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Synthesis and Antifungal Activity of Some Bis-Heterocycles Derived from Hydroquinone, Part-I

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In the present work the synthesis of some new bis-1,4-(5-arylamino-2-oxymethyl-1,3,4-thiadiazol-2-yl) benzenes and bis-1-4-(3-mercapto-4-aryl-5-oxymethyl-1,2,4-triazol-5-yl) benzenes were synthesized and were screneed for their antifungal activity.

INTRODUCTION

Substituted thiadiazoles[1] and triazoles[2] have been reported to display various biological activities. Keeping in view the above facts, it was thought of interest to synthesise some new bis-1,4-(5-arylamino-2-oxymethyl-1,3,4-thiadiazol-2-yl) benzenes and bis-1-4-(3-mercapto-4-aryl-5-oxymethyl-1,2,4-triazol-5-yl) benzenes by the cyclization of hydroquinone diacetyl bis-(4-aryl-3-thiosemicarbazides), obtained by the reaction of hydroquinone diacetyl chloride and 4-aryl thiosemicarbazides, with H_3PO_4 and NaOH respectively. All these compounds were screened for their antifungal activity.

EXPERIMENTAL

M.ps. were taken in open capillaries in a H_2SO_4-bath and are uncorrected. IR spectra (KBr) were recorded on a Perkin-Elmer spectrophotometer and PMR spectra (DMSO-d_6) on a EM-360 spectrometer (60 MHz) using TMS as an internal standard. Hydroquinone diacetic acid (**1**)[3], hydroquinone diacetyl chloride (**2**)[4] and 4-aryl thiosemicarbazides[5] were synthesised by reported methods.

Hydroquinone diacetylbis-(4-aryl-3-thiosemicarbazides) (**4**)*:* A mixture of phenyl thiosemicarbazide (6.68 g, 0.04 mol), hydroquinone diacetyl chloride (5.26 g, 0.02 mol) and triethylamine (4.04 g, 0.04 mol) was refluxed in a mixture of dimethylformamide and dioxane (1 : 1; 50 mL) for 6–8 h. It was then poured into cold water (500 mL). The solid thus obtained was washed with a saturated solution of sodium bicarbonate followed by water, dried and crystallized from ethanol-acetic acid to give **4a** (8 g, 77%), m.p. 200°C (Found: N, 15.71; $C_{24}H_{24}O_4N_6S_2$ requires: N, 15.78%; ν_{max} 3220 ν(NH), 1680 ν(CONH), 1615 ν(C=C, aromatic), 1210 ν(C=S) and 815 cm^{-1} (1,4-disubstituted benzene); δ7–7.4 (14H, m, ArH), 2.2 (4H, s, $2OCH_2$). Other compounds (yields 65–83%) were synthesised similarly: m.p. **4b**, 260°C; **c**, 210°C; **d**, 200°C; **e**, 160°C.

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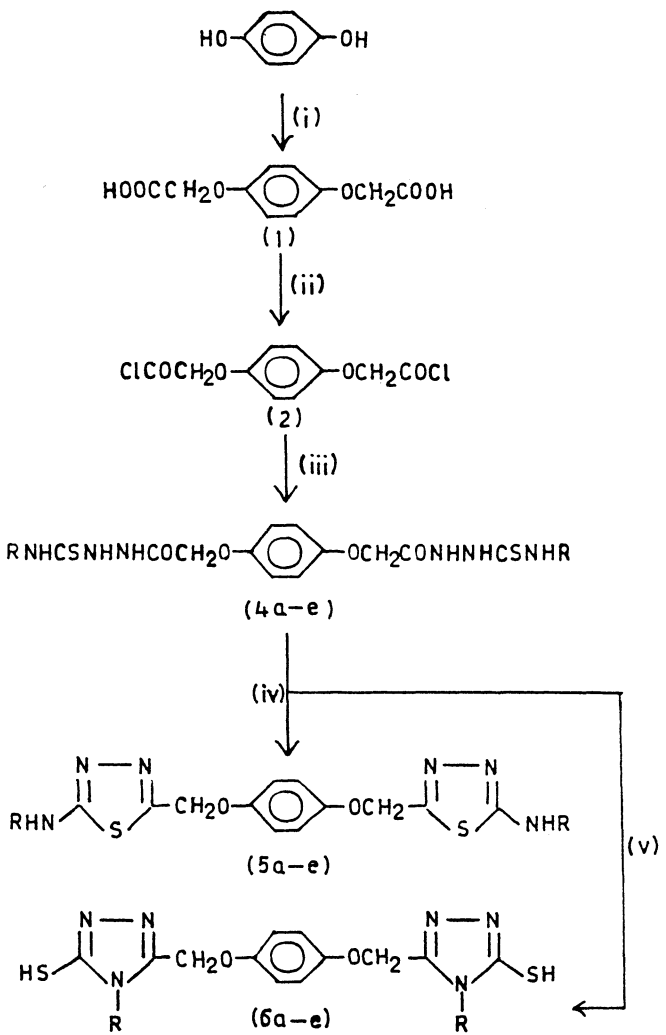
Bis-1,4-(5-arylamino-2-oxymethyl-1,3,4-thiadiazol-2-yl) benzenes (**5**): Compound **4e** (5.8 g, 0.01 mol) was added with stirring to anhydrous phosphoric acid (20 mL) during 20 min. The mixture was heated on an oil-bath at 120°C for 0.5 h and the slurry poured over ice-cold water. The solid that separated was crystallised from methanol to give **5e** (3.8 g, 69%), m.p. 240°C (Found: N, 14.51; $C_{26}H_{24}N_6O_4S_2$ requires: N, 14.58%); ν_{max} 3240 ν(NH), 1640 ν(C=N), 1690 ν(C=C, aromatic), 1440 ν(C—N) and 810 cm^{-1} (1,4-disubstituted benzene); δ 6.75–7.45 (12H, m, ArH), 3.65 (10H, s, $2OCH_2 + 2OCH_3$). Other compounds (yields 74–80%) were synthesised similarly: m.p. **5a**, 140°C; **b**, 220°C; **c**, 160°C; **d**, 195°C.



(a) R = C_6H_5, (b) R = $CH_3C_6H_4$, (c) R = *p*-Cl·C_6H_4, (d) R = *p*-Br·C_6H_4, (e) R = *p*-OCH_3·C_6H_4

Scheme 1. Reagents: (i) $ClCH_2COOH$, (ii) PCl_5, (iii) $RNHCSNHNH_2$ (3a–e), (iv) H_3PO_4 and (v) NaOH

Bis-1,4-(3-mercapto-4-aryl-5-oxymethyl-1,2,4-triazol-5-yl) benzenes (**6**): Compound **4a** (5.24 g, 0.01 mol) was refluxed in a solution of 8% NaOH (50 mL) for 4–6 h. The reaction mixture was then cooled and diluted with water and filtered. The filtrate on acidification with cold dilute acetic acid gave a white solid which was crystallised from ethanol to give 6a (2.9 g, 60%), m.p. 250°C (Found: N, 16.35; $C_{24}H_{20}N_6O_2S_2$ requires: N, 16.27%); ν_{max} 2900 ν(C—H), 1635 ν(C=N), 1580 ν(C=C, aromatic) and 810 cm^{-1} (1,4-disubstituted benzene); δ 6.95–7.45 (14H, m, ArH), 3.1 (4H, s, $2OCH_2$). Other compounds (yields 48–65%) were synthesised similarly: m.p. **6b**, 250°C; **c**, 245°C; **d**, 250°C; **e**, 250°C.

Antifungal activity: Compounds **4–6** were screened for their antifungal activity against *Aspergillus flavus*, *Penicillium decombens* and *Helminthosporium tetramera* by paper-disc plate method[6]. Generally, all the compounds exhibited moderate antifungal activity against all the fungi.

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