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Synthesis of Benzofuro[3,2-*e*]-1,4-diazepines of Pharmacological Interest

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Abstract: The title compounds (**4a,b)** were prepared by chloroacetylation of 2-acyl-3-aminobenzofuran**(1a,b)** and subsequent treatment with hexamethylene tetramine in ethanol *via* the complex salts (**3a,b).** Similar reaction with ethyl 3-aminobenzofuran-2 carboxylate (**5)** produced 3*H*-benzofuro[3,2-*e*]-1,4-diazepin2,5(1*H*,4*H*)-dione (**7)** in good yield. All the newly synthesized compounds are characterized by elemental analysis and spectral studies, and evaluated for antimicrobial and anticonvulsant activities.

Keywords: Benzofuran, Diazepines, Antimicrobial activity, Anticonvulsant activity

Introduction

The synthesis of condensed diazepine heterocycles has been explored to a maximum extent owing to their association with wide spectrum of pharmacological activities such as sedatives, anxiolytics, hypnotics, anticonvulsant, antipsychotic, muscle relaxants *etc*., in recent years[1-6]. Attempts have been made to build 1, 4-diazepine moiety on other biologically potent heterocycles in order to obtain drugs with more efficacy[7-11]. Encouraged by these facts and in continuation of our research program on synthesis of pharmacologically interesting furan derivatives[12-16], we report in this paper annulation of 1,4-diazepine on benzo[2,1-*b*]furan moiety and screening the compounds for antimicrobial and anticonvulsant activities. The strategy adopted for the synthesis of these new condensed tricyclic heterocyclic compounds involved successive building up of 1, 4-diazepine ring on benzofuran[17].

Experimental

Melting points were determined in open capillary and are uncorrected. Purity of the compounds was checked by TLC in Silica gel G. PMR spectra were recorded on various A-60, FT-80, FT-270 and XL-100 spectrometer using TMS as internal reference. Chemical shifts are expressed in terms of δ ppm through out. IR spectra were recorded (nujol) on Perkin-Elmer 277 spectrophotometer. Wave number is expressed in cm^{-1}.

*2-Acyl –3-chloroacetamidobenzofurans (**2a,b**)*

A mixture of 2-acyl-3-aminobenzofuran (0.02 mol) and chloroacetyl chloride (5 mL) was warmed on water bath for 30 min and poured into ice water with stirring. The solid, which separated, was collected and recrystallized from ethanol as colourless needles.

*Hexamethylenetetramine salt of compound (**3a, b**)*

A mixture of compound **2a, b** (0.002 mol), hexamethylenetetramine (0.6 g, 0.0047 mol) and potassium iodide (0.2 g) in chloroform (10 mL) was refluxed on steam bath for 10 h, the residual solid obtained, after removal of solvent, was thoroughly washed with chloroform and then with water to remove excess of HMTA. The product **3a,b** on recrystallization from ethanol was obtained as colourless needles.

*5-Methyl/phenyl-1, 3-dihydro-2H-benzofuran[3,2-e]-1,4-diazepin-2-one(**4a,b**)*

Method A

Complex salt **3a, b** (0.00128 mol) was refluxed with ethanol (10 mL) for 10h. The excess of solvent was removed under reduced pressure and the residual solid was recrystallised from ethanol yellowish/colourless needles.

Method B

A mixture of **2a, b** and hexamethylenetetramine (0.6 g, 0.0047 mol) in ethanol (10 mL) was heated under reflux for 12 h. the reaction mixture was cooled and the solid separated was filtered and washed with ethanol. The pure compound was obtained by recrystalised with ethanol. The mixed melting points with the compounds obtained by method A were not depressed.

*Ethyl 3-chloroacetamido benzofuran-2-carboxylate(**6**)*

Chloroacetylation of ethyl 3-amino benzofuro-2-carboxylate **(5)** (0.025 g, 0.01 mol) using chloroacetylchloride (5mL) under the reaction conditions described for compounds 3a,b gave the title compound as colourless needles when recrystallized in ethanol.

*3H-Benzofuran[3,2-e]-1,4-diazepine-2,5(1H,4H)-dione (**7**)*

Through suspension of **6**(0.5 g, 0.00178 mol) in absolute methanol (10 mL), cooled in freezing mixture, dry ammonia gas was passed till saturation. The resulting solution was left room temperature for 4 days. The cloudy solution was concentrated under reduced pressure and then diluted with ether. The solid which separated was filtered and recrystallization from methylene chloride-petroleum ether as colourless granules.

Results and Discussion

The starting material 2-acyl-3-aminobenzofurans **(1a, b)**[18] were chloro acetylated to yield compounds **2a,b** and were subjected to cyclisation using ammonia. But compound **2a** failed to react with ammonia, it did not even produce the expected intermediate 3-amino-acetamido-2-acetylbenzofuran. However, the desired ring closure was accomplished by

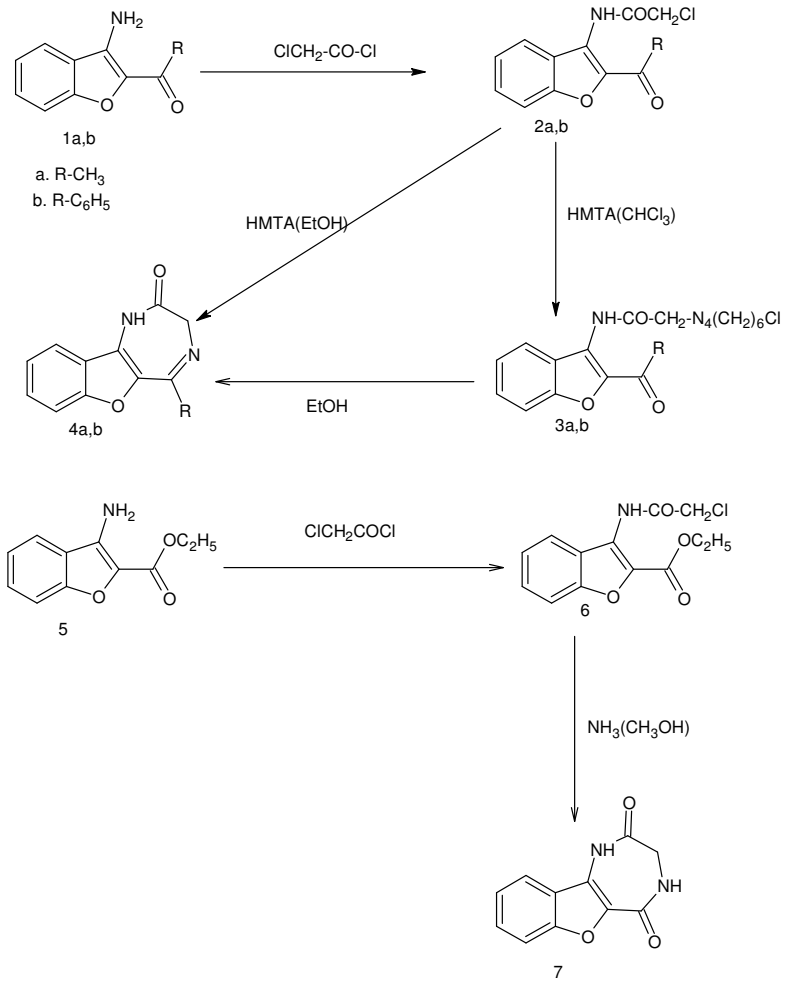
employing hexamethylene tetramine (HMTA). Thus, compound **2a** on reaction with HMTA in chloroform produced a complex salt **3a**, which on heating with ethanol, underwent cyclization to 5-methyl-1,3-dihydro-2*H*-benzofuro[3,2-*e*]-1,4-diazepin–2-one**(4a).** The direct conversion of **2a** to **4a** was also possible by heating **2a** with HMTA in ethanol. Similar observations have been made earlier while synthesizing 1, 4-diazepine derivatives[19]. The IR, PMR and mass spectra of **4a** were recorded to substantiate the structure assigned. The IR spectrum showed absorption bands at 1680 and 1625 cm^{-1} due to C=O and C=N also a broad band at 3440 cm^{-1}due NH stretching frequency. The PMR spectrum of **4a** exhibited a singlet at 2.63, integrating for three of $–CH_3$ group, another singlet at 4.26, integrating for two protons of $–CH_2$- group, a multiplet at 7.25-8.50 due to four aromatic protons and a broad singlet (D_2O exchangeable) at 11.04 due to NH proton. It's mass spectrum showed molecular ion peak at 314 *m/z*, corresponding to its molecular weight and fragmentation pattern also confirmed the structure assigned.

The additional stimulation for our interest in the 5-phenyl analogue **(4b)** was due to the fact that phenyl group at position 5 of diazepine moiety enhances the activity[20]. Thus chloroacetylation of 2-benzoyl-3-aminobenzofuran **1b** gave the corresponding chloroacetamide compound **2b** and subsequent treatment of **2b** with HMTA in ethanol gave 5-phenyl-1,3-dihydro-2H-benzofuro[3,2-*e*]1,4-diazepin-2-one(**4b**) via the salt **3b** and or directly. Three predominant absorption bands were observed in the IR spectrum of **4b** at 1620, 1682 and 3470 cm^{-1} due to C=N,C=O and NH stretching frequencies. The compound **4b** exhibited the following PMR data: 4.28(s, 2H, ring CH_2); 7.25-8.52(m, 9H, Ar-H); 11.54 δ(s, 1H, NH), which is in good agreement with the diazepine structure assigned. Another starting material ethyl 3-aminobenzofuran-2-carboxylate **(5)**[21] was also used to build the 1, 4-diazepine moiety on the similar lines. Thus, treatment of compound **5** with chlroacetyl chloride, gave the 3-chloroacetamide compound **6,** which was subjected to ring closure using methanolic ammonia. Such cyclisations were reported to produce either six memberd pyrimidone or seven memberd 1, 4-diazepine-dione depending on the reaction conditions.[22] However , under the present experimental conditions 3*H*-benzofuro[3,2-*e*]-1,4-diazepin-2,5(1*H*,4*H*)-dione(**7**), was formed in good yield. The structure of compound **7** is very evident from its IR spectrum which exhibited absorption bonds at 1685 and 3335 cm^{-1} due to carbonyl and –NH groups respectively. ^{1}H NMR spectrum of **7** is found to be in agreement with the assigned structure (Scheme 1).

The physical data of the newly synthesized compound is presented in Table 1.

Table 1. Characterization data of compounds

Compd. No.	R	% Yield	M.P ^{0}C	Mol. formula	Found (calculated)		
					C	H	N
2a	CH_3	60	112	$C_{12}H_{10}NO_3Cl$	57.12 (57.25)	3.82 (3.98)	5.59 (5.57)
2b	C_6H_5	93	120	$C_{17}H_{12}NO_3Cl$	65.12 (65.07)	3.79 (3.83)	4.41 (4.47)
3a	CH_3	64	174	----------	------	----	-----
3b	C_6H_5	72.13	149	----------	-----	------	-------
4a	CH_3	91.4	265	$C_{12}H_{10}N_2O_2$	67.25 (67.30)	4.62 (4.67)	13.18 (13.08)
4b	C_6H_5	69	265	$C_{17}H_{12}N_2O_2$	73.82 (73.91)	4.28 (4.35)	10.06 (10.15)
6	----	89	149	$C_{13}H_{12}NO_4Cl$	55.3 (55.42)	4.35 (4.46)	5.11 (4.97)
7	-----	78.2	310	$C_{11}H_8N_2O_3$	60.92 (61.11)	3.65 (3.70)	12.89 (12.96)



Scheme 1.

Antimicrobial activity

The newly synthesized diazepine compounds have been evaluated for antibacterial activity against *Staphylococcus aureus* and *Klebsiella pneumoniae* and antifungal activity against *Aspergillus niger* and *Candida albicans* by using ciprofloxacin and ciclopirox olamine as standards for comparison for antibacterial and antifungal activity respectively, by cup-plate method[23]. The results indicate that the compounds were either weakly active or inactive against all the four microorganisms.

Anti convulsant activity

The compounds were screened for anticonvulsant activity by maximal electroshock (MES) induced convulsant method[24] on albino rats (Wistar strain) using diazepam at the dose of 25 mg/kg body weight, as standard. After carrying out dose fixation studies, by stair-case method, the compounds were at the dose of 80 mg/kg body weight. A current of 150 ma was applied to the rats for 0.2 seconds, through corneal electrodes and the time

spent by the rats in different stages of convulsions were noted. The diazepine **4b** was found to possess considerable anticonvulsant activity, since it reduced the extensor phase of the MES convulsions to a greater extent than **4a** and comparable with that of standard drug. Electron with drawing phenyl group present on diazepine ring may be responsible for its enhanced activity as compared with 4a which contains electron donating group in the same position.

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