for the preparation of of Dibenzo (*b,f*) azepine-5-carboxylic acid [4-(substituted benzylidene)-5-oxo-2-phenyl-4,5-dihydro-imidazol-1-yl]amide 4a-l

2-Phenyl-4-benzylidene-5-oxazolone (2.49 g, 0.01 mol) was heated with an equimolar quantity of 5*H*-dibenzo (*b,f*) azepine-5-acid hydrazide 2 (0.01 mole) in pyridine on oil bath at 140 °C for 4 hours. The resulting jelly-like mass was taken in an organic solvent and refluxed for 6 hours with continuous removal of water, cooled, excess solvent removed under vacuum and the resultant solid was worked up and purified over a column of silica gel, and the solid recrystallised from light petroleum to get 5-imidazolinone and was found chromatographically homogeneous.

Characterization of Dibenzo (*b,f*) azepine-5-carboxylic acid [4-(4-methoxy benzylidene)-5-oxo-2-phenyl-4,5-dihydro-imidazol-1-yl]amide 4a

Orange-Yellow crystals, **IR** (KBr) νmax (cm−1)**:** 3008–3080 (Ar---CH), 2972–2916 (C=C str.), 1747 (C=O str.),1650 (C=O amide str.), 1251 (C-O-C Asymmetric Strech), 1161 (C=O str.), 1026(C-O-C Symmetric Strech), **^{1}H-NMR** (DMSO-d6) **:** δ 8.54 (s, 1H, -NH), 6.94 to 7.82 (m, 17H, Ar-H), 6.67 (s, 2H, CH=CH), 6.33 (s, 1H, Ar-C=CH), 3.76 (s, 3H, -OCH_3), **LC-MS :** 513.4 (M+),320.0 (M), 293.2 (M+), 277.4 (M), 263.1 (M), 192 (M+), 177.4 (M).

Similarly all the other compounds 4b-l where prepared in the similar way. The reaction scheme is given in Figure-1 and their physical and spectral data are recorded in Table-1.

Table-1: Physical and Spectral Data for 4a-l

Com	R	M.P. (°C)	Yield (%)	R.S	^{1}H-NMR ($CDCl_3$ & DMSO-d_6) (δ ppm)	Found & (Calculated) % C	%H	%N
4a	4-OCH_3	128	62.0	1	δ 8.54 (s, 1H, -NH), 6.76 to 7.82 (m, 17H, Ar-H), 6.67 (s, 2H, CH=CH), 6.33 (s, 1H, Ph-C=CH), 3.85 (s, 3H, -OCH_3).	74.73 (74.99)	4.60 (4.72)	10.78 (10.93)
4b	4-Cl	160	67.0	3	δ 8.52 (s, 1H, -NH), 6.80 to 7.85 (m, 17H, Ar-H), 6.65 (s, 2H, CH=CH), 6.21 (s, 1H, Ph-C=CH),.	72.25 (72.02)	4.06 (4.09)	10.70 (10.84)
4c	4-OH	158	60.0	3	δ 8.50 (s, 1H, -NH), 6.85 to 7.80(m, 17H, Ar-H), 6.71 (s, 2H, CH=CH), 6.21 (s, 1H, Ph-C=CH), 4.54 (s, -OH).	74.45 (74.69)	4.32 (4.45)	11.10 (11.24)
4d	4-$N(CH_3)_2$	167	61.0	4	δ 8.52 (s, 1H, -NH), 6.90 to 7.84 (m, 17H, Ar-H), 6.80 (s, 2H, CH=CH), 6.24 (s, 1H, Ph-C=CH), 3.65 (s, 6H, -$NCH_3)_2$).	75.20 (75.41)	5.05 (5.18)	13.22 (13.32)
4e	4-F	178	70.0	1	δ 8.52 (s, 1H, -NH), 6.92 to 7.89 (m, 17H, Ar-H), 6.82 (s, 2H, CH=CH), 6.21 (s, 1H, Ph-C=CH).	74.25 (74.39)	4.14 (4.23)	11.09 (11.19)
4f	2-NO2	146	61.0	3	δ 8.48 (s, 1H, -NH), 6.90 to 7.75 (m, 17H, Ar-H), 6.80 (s, 2H, CH=CH), 6.18 (s, 1H, Ph-C=CH).	70.32 (70.58)	3.90 (4.01)	13.18 (13.28)
4g	2-OH	138	60.0	3	δ 8.52 (s, 1H, -NH), 6.85 to 7.80 (m, 17H, Ar-H), 6.71 (s, 2H, CH=CH), 6.21 (s, 1H, Ph-C=CH), 4.50 (s, 1H, -OH).	74.45 (74.69)	4.32 (4.45)	11.10 (11.24)
4h	3-OCH_3, 4-OH	146	61.0	2	δ 8.52 (s, 1H, -NH), 6.89 to 7.78 (m, 16H, Ar -H), 6.70 (s, 2H, CH=CH), 6.21 (s, 1H, Ar - C=CH), 4.60 (s, 1H, -OH), 3.85(s, 3H, -OCH_3),	72.59 (72.72)	4.50 (4.58)	10.49 (10.60)
4i	3,4,5-OCH_3	155	68.0	4	δ 8.54 (s, 1H, -NH), 6.76 to 7.82 (m, 15H, Ar-H), 6.67 (s, 2H, CH=CH), 6.33 (s, 1H, Ph-C=CH), 3.85 (s, 3H, -OCH_3).	71.45 (71.32)	4.83 (4.93)	9.70 (9.78)
4j	1-Napthyl	126	65.0	4	δ 8.45 (s, 1H, -NH), 6.80 to 7.88 (m, 20H, Ar-H), 6.71 (s, 2H, CH=CH), 6.21 (s, 1H, Ar-C=CH).	78.82 (78.93)	4.40 (4.54)	10.45 (10.52)
4k	2-Cl-Quinoline	155	68.0	4	δ 8.48 (s, 1H, -NH), 6.75 to 7.81 (m, 18H, Ar-H), 6.65 (s, 2H, CH=CH), 6.21 (s, 1H, Ar-C=CH).	71.95 (71.89)	3.85 (3.90)	12.30 (12.35)
4l	H	172	60.0		δ 8.60 (s, 1l1, -NH), 6.90 to 7.84 (m, 18H, Ar-H), 6.65 (s, 2l1, CH=CH), 6.21 (s, 1H, Ar-	77.08 (77.16)	4.52 (4.60)	11.52 (11.61)

R.S = Recrystallization Solvents
1. Methanol; 2. Methanol/DMF; 3.Dioxane/Water; 4. DMF

Results and Discussions

The structures of all compounds were confirmed by IR, ^{1}H –NMR, Mass Spectra and Elemental analyses. The IR Spectrum of compound 2 showed the NH bands at 3326 cm^{-1} 3276 cm^{-1}, and the amide C=O band at 1622 cm-1. The I.R Spectra of 4a-l gave two bands at 1747 (C=O str.) and 1161 (C=O str.) which correspond to the carbonyl in 5-imidazolone and the carbonyl of amide at 1650, which indicated the presence of both the carbonyl group.

The ^{1}H NMR spectrum of 2 shows two broad peaks at 5.85 and 3.41 ppm which were assigned as –NH and $–NH_2$ groups of hydrazide respectively. In the spectra of 4a-l the –NH proton shifted in downfield at 8.54 ppm which is due to the C=O and heterocyclic ring system. The arylidene proton gave a singlet at 6.33 ppm the other entire proton where obtained in the aromatic region.

The MS, showed molecular ions of different intensity. The mass spectrum of compound 2 fragmented via the common routes, the first and second involved the cleavage of the $-NH_2$ and –NH followed by –C=O which gave fragments at m/z 234 (M +), 221 (M+) and 192 (M) respectively, here the direct cleavage of the CO-NH gave fragment at 192, which was the base peak. In case of 4a-l, the LC-MS spectra for 4a, gave 513 (M+1), which was the molecular ion peak, which fragmented to give two fragment at 320 (M) of 4-Arylidene-2-phenyl-5-imidazolone-3-carboxiamido ion and dibenzo (*b,f*) azepine ion 192 (M+1), the base peak. The latter fragmented to dicyclo1,3-hexadieneyl diene at m/z 177 (M).

Conclusions

The 5*H*-dibenzo (*b,f*) azepine on phosgenation gave 5*H*-dibenzo (*b,f*) azepine-5-carbonyl chloride 1, this when reacted with hydrazine hydrate gave 5*H*-dibenzo (*b,f*) azepine -5-acid hydrazide 2. These compound resemble to the tricyclic antidepressants and so these compounds can be further studied for their biological evaluation along with the prepared Imidazolinone 4a-l derivatives to study the possible efficacy of the prepared compounds.

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