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SYNTHESIS AND BIOLOGICAL TESTING OF 2,3-DIHYDRO-3-ARYLHYDRAZONO-4-METHYL-1H-1,5-BENZODIAZEPIN-2-ONES, AS POTENTIAL PSYCHOSEDATIVE AND ANXIOLYTIC AGENTS

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Condensation of (o) phenylenediamine with different ethyl α-arylhydrazono-β-oxobutyrates under neutral, acidic or basic condition is described. A series of 2,3-dihydro-3-arylhydrazono-4-methyl-1H-1,5-benzodiazepin-2-ones was synthesized. The IR and ^{1}H NMR of some selected compounds are reported. The preliminary biological testing showed that some of the prepared benzodiazepinones possess promising CNS depressant activity.

Key words: 1,5-Benzodiazepin-2-ones, 2-Methylbenzimidazole, CNS depressants.

Introduction

It has been previously demonstrated that the 4-phenylhydrazono-1,5-benzodiazepin-2-one derivatives are active as CNS depressant agents [1]. As a part of our studies directed towards the development of a new arylhydrazono derivatives of pharmaceutical interest [2-7], and in the course of our work on novel psychosedative and anxiolytic agents, it became of interest to develop a general method for the synthesis of 2,3-dihydro-3-arylhydrazono-4-methyl-1H-1,5-benzodiazepin-2-ones, such as (2). We report here the condensation of (o)-phenylenediamine with ethyl α–arylhydrazone-β-oxobutyrates (1) under neutral, acidic or basic conditions. We also report the preliminary biological testing of some of the products (2).

Experimental

IR studies were carried out on a Unicam SP 1000 spectrophotometer using (KBr) discs. ^{1}H NMR were obtained with a varian EM 390 and FT-200 spectrometer in $CDCl_3$ or DMSO d_6 with TMS as internal standard. All mps were taken in open capillaries and are uncorrected.

2,3-Dihydro-3-arylhydrazono-4-methyl-1H-1,5-benzodiazepin-2-ones (2a-f). Method 1, *In neutral medium.* To a stirred boiling solution of (o)-phenylenediamine (0.01 mole) in dry xylene (30 ml), was added a solution of the appropriate ethyl α-arylhydrazono-β-oxobutyrate (1) (0.01 mole) in dry xylene (30 ml) in dropwise manner. The reflux was continued for 24 hr, after which the solvent was removed by evaporation under reduced pressure. The residue obtained was triturated with light petroleum (b.p. 60-80°). The solid was collected by filtration and recrystalized from benzene. Analytical data were collected in Table 1. IR 1660 cm^{-1} (C=O) 3335 cm^{-1} (NH). ^{1}H NMR (compound 2b): δ 2.3 (s, 3H, Ar-CH_3), 2.6 (s, 3H, 4-CH_3), 3.4 (bs, 1H, N-NH), 6.8-7.6 (m, 8H, Ar-*H*) and 10.7 (bs, 1H, NH-CO-); ^{1}H NMR (compound 2e): δ 1.25 (t, 3H, OCH_2CH_3), 3.8 (q, 2H, OCH_2-C-), 2.6 (s, 3H, CH_3), 3.25 (bs, 1H, NHN), 6.7-7.5 (m, 8H, Ar-H) and 11.00 (bs, 1H, NH-CO).

Method 2; In acidic medium. A mixture of (o)-phenylenediamine (0.004 mole) and the appropriate etheyl α-arylhydrazono-β-oxobutyrate (0.004 mole) in PPA (15 ml) was heated

TABLE 1. YIELD, MELTING POINT AND ELEMENTAL ANALYSIS OF COMPOUNDS 2 a-k.

Cmpd. No.	Method	Yield %	M.P. °C	Formula		Analyses % C	H	N
2a	1	45	149-151	$C_{17}H_{16}N_4O$	Calcd.	69.9	5.5	19.2
	2	55			Found	70.2	5.3	19.4
b	1	50	158-160	$C_{17}H_{16}N_4O$	Calcd.	69.9	5.5	19.2
	2	60			Found	69.6	5.8	19.0
c	1	40	108-110	$C_{17}H_{16}N_4O_2$	Calcd.	66.2	5.2	18.1
	2	50			Found	66.6	5.4	18.3
d	1	55	138-140	$C_{17}H_{16}N_4O_2$	Calcd.	66.2	5.2	18.1
	2	63			Found	66.6	5.2	18.1
e	1	50	133-135	$C_{18}H_{18}N_4O_2$	Calcd.	67.1	5.6	17.4
	2	60			Found	66.7	5.2	17.2
f	1	40	163-165	$C_{20}H_{16}N_4O$	Calcd.	73.2	4.9	17.1
	2	52			Found	72.9	4.7	17.1
g	1	30	218-220	$C_{16}H_{13}BrN_4O$	Calcd.	53.7	3.6	15.7
					Found	53.7	3.9	16.0
h	1	25	163-165	$C_{16}H_{13}ClN_4O$	Calcd.	61.4	4.2	17.9
					Found	61.8	4.5	18.2
i	1	25	194-195	$C_{16}H_{12}Cl_2N_4O$	Calcd.	55.3	3.5	16.1
					Found	55.4	3.6	15.9
j	1	18	178-180	$C_{17}H_{15}N_5O_3$	Calcd.	57.0	4.2	19.8
					Found	56.7	4.5	20.0
k	1	20	218-220	$C_{18}H_{17}N_5O_3$	Calcd.	58.8	4.6	19.0
					Found	58.6	5.0	18.9

at 100° for 2 hr. After cooling, the reaction mixture was poured into ice-water (100 ml) and neutralized with ammonia solution. The solid product was collected by filtration, washed with H_2O, dried and recrystallized from benzene to give (*2a-f*).

2,3-Dihydro-3-arylhydrazono-4-methyl-1H-1, 5-benzodiazepin-2-ones (2g-k) and 2-methylbenzimidazole (4). The appropriate ethyl α-arylhydrazono-β-oxobutyrate and (o)-phenylenediamine were reacted under the same experimental procedure previously described (methods 1). After removal of the solvent by evaporation under reduced pressure, the residue was triturated with light petroleum (b.p 60-80°). The solid product was filtered, dried and recrystallized from benzene. This product was identified by comparison (tlc, mp, mmp) with an authentic sample, to be 2-methylbenzimidazole *(4)* yield (30%) m.p. 174-176° (Lit [11], 174-176°).

Anal. calcd. for $C_8H_8N_2$: C, 72.7; H, 6.1; N, 21.2. Found: C, 72.7; H, 6.2; N, 21.00.

The light petroleum filtrate was evaporated under reduced pressure and the solid residue was recrystallized from benzene/light petroleum (b.p. 60-80°) to give (*2g-k*) in relatively poor yield. Analytical data are recorded in Table 1.

Condensation of (o)-phenylenediamine with ethyl α-aryl-hydrazono-β-oxobutyrates in basic medium. To a boiling solution of (o)-phenylenediamine (0.01 mole) in dry xylene (30 ml) containing few drops of piperidine, was added a solution of ethyl α-arylhydrazono-β-oxobutyrate (0.01 mole) in dry xylene (30 ml), in dropwise manner. The mixture was heated at reflux for 24 hr, after which the solvent was removed by evaporation under reduced pressure. The residue was triturated with light petroleum and the solid was collected by filtration. Recrystalization from benzene afforded 2-methylbenzimidazole (*4*) .

Condensation of (o)-phenylenediamine with ethyl α-(4-ethoxycarbonylphenyl) hydrazono-β-oxobutyrate. 1. *In neutral medium.* A solution of the title compounds (0.01 mole) in dry xylene (60 ml) was heated under reflux for 24 hr. After evaporation under reduced pressure, the solid residue was identified as 2-methylbenzimidazole (*4*).

2. *In basic medium.* On carrying out the above condensation in presence of piperidine (5 drops), only 2-methylbenzimidazole (*4*) was obtained, together with tary non identified material.

Coupling of 2,3-dihydro-4-methyl-1H-1, 5-benzodiazepin-2-one with 4-ethoxy-2-nitrophenyldiazonium chloride. A solution of 4-ethoxy-2-nitroaniline (0.01 mole) in glacial acetic acid (2 ml) and conc. hydrochloric acid (3 ml) was cooled and diazotized with sodium nitrite (0.69 g; 0.01 mole) in water (5 ml). The cold diazonium salt was slowly added with stirring to a cold solution of 2,3-dihydro-4-methyl-1H-1, 5-benzodiazepin-2-one (0.01 mole) in aq. alcoholic sodium hydroxide (20 ml; 2g NaOH in 5 ml H_2O then diluted to 20 ml with ethanol) and sodium acetate (3 g). The mixture was left overnight, acidified with HCl (pH 2)) and the solid product was collected by filtration. The product was proved to be (2k)

N-(2-Aminophenyl)-2-(p-tolylhydrazono)-3-oxobutyramide(3). A solution of ethyl α-(*p*-tolyl)hydrazono-β-oxobutyrate(0.01 mole) in xylene (25 ml) was added to a boiling solution of *(o)* -phenylenediamine (0.01 mole) in xylene (25 ml). The mixture was heated under reflux for 8 hr. The solvent was evaporated under reduced pressure and the residue was recrystallized from benzene to afford 50% of yellow crystals m.p. 140° ^{1}H-nmr (DMSO-d_6): δ 2.35 (s, 3H, Ar-CH_3), 3.65 (s, 3H, CH_3-CO-), 4.20 (bs, 1H, = NN*H*, D_2O exchangeable) 4.7 (s, 2H, NH_2, D_2O exchangeable), 6.40 (d, 2H, Ar-H), 7.15 (s, 4H, Ar-H), 7.45 (d, 2H, Ar-H) and 10.5 (bs, 1H, NHC=O, D_2O exchangeable).

Anal. calcd. for $C_{17}H_{18}N_4O_2$: C, 65.80; H, 5.8; N, 18.1. Found: C, 65.10; H, 5.6; N, 17.9%.

Cyclization of (3) to (2b). A solution of (*3*) (0.002 mole) in PPA (10 ml) was heated with stirring for 1 hr. at 100°. After cooling the reaction mixture was poured into ice water (50 ml) and the solution was neutralized by addition of NH_4OH solution to afford 2b in 60%-yield.

Ethyl 3-(2-aminophenylimino)-2-(4-ethoxy-2-nitrophenyl-hydrazonobutyrate (5). A solution of ethyl α-(4-ethoxy-2-nitrophenyl) hydrazono-β-oxobutyrate (0.01 mole) in xylene (25 ml) was added to a boiling solution of (*o*)-phenylenediamine (0.01 mole) in xylene (30 ml). The mixture was heated under reflux for 8 hr, then evaporated under reduced pressure. The solid residue obtained was recrystallized from benzene/light petroleum (b.p. 60-80°) to give 40% of (5) m.p. 173-174°

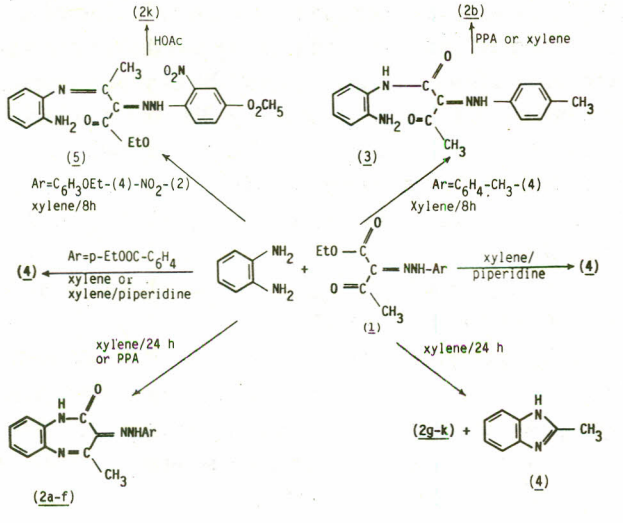
Anal. calcd. for $C_{20}H_{23}N_5O_5$: C, 58.1; H, 5.5; N, 16.9. Found: C, 57.9; H. 5.; N, 16.5%.

Cyclization of (5) t (2k). A solution of (*5*) (0.002 mole) in glacial aceticacid (10ml), was heated under reflux for 3 hr. Aflter cooling the separed product was filtered, dried and recrystallized from benzee/light petroleum (b.p.60-80°) (*2k*) in 45% yield

Discussion

The ethyl α-arylhydrazono-β-oxobutyrates (*1*) were synthesized according to the reported procedures [3,8,9]. Compounds (2a-f) were abtained by reacting *(1a-f)* with *(o)*-phenylenediamine in xylene or polyphosphoric acid (PPA) . The formation of (*2a-f*) took place via cyclization of *N*-(2-aminophenyl)-2-arylhydrazono-3-oxobutyramide (*3*). The intermediate (3) was isolated and identified after 8 hr. reflux

of (*1b*) with (o)-phenylenediamine. Compound (*3*) gave (*2b*) upon heating in PPA. Whereas a mixture of (*2g-k*) and 2-methylbenzimidazole (*4*) was obtained by heating (*1g-k*) with (o)-phenylenediamine in xylene. The treatment of (*1k*) with (*o*)-phenylenediamine in xylene for 8hr resulted in the formation of ethyl 3-(2-aminophenylimino)-2-(4-ethyoxy-2-nitrophenylhydrazono) butyrate (*5*), which upon heating in glacial acetic acid afforded (*2k*). One the other hand, the condensation of (*o*)-phenylenediamine with (*1a-k*) in xylene/piperidine or with 1, (Ar=*p*-ethoxycarbonyphenyl) in xylene gave compound (*4*) only, Scheme 1.



1 or 2	Ar
a	- $C_6H_4CH_3$-(2)
b	- $C_6H_4CH_3$-(4)
c	- C_6H_4OMe-(2)
d	- C_6H_4OMe-(2)
e	- C_6H_4OEt-(4)
f	- α-$C_{10}H_7$

1 or 2	Ar
g	- C_6H_4Br-(4)
h	- C_6H_4Cl-(4)
i	- $C_6H_3Cl_2$-(2,4)
j	- C_6H_3OMe-(4)-NO_2-(2)
k	- C_6H_3OEt-(4)-NO_2-(2)

Scheme 1.

In summary then, 2,3-dihydro-3-arylhydrazono-4-methyl-1H-1,5-benzodiazepin-2-ones can be readily prepared by condensation of (o)-phenylenediamine with ethyl α-arylhydrazono-β-oxobutyrates under neutral or acidic condition. If the arylhydrazono moiety bears a group or atom that displays -M, -I or +M, -I effects, a mixture of benzodepinone and 2-methylbenzimidazole was obtained. Under basic condition, only 2-methylbenzimidazole was produced.

Biological testing. Compounds 2b, 2c, 2g, 2h and 2k were subjected to laboratory screening for their pharmacological profile and acute toxicity study in adult albino mice of both sexes. These compounds were administered by intraperitoneal "I.P." injection in mice in test doses extending from 2 up to 200 mg/kg body weight, as uniform suspension in appropriate volume of carboxy methyl cellulose exceeding 0.5 ml/mouse in the case of 200 mg/kg does level.

Compounds 2b and 2g did produce definit sedation and reduction of the spontaneous motor activity after a latency period of 3-5 minutes following "I.P." injection of 10, 15, 25 and 50 mg/kg doses. Deep sedation passing into varying grades of hyponsis lasting 1-1 $^{1/2}$ hr was noted to occur following "I.P." injection of 100, 200 mg/kg of 2g.

Higher doses of compound 2 g produced a state of CNS lepression reflected by loss of consciousness and normal posture leading to deep coma, slow and gasping respiration with cyanosis and ultimate death of animals by cessation of breathing.

The acute "I.P." toxicity data of compound 2 g in albino mice of both sexes as obtained by the method of Litch field and Wilcoxon [10], gave the following LD values "expressed in mg/kg body weight:"

I.P: LD_{16} = 75; I.P: LD_{50} = 300 and I.P. Ld_{84} = 980.

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