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Synthesis and Microbial Screening of Seven Membered Heterocyclic ring Compounds from 1, 2-diaminobenzene

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Abstract: A series of seven membered heterocyclic rings were made by condensing 1, 3-dicarbonyl compounds with 1, 2-diaminobenzene using moderate reaction conditions. These compounds were screened for antimicrobial activity.
Key words: Pyrozolines, oxybutyrates

Introduction

Pyrazoline derivatives possess diverse chemical reactivity and broad spectrum of biological activities. The anti-inflammatory activities are shown by some pyrazolones[1]. Some pyrazolone derivatives are claimed as anticancer against stomach carcinoma, colon cancer, liver cancer, lung cancer and mammary cancer[2]. In view of these literature searches it was considered to synthesize new seven membered pyrazoline-7-one ring compounds. Seven membered rings are rather difficult to synthesize because in such cases strain and distance factor becomes worse[3,4]. In our earlier attempt we have synthesized seven membered rings by displacement of activated hydrogen from chloroaldehydes with 1, 2-diamino benzene using drastic conditions such as keeping pH in the range of 3 to 5 and refluxing the reaction mixture for 16 hours. It formed benzodiazepine derivatives in the range of 65-70% yield as shown in **scheme-I.**

In continuation of our work of synthesis of seven membered heterocyclic rings we attempted to condense 1, 3-dicarbonyl compounds with 1, 2-diaminobenzene using much mild conditions to construct seven membered ring compounds. To achieve our aim oxobutyrates (IVa-g) were cyclised with 1, 2-diaminobenzene which furnished 1-hydro-5-methyl-6-(aryl hydrazone) -4-pyrazoline-7-ones (Va-g) as shown in **scheme-II**.

The spectral data indicates that these compounds exist in hydrazono form. The structure requires that the >C=O group in position 7 should be in conjugation with >C=N group. A strong band appears at 1564 and 1650cm^{-1}. The presence of low frequency band may be attributed to the conjugation of cyclic >C=O group at position 7 with >C=N group. The lower frequency of >C=O group may be due to participation of >C=O group at position 7 in hydrogen bonding with N-H group as shown in structure. Hydrazono structure is further supported by NMR spectral studies. The NMR spectra exhibit signal at 13.52δ which could be assigned to-N-H grouping.

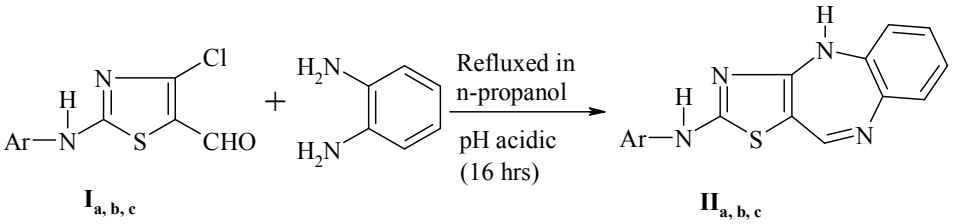
It is possible only when N-H proton at position 1 or 9 migrates to carbonyl oxygen as shown in **scheme-II**. Here possible shift of proton shown in route 'b' can be eliminated as IR band for N=N group was found absent in compounds Va-g. The N-H proton found at position 1 in compound Va-g is only responsible for tautomeric shifts. If compound Va-g undergoes tautomerization as shown in route 'b' then it would form diazocompounds V". Such diazocompounds are susceptible to acid solutions. These undergo decomposition in acid solutions[5]. Since compounds Va-k are recrystallized in acetic acid and do not decompose in acid solutions these eliminates the possibility of tautomerization via route 'b' and migration of N-H proton to carbonyl oxygen. Here we suggest the tautomeric shift of N-H proton at position -1 as shown in route 'a' to get enolic forms V.

Various attempts were made to get seven membered pyrazoline-7-ones with Ia, If, Ih and Ik such as increase in reaction time for 2 to 10 hours, increase in temperature and change in solvent but we could not get these products (Va,Vf,Vh, Vk).

The yields of the compounds Vi and Vj remain in the range 13 to 14% even after changing many parameters.

All these compounds were characterized by using elemental analysis, IR and H^1 NMR.

The starting oxobutyrates inturn were prepared by treating diazonium salts of substituted aromatic primary amines with sodium acetate and ethyl aceto acetate.

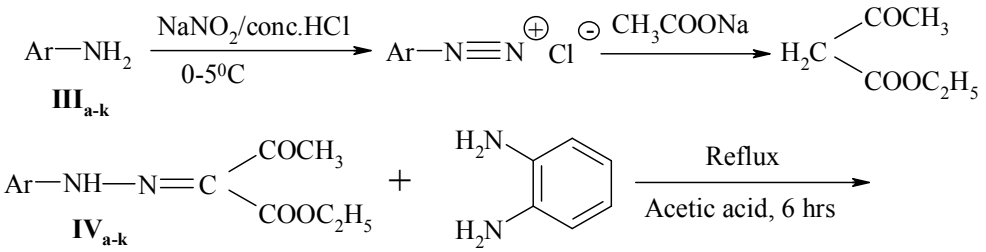


$I_{a, b, c}$ **$II_{a, b, c}$**

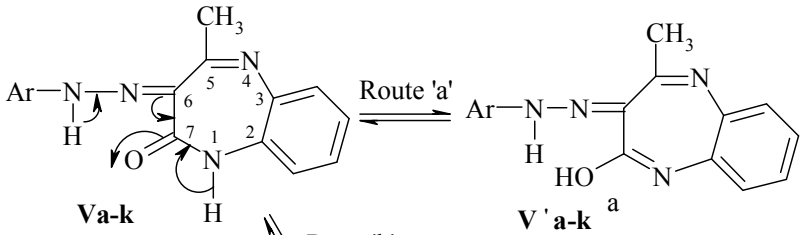
a, Ar = c, Ar =

b, Ar =

Scheme-I



III_{a-k} **IV_{a-k}**



Va-k **V 'a-k** **V ''a-k**

a, Ar = g, Ar =

b, Ar = h, Ar =

c, Ar = i, Ar =

d, Ar = j, Ar =

e, Ar = k, Ar =

f, Ar=

Scheme-II

Experimental:

Preparation of Ethyl-2-substituted hydrazone-3-Oxobutyrates (III): -

Substituted anilines (0.01 mole) were dissolved in a mixture of conc. HCl (5ml) and water (8ml). This solution was cooled to 0^0C by keeping in an ice bath. 1 gm of sodium nitrite was dissolved in water (5ml) and this solution was also cooled to 0^0C in an ice bath. After attaining 0^0C temperature, $NaNO_2$ solution was added to substituted aniline hydrochloride solution in a drop wise manner with constant stirring. During complete addition temperature of reaction mixture was kept below 10^0C. . The diazonium salt solution was then filtered into a cooled solution of ethyl acetoacetate (1.3gm, 0.01 mole) and sodium acetate (8.0gm, 0.12 mole) in 25ml of ethanol and the resulting yellow solid was washed with water and then recrystallized from ethanol. The yield and m.p. are recorded in **table-I**.

Preparation of 1-hydro-5-methyl-6-(aryl hydrazone)-4-pyrazoline-7-ones (Va-k): -

To compounds IV (a-k) (0.01 mole) dissolved in glacial acetic acid (20ml), 1, 2-diamino benzene (0.01 mole) in glacial acetic acid was added and the mixture was heated on water bath for 6 hours. It was then cooled and allowed to stand overnight. The resulting solid was filtered, dried and recrystallized from acetic acid to furnish Va-k. The yield, m.p. and elemental analysis are given in **table-II**.

Antibacterial activity:

The compounds Va-k were screened for *in vitro* antibacterial activity against *Escherichia coli, Staphylococcus aureus* and *Pseudomonas aeruginosa* using paper disc diffusion method using DMF as solvent. Some of them showed moderate to mild activity against the three strains shown in **table-III**.

Table-I

Compound number	Name of the Compound	Yield (%)	M. P. ^{0}C	Lit. M.P. ^{0}C
Ia	Ethyl-2-(-phenyl) hydrazono-3-oxobutyrate	70	65	Not reported
Ib	Ethyl-2-(2-nitrophenyl) hydrazono-3-oxobutyrate	85	88	89
Ic	Ethyl-2-(3-nitrophenyl) hydrazono-3-oxobutyrate	74	115	Not reported
Id	Ethyl-2-(4-nitrophenyl) hydrazono-3-oxobutyrate	80	120	119
Ie	Ethyl-2-(2-chlorophenyl) hydrazono-3-oxobutyrate	87	63	60
If	Ethyl-2-(3-chlorophenyl) hydrazono-3-oxobutyrate	80	65	Not reported
Ig	Ethyl-2-(4-chlorophenyl) hydrazono-3-oxobutyrate	76	118	Not reported
Ih	Ethyl-2-(2-methylphenyl) hydrazono-3-oxobutyrate	71	44	45
Ii	Ethyl-2-(4-methylphenyl) hydrazono-3-oxobutyrate	84	63	65
Ij	Ethyl-2-(2-methoxylphenyl) hydrazono-3-oxobutyrate	76	78	Not reported
Ik	Ethyl-2-(4-methoxylphenyl) hydrazono-3-oxobutyrate	72	60	65

Table-II

Compound number	R	M. F.	Yield (%)	M.P. ^{0}C	Elemental analysis		
					C% Obs. (Cal)	H% Obs. (Cal)	N% Obs. (Cal)
V''a	H	-	-	-	-	-	-
V''b	2-NO_2	$C_{16}H_{13}N_5O_3$	19.95	260-261	59.32 (59.44)	3.96 (4.02)	21.52 (21.67)
V''c	3-NO_2	$C_{16}H_{13}N_5O_3$	26.86	230-231	59.38 (59.44)	4.00 (4.02)	21.62 (21.67)
V''d	4-NO_2	$C_{16}H_{13}N_5O_3$	33.00	185-187	59.40 (59.44)	3.92 (4.02)	21.62 (21.67)
V''e	2-Cl	$C_{16}H_{13}N_4OCl$	28.26	220-221	59.40 (59.44)	3.92 (4.02)	21.62 (21.67)
V''f	3-Cl	-	-	-	-	-	-
Vg	4-Cl	$C_{16}H_{13}N_4OCl$	40.45	225-227	61.40 (61.44)	4.10 (4.16)	17.88 (17.92)
V''h	2-CH_3	-	-	-	-	-	-
Vi	4-CH_3	$C_{17}H_{16}N_4O$	13.00	215-217	69.80 (69.86)	5.38 (5.47)	19.08 (19.17)
V''j	2-OCH_3	$C_{17}H_{16}N_4O_2$	13.00	218-220	66.12 (66.23)	5.04 (5.19)	18.10 (18.18)
V''k	4-OCH_3	-	-	-	-	-	-

Spectral Data

Comp. No.	I.R. (KBr) cm^{-1}	H' NMR, δ ppm.
V''b	3103 (N-H), 1564 (C=N), 1660 (C=O), 3301 (OH)	2.36 δ (S,3H,CH_3),7.58-7.51 δ (M,4H, Ar), 8.35-8.28 δ (M,4H, Ar), 13.52 δ (S,1H,N-H), 10.7 δ (S,1H,OH)
V''c	3103 (N-H), 1564 (C=N), 1660 (C=O), 3301 (OH)	2.38 δ (S,3H,CH_3),7.58-7.52 δ (M,4H, Ar), 8.32-8.28 δ (M,4H, Ar), 13.5 δ (S,1H,N-H), 10.6 δ (S,1H,OH)
V''d	3101 (N-H), 1554 (C=N), 1650 (C=O), 3301 (OH)	2.38 δ (S,3H,CH_3),7.52-7.46 δ (M,4H, Ar), 7.88-7.84 δ (M,4H, Ar), 12.9 δ (S,1H,N-H), 10.6 δ (S,1H,OH)
V''e	3178 (N-H), 1593 (C=N), 1662 (C=O), 3309 (OH)	2.65 δ (S,3H,CH_3),7.47-7.42 δ (M,4H, Ar), 7.65-7.63 δ (M,4H, Ar), 12.99 δ (S,1H,N-H), 10.7 δ (S,1H,OH)
Vg	3172 (N-H), 1552 (C=N), 1654 (C=O)	2.61 δ (S,3H,CH_3),7.93-7.91 δ (M,4H, Ar), 7.39-7.37 δ (M,4H, Ar), 12.52 δ (S,1H,N-H)
Vi	3100 (N-H), 1556 (C=N), 1651 (C=O)	2.3 δ (S,3H,CH_3), 2.5 δ (S,3H,CH_3),7.28-7.26 δ (M,4H, Ar), 7.53-7.51 δ (M,4H, Ar), 12.65 δ (S,1H,N-H)
V''j	3100 (N-H), 1556 (C=N), 1651 (C=O), 1264 (C-O-C), 3400 (-OH)	3.36 δ (S,3H,OCH_3), 2.41 δ (S,3H,CH_3),7.26-7.23 δ (M,4H, Ar), 7.79-7.77 δ (M,4H, Ar), 12.78 δ (S,1H,N-H), 10.6 δ (S,1H,OH)

Table-III (Biological Activity)

Compound	*E. coli*	*S. aureus*	*P. aeruginosa*
Vb	-	-	-
Vc	-	-	-
Vd	-	-	-
Ve	6	8	7
Vg	13	-	13
Vi	-	-	-
Vj	8	7	7

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