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Synthesis of Azo-coupled Etaconic Acid Anhydride and Its Reactions with Nucleophiles

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3,4-Methylenedioxy-benzylidene succinic anhydride (**I**) was condensed with diazonium salts of various aromatic amines (**a–d**) to form hydrazones or dyes (**II a–d**) which were further treated with nucleophiles like 10% NaOH and $NaBH_4$ to give various pyrazolinone derivatives (**III a–d**) respectively and cyclic imide derivatives (**V a–d**) of the corresponding hydrazones.

Key Words: Etaconic acid anhydride, Nucleophiles.

INTRODUCTION

From the literature survey[1-3] cyclic anhydrides having an active methylene group are convenient starting materials that can yield the derivatives of pyridazinones and pyridones. It is common to see that these compounds possess some bioactivity. Azo-coupling reaction is an electrophilic attack of aryl diazonium cation on the potentially nucleophilic centres. The azo-coupling reaction on active methylene compound produces the corresponding hydrazones[4-8]. From the literature survey[4-8] six-membered cyclic anhydrides having an active methylene group have been used as the starting material that can yield many heterocyclic derivatives possessing physiological properties. Since five-membered cyclic anhydrides have not been exploited it was thought worth while to synthesize hydrazones and its rearrangement derivatives starting from five-membered cyclic anhydride containing an active methylene group.

Itaconic acid system contains an active methylene group due to which it could be subjected to azo-coupling reactions for synthesis of hydrazones, which further provide an active centre for a number of nucleophilic reactions.

The present paper reports the synthesis of 3,4-methylenedioxybenzylidene succinic anhydride (**I**), and the condensation of (**I**) with aromatic amines like aniline (**a**), 2,6-dimethyl aniline (**b**), 3-chloro aniline (**c**) and 4-nitro aniline (**d**) to give 4-(3,4-methylenedioxybenzylidene)-3-(substituted phenylhydrazo)-2,5-(5H)-furan dione derivatives (**II a–d**).

Cyclic anhydrides when suitably substituted at their α-position by reactive functionality like —COR, —CHO, —COOEt, hydrazone etc. α-Substitution plays a decisive role in governing the ring cyclization step. The basic reaction in this case is the attack of the nucleophile at the carbonyl carbon, which leads to the ring opening and subsequent favourable ring closure[9].

On this basis the hydrazones synthesized above **(II a–d)** were subjected to various nucleophilic reactions.

On treatment with 10% NaOH, $NaBH_4$ and aniline, the hydrazones **(IIa–d)** gave 3-carboxy-4-(3,4-methylenedioxybenzylidene)-1-(substituted phenyl)-5-pyrazolone derivatives **(IIIa–d),** 3-hydroxymethyl-4-(3,4-methylenedioxybenzylidene)-1-(substituted phenyl)-5-pyrazolone derivatives **(IVa–d)** and 3-(substituted-phenylhydrazo)-4-(3,4-methylene dioxybenzylidene)-1-phenyl-2,5-pyrroledione **(Va–d)** respectively.

EXPERIMENTAL

Synthesis of 3,4-methylenedioxybenzylidene succinic anhydride or 3-(3,4-methylenedioxybenzylidene)-2,5-(5H)-furan dione (I): To a solution of 3,4-methylenedioxybenzylidene succinic acid (20 g) in dry chloroform (75 mL) redistilled acetyl chloride (30 mL) was added. The reaction mixture was refluxed on a water bath for about 3 h. The reaction mixture was allowed to stand for some hours. Excess of chloroform and acetyl chloride was removed by distillation. An insoluble anhydride precipitated was crystallized from ethyl acetate into yellow needles.

Synthesis of 4-(3,4-methylenedioxybenzylidene)-3-(phenyl/substituted phenyl hydrazo)-2,5-(5H)-furan dione (IIa–d): Aromatic amine **(a–d),** (0.002 mol) was dissolved in 1.2 mL of 6 N HCl and was diazotized by dropwise addition of aqueous $NaNO_2$ solution (0.138 g or 0.002 mole dissolved in 2 mL of water) at 0°C with stirring continuously for 15 min. This was then added dropwise to a solution of 3-(3,4-methylenedioxybenzylidene)-2,5-(5H)-furan dione **(I)** 0.464 g (0.002 mol) in 16 mL acetone at 0°C with constant stirring. The reaction mixture was stirred for 30 min more when an orange coloured solid separated out. About 50 mL of water was added to it and then the dye was filtered. It was then washed with water, dried and crystallized from chloroform.

Synthesis of 3-carboxy-4-(3,4-methylenedioxybenzylidene)-1-phenyl/substituted phenyl-5-pyrazolone (III a–d): 15 mL of 10% aqueous NaOH solution was added to 4-(3,4-ethylenedioxybenzylidene)-3-(phenyl/substituted phenyl-hydrazo)-2,5-(5H)-furan dione **(IIa–d)** (0.001 mole) and the reaction mixture was refluxed for 2 h. The clear solution obtained was cooled and acidified with 1 : 1 HCl, when a pale yellow solid separated out. It was filtered, washed with water and was crystallized from ethyl acetate.

Synthesis of 3-hydroxy-methyl-4-(3,4-methylenedioxybenzylidene)-1-phenyl-5-pyrazolone (IVa–d): Sodium borohydride 0.0094 g (0.00025 mol) was added to a suspension of 4-(3,4-methylenedioxybenzylidene)-3-(phenyl/substituted phenylhydrazo)-2,5-(5H)-furan dione **(IIa–d)** (0.001 mole) in methanol. A vigorous reaction at room temperature yielded a clear and almost colourless solution. The clear solution obtained was acidified with 1 : 1 HCl when a pale yellow solid separated out. It was filtered, washed with water and was crystallized from ethanol : water (1 : 1) mixture.

TABLE-1
PHYSICAL DATA OF THE COMPOUNDS

Compd. No.	R	m.f.	m.p. (°C)	Yield (%)	IR (cm^{-1})	UV (nm)
I	—	$C_{12}H_8O_5$	135	92.00	1767, 1707	—
IIa	—	$C_{18}H_{12}N_2O_5$	185	79.21	2925, 1765, 1706	181, 310
IIb	2,6-Dimethylphenyl	$C_{20}H_{16}N_2O_5$	150	69.23	2916, 1764, 1707	319
IIc	3-Chlorophenyl	$C_{18}H_{11}N_2O_5Cl$	184	54.32	2917, 1769, 1710	292, 316
IId	4-Nitrophenyl	$dC_{18}H_{11}N_3O_7$	160	63.51	2922, 1764, 1707	275, 317
IIIa	—	$C_{18}H_{12}N_2O_5$	190	61.30	1708, 1669	288, 311
IIIb	2,6-Dimethylphenyl	$C_{20}H_{16}N_2O_5$	200	59.80	1705, 1669	283, 311
IIIc	3-Chlorophenyl	$C_{18}H_{11}N_2O_5Cl$	142	63.00	1707, 1669	287, 310
IIId	4-Nitrophenyl	$C_{18}H_{11}N_3O_7$	180	66.00	1706, 1669	290, 310
IVa	—	$C_{18}H_{14}N_2O_4$	190	58.47	3328, 1671	232, 313
IVb	2,6-Dimethylphenyl	$C_{20}H_{18}N_2O_4$	204	68.11	3427, 1679	295, 326
IVc	3-Chlorophenyl	$C_{18}H_{13}N_2O_4Cl$	152	62.19	3433, 1667	293, 316
IVd	4-Nitrophenyl	$C_{18}H_{13}N_3O_6$	168	69.85	3431, 1684	275, 313
Va	—	$C_{24}H_{17}N_3O_4$	175	64.35	2982, 1673, 1635	289, 313
Vb	2,6-Dimethylphenyl	$C_{26}H_{21}N_3O_4$	168	66.00	2919, 1703, 1649	298, 335
Vc	3-Chlorophenyl	$C_{24}H_{16}N_2O_4Cl$	190	58.22	2923, 1704, 1649	296, 329
Vd	4-Nitrophenyl	$C_{24}H_{16}N_4O_6$	220	58.43	2919, 1704, 1649	299, 336

TABLE-2
ANTIBACTERIAL ACTIVITY

Compd. no.	Name of the culture used	Minimum inhibition concentration (MIC) in μg						
		1000	800	500	200	100	50	25
IVb	*Klb. pneumoniae*	+	+++	+++	+++	+++	+++	+++
IVc	*Corynebacterium diphtheriae*	–	++	++	++	++	++	++
IVe	*Sarcina*	+	+++	+++	+++	+++	+++	+++
IVf	*S. aureus*	+	++	++	++	++	++	++

– complete inhibition (no growth), + least growth, ++ less growth,
+++ no inhibition (maximum growth).

Synthesis of 3-phenyl hydrazo-4-(3,4-methylenedioxybenzylidene)-1-phenyl/substituted phenyl-2,5-pyrrolidinone (V a–d): 4-(3,4-methylenedioxybenzylidene)-3-(phenyl/substituted phenyl hydrazo)-2,5-(5H)-furan dione **(IIa–d)** (0.001 mole) was refluxed with aniline 0.1 g (0.001 mole) in 15 mL ethanol for 4–5 h on a water bath. Ethanol was distilled off and water was added to the residue obtained. One drop of conc. HCl was added to remove unreacted aniline. Light brown coloured solid separated out which was filtered, washed with water and was crystallised from dil. acetic acid.

RESULTS AND DISCUSSION

NMR data of compounds **(IIb), (IIIb), (IVb)** and **(Vb)** is as follow:

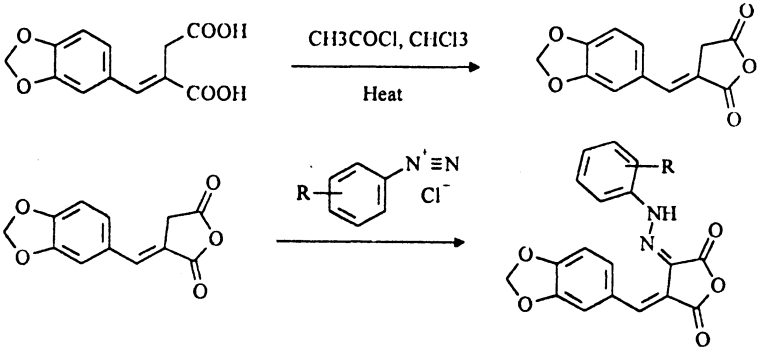
(IIb): Signals occurring at δ 3.4 may be due to six methyl protons of the aromatic ring. A sharp singlet at δ 6.0 ppm could be due to two methylenedioxy protons. Multiplet in the region of δ 6.9–7.8 ppm may be due to seven aromatic protons. A singlet at δ 3.9 ppm may be due to —NH proton.

(IIIb): Signals occurring from δ 3.2–3.6 ppm may be due to six methyl protons of the aromatic ring. A sharp singlet at δ 6.0 ppm was due to two methylenedioxy protons. Multiplet in the region δ 6.9–7.2 ppm was due to six aromatic protons. A sharp singlet at δ 7.6 ppm could be due to methylidene proton. A broad signal at δ 12.5 ppm may be due to —COOH proton.

(IVb): A singlet occurring at δ 3.2 ppm may be due to one alcoholic proton. Signals from δ 3.4–3.8 ppm could be due to six methyl protons of the aromatic ring. A singlet at δ 4.4 ppm may be due to two protons attached to alcoholic —OH group. A sharp singlet at δ 6.2 ppm may be due to two methylenedioxy protons. Multiplet from δ 7.0–7.6 ppm could be due to seven aromatic protons.

(Vb): Signal occurring at δ 3.4 ppm could be due to the six methyl protons of the aromatic ring. A sharp singlet at δ 6.0 ppm may be due to two methylenedioxy protons. Multiplet in the region δ 7.0–7.6 ppm may be due to twelve aromatic protons. A sharp singlet at δ 3.8 ppm could be due to —NH proton.

Synthetic strategy has been outlined below:



a. R = ---
b. R = 2,6-dimethyl
c. R = 3-Cl
d. R = 4-NO_2

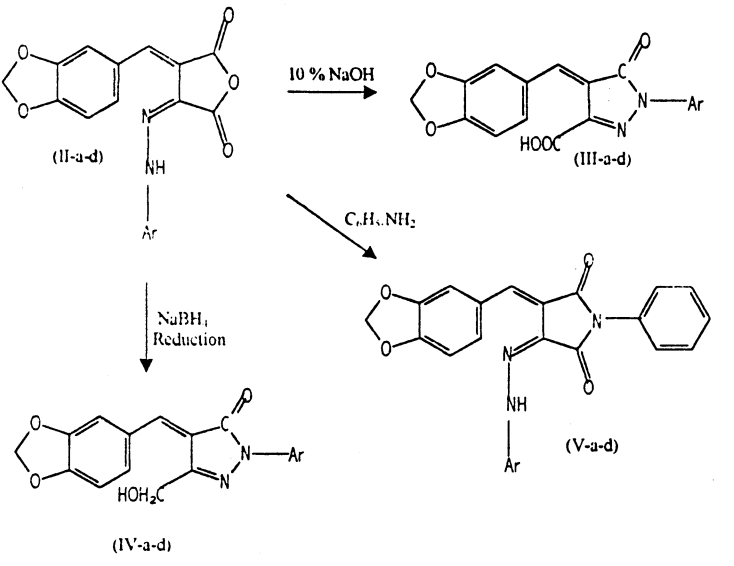


TABLE-3
ANTIFUNGAL ACTIVITY

Compd. No.	Name of the culture used
IVd	*Penicillium*
IVf	*Candida albicans*
IVh	*Penicillium*

All the above compounds showed inhibition for 72 h for the fungal cultures (Table-3). Afterwards the growth was shown.

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