Volume-3, Issue-7, July-2014 • ISSN No 2277 - 8160

Research Paper Chemistry

Synthesis and Characterization of Some New Substituted Diazepine Derivatives

RAJALAKSHMI.S Department of Chemistry, Queen Mary's College, Chennai, India.

ARUNA.S Department of Chemistry, Queen Mary's College, Chennai, India.

ABSTRACT *A series of new substituted diazepine derivatives have been synthesized by condensing substituted phenyl cyano ester with semicarbazide and thiosemicarbazide. These findings promoted us to synthesize compounds containing diazepine moiety and evaluate for anti-inflammatory activity. All these diazepindione derivatives are characterized by IR, 1H, 13C NMR and Mass spectral studies. These compounds are found to possess anti-bacterial activity.*

KEYWORDS : Diazepindione, Diazepinthione, anti-viral, anticancer, anti-bacterial, reflux.

Introduction

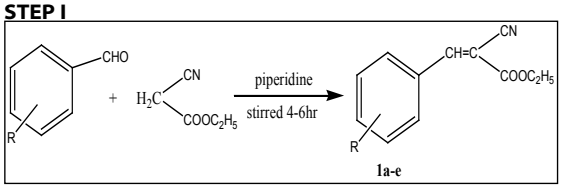
Diazepine is a class of seven-membered ring heterocyclic compounds consisting of two nitrogen atoms in the position-1,2,-1,3 and -1,4 in the cycloheptane ring. Benzodiazepine refers to the structure composed of benzene ring fused to the seven membered diazepine ring[1].Diazepine and benzodiazepines were first introduced for the treatment of anxiety, a large number of these compounds with sedative, hypnotic, anticonvulsant, and muscle reluctant properties combind with low toxicity have been synthesized[2-4]. The development of new approaches to be essential for the construction of number of heterocyclic continues to be essential for accessing natural products and their structure analogues. Among them, 1H-1,4-diazepines derivatives scaffolds over the years have gained an ongoing interest for biological activities as anticancer[5,6], anti-bacterial[7], psychotropics[8], anticonvulsant[9], anti-viral[10] and herbicidial[11]. Substituted 1,4-diazepine and their derivatives posses anti-HIV activity[12]. Benzodiazepine derivatives are also commercially used as dyes for acrylic fibers[13]. Moreover, 1,5-benzodiazepines derivatives are valuable synthons that can be in preparation of other fused ring compounds such as triazolo, oxadiazolo, oxazino, or furanobenzodiazepines[14]. Attempts have been made to build 1,4-diazepine moiety on other biologically potent. Heterocycles in order to obtain drugs with more effiacy[15-19]. Benzodiazepines enhance the effect of the neurotransmitter gamma-amino butyric acid (GABA-A), resulting in sedative, hypnotic (sleep-inducing), anxiolyic (ant anxiety), anticonvulsant, and muscle relaxant properties also seen in the applied pharmacology of high dose of many shorter-acting benzodiazepines are amnesic-dissociative actions, These properties make benzodiazepines useful in treating anxiety, insomnia, agitation, seizures, muscle spasms, alcohol withdrawal and as a premedication for medical or dental procedures. Benzodiazepine are categorized as either short, intermediate or long acting. Short and intermediate acting benzodiazepines are preferred for the treatment of insomnia; longer-acting benzodiazepines are recommended for the treatment of anxiety[20].

MATERIAL AND METHODS

All the chemicals and the reagents used in the study were of synthesis grade purity. Ethyl cyano acetate, substituted benzaldehde, semicarbazide and thiosemicarbazide are purchased from Qualigents Fine Chemicals Company. Solvents used were purified by distillation. All substance prepared for studies were purified by crystallization using appropriate solvents and established procedures. Melting points were measured on a sigma melting point apparatus using capillary tubes. Analytical TLC was performed on precoated sheets of silica gel to monitor the process of the reaction as well as to check the purity. The spots were visualized by using iodine vapour.IR spectra were recorded on FTIR-8300 shimadzu spectrometer. ^{1}H&^{13}C NMR spectra were recorded on Jeol GSX (400 MHz) and DPX 200 (200MHz). Mass spectra were recorded on Jeol-JMS-DX 30hf.

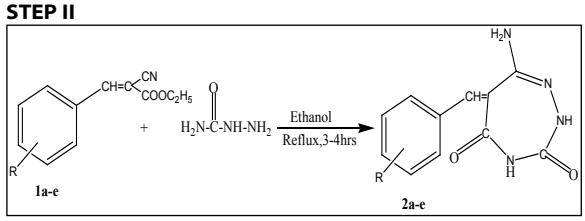
SCHEME I

STEP I



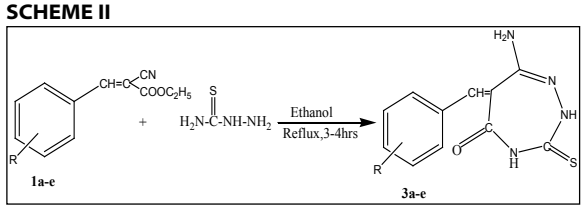
R= H, (p-OCH_3, m-OH,), p-chloro, p-hydroxy, p-OCH_3.

STEP II



R= H, (p-OH, m-OCH_3), p-chloro, p-hydroxy, p-OCH_3.

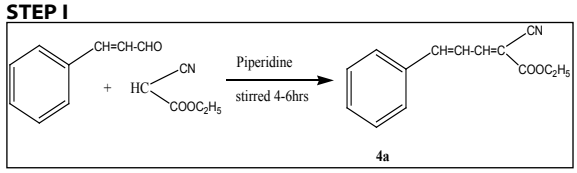
SCHEME II



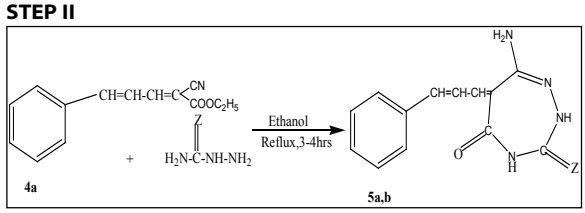
R= H, (p-OH, m-OCH_3), p-chloro, p-hydroxy, p-OCH_3.

SCHEME III

STEP I



STEP II



Z= O, S

EXPERIMENTAL

SYNTHESIS OF SUBSTITUTED ETHYL-2-CYANO-3-PHENYLESTER:1a-e

Substituted Benzaldehyde (2.21g,0.05mol) and ethylcyanoacetat(2.26g,0.05mol) and two drops of piperidine were added in 10ml of rectified spirit. The mixture was stirred for 4 to 6 hours at room temperature. The resulting yellow colour liquid was added to an ice water. The separated solid was filtered washed with water and crystallized from ethanol. The substituted ethyl-2-cyano-3-phenyl ester 1a-e was prepared.

6 – AMINO – 5 – BENZYLIC DIAZEPINE -4, 2– DIONE:2a

A mixture of ethyl-2-cyano-3-phenyl ester 1a (1.21g, 0.01mol) with semicarbazide (1.26g, 0.02mol) in ethanol was refluxed on water bath for 3 hours. The reaction mixture was concentrated in vacuo and added to crush ice. Crystalline masses that deposited from the solution during ice cooling were purified by recrystallization from ethanol. The substituted 6 – amino 5 – benzylic diazepine– 2, 4-dione 2a was prepared. M.p: 171°C . ^{1}H NMR: δ 1.44 (NH_2), 6.9(=CH), 4.31-4.37 (NH), 7.25-8.11 (Ar-H). ^{13}C NMR : δ 99.09, 111.18, 114.92, 116.43, 124.31,128.80, 146.84, 150.86, (C=O) 154.7, 162.2. IR: 1580-1700cm^{-1} (keto carbonyls); 3378cm (NH_2); 1510 cm^{-1}(C=N). Mass : (m/z): 230.

6 –AMINO-5(-4-HYDROXY 3-METHOXY) BENZYLIC DIAZEPINE– 4,2 – DIONE:2b

A mixture of ethyl-2-cyano-3-(3-methoxy-4-hydroxy)-phenyl ester 1b (1.47g, 0.01mol) with semicarbazide (1.2g, 0.02mol) in ethanol by the usual workup afforded 6–amino 5-(3-methoxy-4-hydroxy) –benzylic diazepine – 2, 4-dione 2b. M.p:162-165°C. ^{1}H NMR : δ 1.40 (NH_2), 3.82(OCH3), 4.35(OH),6.8(=CH), 7.46-8.12 (Ar-H). ^{13}C NMR: δ 56.19, 99.09, 111.19, 115.02, 118.43, 123.31, 128.70, 146.83, 150.85, (C=O) 154.8, 163.1. IR: 1577-1700cm^{-1} (keto carbonyls);2845cm^{-1}(OCH_3) ;3739(OH);3122 (N-H); 3375cm (NH_2); 1508 cm^{-1}(C=N). Mass : (m/z): 276

6 – AMINO – 5-(3-CHLORO) – BENZYLIC DIAZEPINE -4,2 – DIONE:2c

A mixture of ethyl-2-cyano-3-(4-chloro) phenyl ester 1c (2.35g, 0.01mol) with semicarbazide (1.2g, 0.02mol) in ethanol by the usual workup afforded 6 – amino- 5-(4-chloro)–benzylic diazepine– 2,4-dione 2c. M.p:197°C. ^{1}H NMR : δ 1.42 (NH_2), 4.23 (NH), 7.221-7.80 (Ar-H), 8.23 (=CH). ^{13}C NMR : δ 96.09, 112.18, 113.92, 116.53, 126.31, 129.80, 145.84, 150.66, (C=O) 154.9, 162.4. IR: 1582-1700cm^{-1} (keto carbonyls); 3380cm (NH_2); 1512 cm^{-1}(C=N). Mass : (m/z): 264

6 –AMINO-5 (4-HYDROXY) BENZYLIC DIAZEPINE – 4,2– DIONE:2d

A mixture of ethyl-2-cyano-3-(4- hydroxy) phenyl ester 1d (2.17g, 0.01mol) with semicarbazide (1.2g, 0.02mol) in ethanol by the usual workup afforded 6–amino-5-(4- hydroxy) –benzylic diazepine–2,4-dione 2d. M.p: 165°C. ^{1}H NMR : δ 1.43 (NH_2), 4.34 (NH),6.8(=CH), 7.65-8.79 (Ar-H), 8.39(OH). ^{13}C NMR: δ 98.09, 112.18, 114.62, 118.43, 126.31, 129.80, 143.84, 150.96, (C=O) 154.4, 162.2. IR: 1579-1700cm^{-1} (keto carbonyls);3738 cm^{-1} (OH);3123 cm^{-1} (N-H); 3376 cm^{-1} (NH_2); 1508 cm^{-1}(C=N). Mass : (m/z): 245.

6–AMINO-5-(4-METHOXY) BENZYLIC DIAZEPINE–2,4–DIONE:2e

A mixture of ethyl-2-cyano-3-(4-methoxy) phenyl ester 1e (2.31g, 0.01mol) with semicarbazide (1.2g, 0.02mol) in ethanol by the usual workup afforded 6–amino-5-(4-methoxy) –benzylic diazepine –2, 4-dione 2e. M.P:163-165°C. 1H NMR: δ1.43 (NH_2), 4.34 (NH), 6.8(=CH), 7.65-8.79(Ar-H), 3.6(OCH_3).^{13}CNMR:58.6, 99.07, 113.18, 116.92, 118.43, 127.31, 128.90, 148.84, 150.76, (C=O) 153.7, 162.5. IR: 1579-1700cm^{-1}(keto carbonyls); 2846cm^{-1}(OCH_3); 3125 (N-H); 3374cm^{-1} (NH_2); 1509 cm^{-1}(C=N). Mass: (m/z): 248.

6–AMINO-5–BENZYLIC DIAZEPINE –2-THIO-4-ONE: 3a

A mixture of ethyl-2-cyano-3-phenyl ester 1a (1.21g, 0.01mol) with thiosemicarbazide (1.26g, 0.02mol) in ethanol was refluxed on water bath for 3 hours. The reaction mixture was concentrated in vacuo and added to crush ice. Crystalline masses that deposited from the solution during ice cooling were purified by recrystallization from ethanol. The substituted 6–amino-5 – benzylic diazepine –2-thio-4-one 3a was prepared. M.P: 156-158°C. ^{1}H NMR: δ 1.54 (NH_2), 6.84(=CH), 4.41-4.57 (NH), 7.35-8.21 (Ar-H). ^{13}C NMR: δ 97.09, 111.28, 114.72, 115.43, 125.31, 129.80, 146.94, 150.76, (C=O), 154.8, 162.3, (C=S) 181.72. IR: 1050cm^{-1} (thiocarbonyls); 1582-1700cm^{-1} (keto carbonyls); 3386cm^{-1} (NH_2): 1512 cm^{-1}(C=N). Mass: (m/z):246 .

6-AMINO-5-(3-METHOXY-4-HYDROXY)-BENZYLIC DIAZEPINE –2-THIO-4–ONE: 3b

A mixture of ethyl-2-cyano-3-(3-methoxy-4-hydroxy) phenyl ester 1b (1.47g, 0.01mol) with thiosemicarbazide (1.52g, 0.02mol) in ethanol by the usual workup afforded 6–amino 5-(3-methoxy-4-hydroxy)–benzylic diazepine –2-thio-4-one 3b. M.P: 135-136°C. ^{1}H NMR: δ1.48 (NH_2),3.72(OCH3),4.45(OH),6.8(=CH),7.66-8.22(Ar-H). ^{13}C NMR: δ 61.2, 98.09, 113.28, 114.92, 116.43, 127.31, 129.88, 146.95, 150.66, (C=O) 154.9, 163.3, (C=S) 190.69. IR:1060 cm^{-1}(thio carbonyls); 1579-1700cm^{-1} (keto carbonyls);2848cm^{-1}(OCH_3) ;3742 cm^{-1} (OH);3126 cm^{-1} (N-H); 3378cm (NH_2); 1506 cm^{-1}(C=N). Mass: (m/z):275.

6–AMINO–5-(4-CHLORO)–BENZYLIC DIAZEPINE –2-THIO-4–ONE: 3c

A mixture of ethyl-2-cyano-3-(4-chloro) phenyl ester 1c (2.35g, 0.01mol) with thiourea (1.52g, 0.02mol) in ethanol by the usual workup afforded 6–amino-5-(4-chloro) –benzylic diazepine – 2-thio-4-one 3c. M.P: 165-167°C. ^{1}H NMR: δ 1.44 (NH2), 4.35 (NH), 7.41-7.90 (Ar-H), 8.53 (=CH). ^{13}C NMR: δ 97.99, 112.28, 114.82, 115.83, 125.91, 129.87, 146.54, 150.56, (C=O) 153.8, 162.5, (C=S) 188.92. IR: 1082cm^{-1} (thio carbonyls); 1588-1700cm^{-1} (keto carbonyls); 3384cm (NH_2); 1514 cm^{-1}(C=N). Mass: (m/z): 280 .

6–AMINO-5-(4-HYDROXY)-BENZYLIC DIAZEPINE –2-THIO-4–ONE: 3d

A mixture of ethyl-2-cyano-3-(4- hydroxy) phenyl ester 1d (2.17g, 0.01mol) with thiosemicarbazide (1.52g, 0.02mol) in ethanol by the usual workup afforded 6 – amino 5-(4- hydroxy) –benzylic diazepine – 2-thio-4-one 3d. M.p:147-150°C. ^{1}H NMR: 4.32 (NH2), 4.44 (NH), 6.6(=CH), 7.85-8.29 (Ar-H), 8.49(OH). ^{13}C NMR: δ 99.79, 113.28, 113.72, 117.43, 126.31, 129.70, 146.84, 152.76, (C=O) 155.8, 162.4,(C=S)187.8. IR: 1102cm^{-1}(thio carbonyls); 1580-1700cm^{-1} (keto carbonyls); 3740 cm^{-1} (OH):3126 cm^{-1} (N-H); 3378 cm^{-1} (NH_2); 1510 cm^{-1}(C=N). Mass: (m/z): 261.

6–AMINO-5-(4-METHOXY)-BENZYLIC DIAZEPINE –2-THIO-4–ONE: 3e

A mixture of ethyl-2-cyano-3-(4- methoxy) phenyl ester 1e (2.31g, 0.01mol) with thiosemicarbazide (1.52g, 0.02mol) in ethanol by the usual workup afforded 6 – amino 5-(4- methoxy) –benzylic diazepine – 2-thio-4-one 3e. M.p:95-97°C. ^{1}H NMR: δ 1.45 (NH_2), 4.36 (NH), 6.7(=CH), 7.75-8.79 (Ar-H),3.8(OCH_3).^{13}C NMR: δ61.4, 96.09, 114.28, 114.82, 114.43, 129.31, 128.88, 146.85, 150.86, (C=O)153.9, 163.5, (C=S) 185.69. IR: 1899cm^{-1} (thio carbonyls); 1578-1700cm^{-1} (keto carbonyls);2847cm^{-1}(OCH_3);3125 (N-H);3376cm (NH_2); 1512 cm^{-1}(C=N). Mass: (m/z):257.

SYNTHESIS OF ETHYL-2-CYANO-3-(ALLYL PHENYL)-ESTER: 4a

Cinnamaldehyde (2.21g, 0.05mol) and ethylcyano acetate (2.26g, 0.05mol) and two drops of piperidine were added in 10ml of rectified spirit. The mixture was stirred for 4 to 6 hours at room temperature. The resulting yellow colour liquid was added to ice water. The separated solid was filtered washed with water and crystallized from ethanol. The ethyl-2-cyano-3-(allyl phenyl) ester 4a was prepared.

6 – AMINO 5-(ALLYL PHENYL)-DIAZEPINE-4, 2 DIONE :5a

A mixture of ethyl-2-cyano-3-(allyl phenyl ester) 4a (1.21g, 0.01mol) with semicarbazide (1.26g, 0.02mol) in ethanol was refluxed on water bath for 3 hours. The reaction mixture was concentrated in vacuo and added to crushed ice. Crystalline masses that deposited from the solution during ice cooling were purified by recrystallization from ethanol. The substituted 6 – amino 5–(allyl phenyl)–diazepine-2, 4-dione 5a was prepared. M.p :102-105°C. ^{1}H NMR: δ 1.52 (NH_2), 4.4 (=CH), 3.34 (NH), 7.2-7.8 (Ar-H),8.2 (=CH). ^{13}C NMR: δ 13.06, 62.30, 120, 102.2, 134.4, (C=O)153.9, 163.5,(C=S)188.7. IR : 1588-1700cm^{-1} (keto carbonyls); 3384cm (NH_2); 1518 cm^{-1}(C=N). Mass: (m/z):256.

6–AMINO-5–(ALLYL PHENYL)- DIAZEPINE –2-THIO-4-ONE: 5b

A mixture of ethyl-2-cyano-3-(allyl phenyl ester) 4a (1.21g, 0.01mol) with thiosemicarbazide (1.26g, 0.02mol) in ethanol by the above method afforded 6 – amino 5–(allyl phenyl) diazepine – 2-thio-4-one 5b. M.P: 69-70°C. ^{1}H NMR: δ 1.42 (NH_2), 4.3 (= CH), 3.2 (NH), 7.2-7.4(Ar-H), 7.9 (CH),8.2(=CH). ^{13}C NMR: δ 13.06 , 61.30 , 125.8, 103.2,135.6 , (C=O 157.7 ,162.4, (C=S) 182.10. IR: 1222cm^{-1} (thio carbonyls); 1592-1700cm^{-1} (keto carbonyls); 3386cm (NH_2); 1520 cm^{-1}(C=N). Mass: (m/z):272.

REFERENCES

1.G.W.H. Chesman and S.G Gremberg ,Synthesis and chacterization of -5,6-dihydro-7h- pyrolo[1,2-d][1,4]benzodiazepine-6-one.J.heterocyclic Chem.,16,pp. 241-247,1979. | 2. Heather Ashton, The diagnosis and management of benzodiazepine dependence, Current Opinion in Psychiatry,18, pp.249-255,2005. | 3.R.C.Oude Voshaar, W.J.Gorgeler,A.J.J.Mol,A.J.L.M.Van Balkom, J.Mulder, E.H. Van be Lisdonk, M. H.M. Berteler and F. G. Zitman, Long-term outcome of two forms of randomized denzoiazepine discontinuation,British Journal of Psychiatry, 188,PP.188-189,2006. | 4.A.Chirimi,G.De Sarro, S.Quartarone, M.L.Barreca ,R.Caruso,L.De Luca, and R. Gitto, Search for competitive 2-Amino-3[3-hydro-5-methyl-4-isoxazole] propionic acid receptor antagonist, Synthesis, pharmalogical properties and computational studies,pure Appt. Chem., vol. 76, No. 5, pp.931-939,2004. | 5. Krezel I, Mikiciuk Olasic E, Zurek E and Glowka M L 1999 Pharma. Pharmacol. Commun. 5 485. | 6. Chiba K, Yamamoto K. Miyamoto K, Nakano J, Matsumoto J, Nakamura S and Nakada K jpn. Kokaiokkyo Koho JP 03m 223,289 [91,223,289][Cl. CO7D 495/04], 02 Oct. 1991,JpAppl.89/320,175, 08 Dec. 1989, 11 pp;1992 Chem. Abstr. 116 59403a. | 7.Antoine M.Barreu M, Desconclois J F, Girard P and Picaut G Eur. Pat. Appl .EP,379412/1990., 1991 Chem.Abstr .114 14339p. | 8.Childress S J and Gluckman M I 1964 J.Pharm.Sci 53 577. | 9.Phillips O A, Murthy K S K, Ciakpui C Y and Knaus E E 1999 Can.J. Chem .77 216. | 10.Strokbroekx R A 1989 Eur Pat Appl EP 320 032; 1990 Chem. Abstr. 112 35876y. | 11.V centini C B, Guarneri M, Scatturin A, Giori P and Heilman W 1996 Rarmaco 51 609. | 12.Gorlizer K, Wolpert C, Rubsamen-Waigmann H, Suhartono H, Wang L and Immelmann A 1995 Arch.Pharm.328 273. | 13. Harris, R. C.;Straley, J. M. S. Patent 1, 537,757,1968; chem..Absta. 1970, 73, 10054w. | 14.Aversa, M. C.;Rerlazzo, A.; Gionnetto, P.; Kohnke, F.H. Synthesis 1986, 230.(b) Essaber,M.; Hasnaoui, A.; Benharref, A.; Lavergne, J.P. Synth.commun. 1998, 28, 4097. (c) ElSayed, A.M.; Abdel-Ghany, H.; El-Saghier, A.M.M. Synth. Commun. 1999, 29, 3561. (d) Chimirri,A.; Grasso, S.; Ottana, R.; Romeo, G.; Zappala, M. J. Heterocycl. Chem. 1990, 27, 331. | 15.Zang P, Zang N, Buckword V E and Hosamne R S , Biorg. and Med. Chem., 2007, 15(14), 4933. | 16. Movikov M S. Amer A A and Khlebnikev A F, Tetrahedron let., 2006, 47(5),639. | 17.Braun R V and Muller T J J, Tetrahetron, 2004, 60(42), 9463. | 18.Roma G, Grossi G C, Braccio M D, Ghia M and Mattioli F, Euro. J. Med. Chem.. 1991, 26(5), 489. | 19.Hosamane R S, Vaidya V P and Mi kyung Chung, Nucleosides and Nucleoside, 1991, 10(8), 1693. | 20.Boyd G.V.. Six Membered and Larger Hetero Rings with Maximum Unsaturation, Schauman E. (ed), New York, In Houben-Weyl, 26, 299 (1998). |