TRIAZOLO DERIVATIVES OF DIBENZODIAZEPINES AS POTENTIAL C.N.S. ACTIVE DRUG

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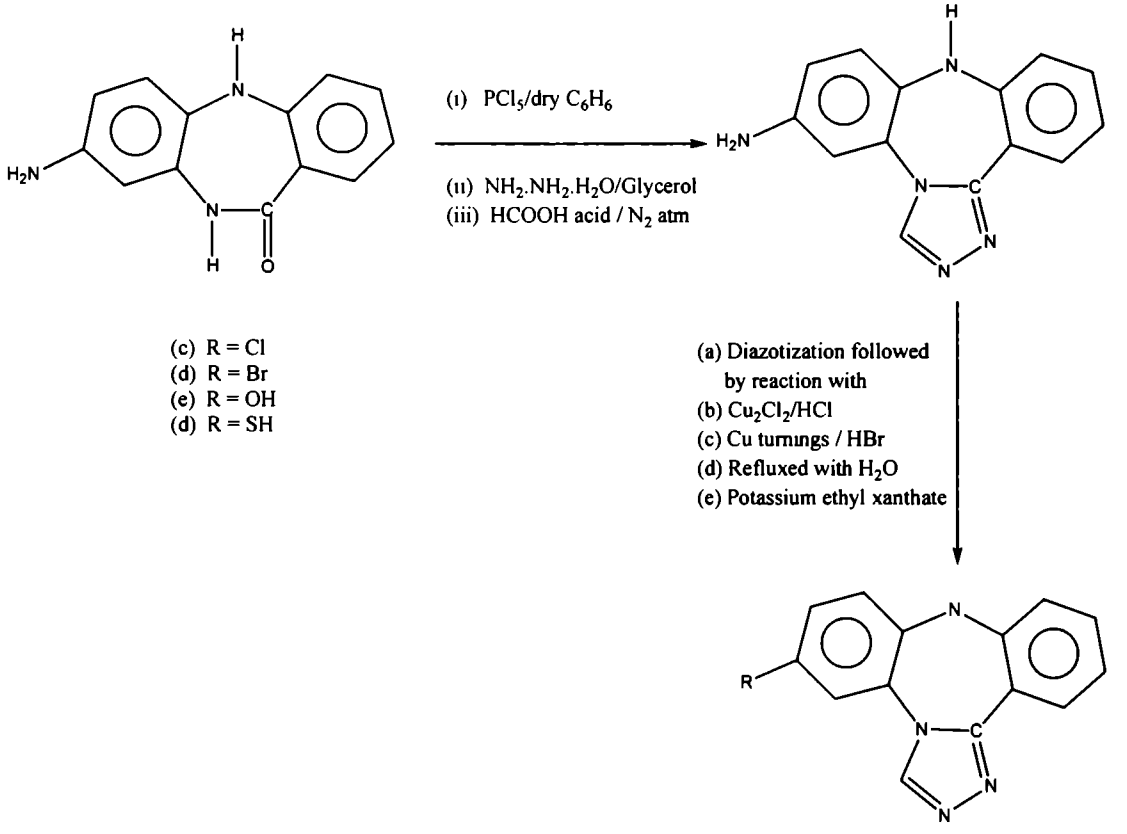
Abstract: The synthesis of a number of substituted triazolo derivatives of Dibenzodiazepines are reported. The medicinal properties were evaluated through various pharmacological assessments applied on albino mice of either sex taking clozapine as standard drug. A triazolo derivatives having substitution at 8-positions Dibenzodiazepines was found to have for better CNS depressant activity properties as compared to the basic Dibenzodiazepines moeity and among other 8-subsituted derivatives amino substitution exhibited 70 - 80 % antiepileptic properties.

Introduction

Dibenzodiazepine series have shown antidepressant, neuroleptic, antihistaminic and many related CNS depressant properties.[1-6] We report here in modified synthesis of Dibenzodiazepine molecule incorporating a traizolo system in an attempt to find some effective antiepileptic behaviour.[7-11] Dibenzodiazepine derivatives having substitution at C-7 position have already proved clinical agents like clozopine and tarpan as antihistaminic and highily effective antipsychotic drugs.[2,12] Among the triazolo derivatives a trend of improvement is studied by making suitable changes at C-8 positions of Dibenzodiazepine by replacing -NH_2 group by Cl, Br, OH and SH group. Their clinical trials have shown depressant and antianxienty properties with the presence of addition liability among other side effects such molecules have to potential to act as a CNS depressant chemical. So apart from modification of methods of synthesis we report herein the pharmacological activity of a series of these bioactive compounds in an effort to get better antiepileptic drug as this type of compounds are reported in literature as having tranquilizing, anticonvulsant and sedative properties and other pharmacological activity.[13-16] However, as most of the methods of their synthesis is patented thus it was thought worthwhile to study these compounds more extensively as it opens an interesting field for study especially in an effort to get better antiepileptic drugs by modifying the molecule at position-3 of triazolo ring, at NH of C-5 position of and at NH_2 at c-8 position of Dibenzodiazepine. Various methods of preparation of triazolo derivatives have been mentioned in literature so far.[17-18] Here the synthesis by a modified route is being discussed.

Result and Discussion

The traizolo derivatives of 8-amino-10, 11-dihydro-5H-dibenzo (b,e) (1, 4) diazepine-11-one(a) was prepared according to the scheme given below via chlorination, followed by reaction with hydrazine hydrate and cyclization. The triazolo derivatives(c-f) were obtained by the replacement of the 8-amino group of Dibenzodiazepines moiety (scheme-1)



The IR spectra of all the triazolo derivatives show the presence of cyclic C = N – N = C bands in the region 1350 and 1550 cm^{-1} which are not observed in the precursor Dibenzodiazepine moiety. Besides, the compounds are also show the presence of the N – C = N bands in the region 2150 – 2130 cm^{-1} and the absence of the NHCO bands indicating the formation of a triazolo ring. The derivatives (a) show the presence NH_2 band in the region at 3420 cm^{-1}. In all other derivatives this band is not observed. IR Bands related to OH and SH group for compounds d and e are observed at 3600 and 2600 cm^{-1} respectively.

The ^{1}HNMR spectra of all the triazolo derivatives show the absence of singlet at □3.9 ppm for the NHCO proton. The singlet for triazolo olefinic proton is observed at □8.6 ppm. A multiplet for aromatic proton is observed in the region □6.5 - 7.5 ppm. In the mass spectra of the compounds the molecular ion peaks were observed in the expected m/Z values. The fragmentation pattern in general corresponded to the elimination of the 8-substituted group from the molecular ion followed by the elimination or triazolo system.

The overall spectral studies are consistent with the formation of the triazolo derivatives. In the pharmacological evaluation of the compounds clozapine was used as a standard drug.[19-20] The screening methods used in evaluation of the pharmacological profile of the synthesized compounds include Acute toxicity and gross effects, locomotor and exploratory activity, potentiation of pentobarbitone - induced hypnosis, Maximal electroshock seizures, pentylene tetrazole-induced seizures, Amphetamine group toxicity test. All drugs were given as a single intraperitoneal injection suspended in gum acacia in 1ml/20gm. and the test dose was 500 mg/kg body weight as a safe dose. Data obtained are assessed for their statistical significance by applying student's 't' test. In all cases it was observed that the compounds were not as efficient as the chosen standard.

Experimental

Synthesis of the precursor 8-amino-10,11-dihydro-5H-dibenzo (b,e) (1, 4) diazepine-11-one (a) for the formation of the ultimate product (b) was initiated by condensation of 2, 4 dinitrochlorobenzene and anthrinilic acid in ethyl alcohol which was then reduced with sodium dithionite followed by cyclization in o-xylene.

To prepare triazolo derivative of Dibenzodiazepine (b) by chlorination of compound (a) with PCl_5 in dry Benzene giving 8-amino-11-chloro derivative of Dibenzodiazepine which on further treatment with hydrazine hydrate using glycerol replaced chloro group by giving 8-amino-11-hydrozino derivative or Dibenzodiazepine. Which after cyclization in formic acid under N_2 atmosphere gave the final product (b). All other triazolo derivatives were synthesized by diazotizing (b) by $NaNO_2$ and HCl. 8-chloro derivative (c) was obtained by reacting diazotized product of (b) with Cu_2Cl_2 and HCl under sandmayer's reaction condition, 8-Bromo derivative (d) was obtained by reaction of diazotized compound (b) and copper turnings and HBr under Gattermann's reaction condition 8-hydroxy derivative (e) was prepared by simply refluxing compound (d) with acidulated water and 8-Thiol derivative (e) was prepared by reacting diazotized compound (b) with Potassium ethyl Xanthate solution. (Scheme-1)

To get them in pure form, they were recrystallized polar solvents and purity was ascertained through T.L.C. they were then characterized by M.P and elemental analysis (Table – 1), IR, ^{1}HNMR and mass spectral analysis melting points were recorded on a gallen kamp apparatus and are uncorrected. The IR spectra were recorded on a Perkin-Elmer model 557 spectrometer and ^{1}HNMR spectra in $CDCl_3$/DMSO-D_6 on a FX 90Q JEOL type spectrometer using TMS as internal standard chemical shift are given in □ppm) CHN analysis were carried out using a Coleman analyzer model-33. The chemicals used were of AR grade.

Table – 1

Melting Point and Elemental Analysis

Compound number	Melting point (°C)	Elemental Analysis (%) Calculated Values (Found values)		
		C	H	N
A	215	69.33 (69.68)	4.88 (4.98)	18.66 (18.45)
B	260	67.46 (67.50)	4.42 (4.46)	28.11 (28.10)
C	250 (d)	62.56 (62.58)	3.53 (3.38)	20.86 (20.85)
D	220 (d)	53.67 (53.69)	2.87 (2.90)	17.89 (17.87)
E	275	67.20 (67.28)	4.00 (4.09)	22.4 (22.20)
F	280 (d)	63.15 (63.20)	3.76 (3.80)	21.05 (21.03)

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