NOVEL ANTIMICROBIAL AGENTS OBTAINED BY ADDITION OF MALEIMIDE DERIVATIVES TO THENALDEHYDE AZINES OR SCHIFF'S BASES†

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Abstract — Condensation of the azines of 2-thenaldehyde or 5-bromo-2-thenaldehyde with various N-arylmaleimides gave the 1:2 adducts 2,9-di(2-thienyl or 5-bromo-2-thienyl)-5,12-diaryl-1,5,8,12-tetraazatetracyclodecane-4,6,11,13-tetraones (1-6). Dehydrogenation of these adducts by boiling in nitrobenzene gave the dehydrogenated products (7-9). Fusion of a mixture of Schiff's bases derived from 5-nitro-2-thenaldehyde or 5-nitrofurfural and aromatic amines with N-arylmaleimides in molar ratio 1:2 gave the spiro adducts 3,5',8',1'-tetrasubstituted 2,4,4',6'-tetraoxo-spiro {pyrrolidin-1,2'-(octahydropyrrolo[3,4-c]pyrroles)} (10-19). The structures of the synthesized compounds were confirmed by elemental analysis, IR, ^{1}H NMR and mass spectra. The preliminary antimicrobial testing of the prepared compounds against some pathogenic microorganisms proved that the spiro adducts particularly the compound (19) of great activity against Staph. aureus.

Several thiophene derivatives[1-3] and nitrofuran derivatives[4] were reported to exhibit a broad spectrum antimicrobial activity. Moreover, many spiro compounds were proved to possess several biological activities[5-8]. These observations prompted the synthesis of unreported series of thiophene or furan derivatives as possible antimicrobial agents.

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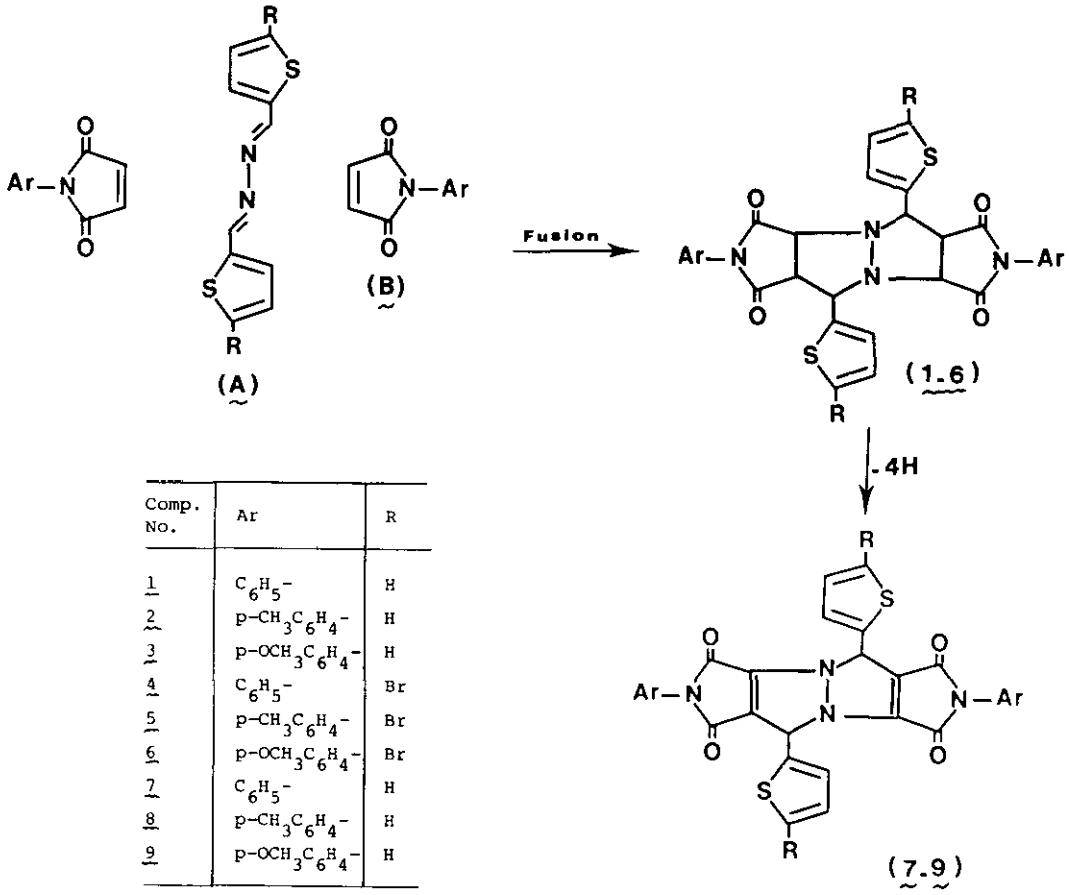
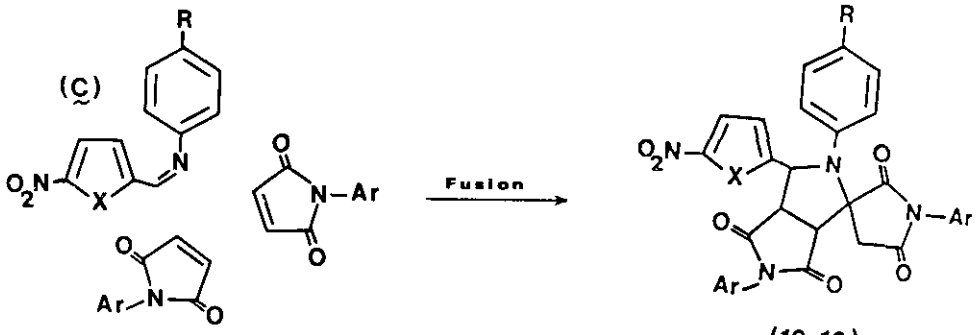
It was reported that the addition of dienophiles on azines in 1,3-2,4 dipolar cycloaddition "Criss-Cross" reactions afforded the 1:2 adducts[9-11]. In the present work, 2-thenaldehyde azine or 5-bromo-2-thenaldehyde azine (A) was condensed with N-arylmaleimides (B) to afford the 1:2 adducts (1-6)[12]. The reaction was carried out by fusion in an oil bath at 170°C for 2 h to afford the products as white crystals in 80-85% yields. The IR spectra of the compounds (1-6) showed characteristic band at 1600-1700 cm^{-1} (CO-N-CO) and a band at 2900 cm^{-1}(saturated -CH-)[11]. The structures of these adducts were further supported by the mass spectra of compounds (1) and (2)[13]. The adducts (1-3) were dehydrogenated by boiling in nitrobenzene for 6 h to afford the products (7-9)[14].



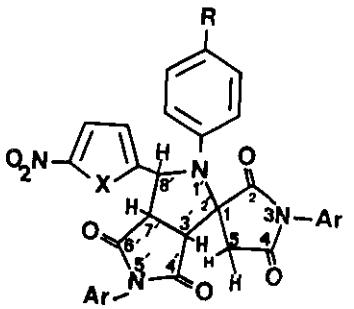
Comp. No.	Ar	R
1	C_6H_5-	H
2	p-$CH_3C_6H_4$-	H
3	p-$OCH_3C_6H_4$-	H
4	C_6H_5-	Br
5	p-$CH_3C_6H_4$-	Br
6	p-$OCH_3C_6H_4$-	Br
7	C_6H_5-	H
8	p-$CH_3C_6H_4$-	H
9	p-$OCH_3C_6H_4$-	H

Certain Schiff's bases had been reported to react with N-arylmaleimides in solvents like acetic acid, xylene or butanol to give the 1:2 spiro adducts, spiro{pyrrolidin-1,2'-(pyrrolidino[3,4-c]pyrroles)}[15,16]. Accordingly, the interaction of Schiff's bases derived from 5-nitro-2-thenaldehyde or 5-nitrofurfural and p-tolui-

dine or p-anisidine (C) with N-arylmaleimides (B) by fusion at 170°C for 3 h gave a brown product which was washed with hot ethanol, dissolved in chloroform and diluted with ethanol to precipitate the adducts (10-19) as an amorphous yellowish brown solid[17]. The IR spectra of these adducts showed characteristic bands at 1700-1750 cm^{-1} (CO-N-CO) and a band at 2900 cm^{-1} attributed to the saturated -CH- and $-CH_2-$ groups. The ^1H NMR spectrum of compound (16) as a representative example in $CDCl_3$ exhibited a multiplet at δ 6.8-7.3 ppm (16H) of the phenyl and furan protons, a singlet at δ 2.2 ppm (3H) of the protons of the methyl group, in addition to signals at δ 3.0, 3.6 and 4.5 ppm of the protons at positions 3', 7' and 8'. The two protons at position 5 appeared to be separated at δ 2.6 and 4.1 ppm (both exist in different configurations)[15].



Comp. No.	X	Ar	R
10	S	C_6H_5-	$-CH_3$
11	S	C_6H_5-	$-OCH_3$
12	S	$p-CH_3C_6H_4-$	$-CH_3$
13	S	$p-CH_3C_6H_4-$	$-OCH_3$
14	S	$p-OCH_3C_6H_4-$	$-CH_3$
15	S	$p-OCH_3C_6H_4-$	$-OCH_3$
16	O	C_6H_5-	$-CH_3$
17	O	C_6H_5-	$-OCH_3$
18	O	$p-CH_3C_6H_4-$	$-CH_3$
19	O	$p-CH_3C_6H_4-$	$-OCH_3$



The compounds (1), (3), (10), (12), (15) and (19) were tested for their in vitro antimicrobial activity against the microorganisms, Escherichia coli, Staphylococcus aureus and Candida albicans. The preliminary results showed that the compounds (1), (3) and (7) are inactive against the tested microorganisms, while the compounds (10), (12), (15) and (19) showed promising activity against Staph.

aureus and the compound (19) was found to be the most active one.

EXPERIMENTAL

Melting points were recorded on an electrothermal melting point apparatus (Fisher-Johns) and are uncorrected. The IR spectra were recorded on a Pye-Unicam SP 1000 spectrophotometer in potassium bromide. ^{1}H NMR spectrum of compound (16) was measured on a Varian EM 300X spectrometer in 90 MHz. The mass spectra were recorded on Perkin-Elmer instrument operated at 70 eV. Satisfactory elemental analysis for C, H and S or N was obtained for all compounds.

Synthesis of the adducts (1-6)

A mixture of 2-thenaldehyde azine or 5-bromo-2-thenaldehyde azine (0.01 mole) and the arylmaleimide derivative (0.02 mole) was heated under reflux on an oil bath at 170°C for 2 h. On cooling, the residue was washed with hot ethanol and crystallized from the proper solvent[12].

Dehydrogenation of the adducts (1-3)

A solution of the adducts (1-3) (1 g) in nitrobenzene (15 ml) was heated under reflux for 6 h. Nitrobenzene was then steam-distilled and the remaining residue was crysallized from the proper solvent to afford the products (7-9)[14].

Synthesis of the spiro adducts (10-19)

A mixture of the Schiff's base (0.01 mole) and the maleimide derivative (0.02 mole) was heated under reflux on an oil bath at 170°C for 3 h. On cooling, the residue left was washed with hot ethanol, dissolved in chloroform and filtered. Ethanol was added dropwise to the clear filtrate till the first turbidity and left at room temperature for 3 h to precipitate the crude products which were filetered, dried and crystallized from the proper solvent[17].

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12. 1: White crystals(AcOH), mp 292°C, 85% yield,
2: White crystals(Acetone), mp 261°C, 85% yield,
3: White crystals(Ethanol), mp 289°C, 83% yield,
4: White crystals(Acetone), mp 255°C, 80% yield,
5: White crystals(AcOH), mp 270°C, 81% yield,
6: White crystals(AcOH), mp 242°C, 80% yield.

13. MS m/z (Rel. Int.) of (1): 566 M^+ (100) (calc. for $C_{30}H_{22}N_4O_4S_2$), 483($M-C_4H_3S$)$^+$ (61), 91 (azatropylium) (81). (2): 594 M^+ (88) (calc. for $C_{32}H_{26}N_4O_4S_2$), 91(tropylium) (100), 83 (C_4H_3S) (52).

14. 7: Greyish white crystals(Benzene), mp 288°C, 45% yield,
8: Greyish white crystals(AcOH), mp 251°C, 50% yield,
9: Greyish white crystals(AcOH), mp 272°C, 43% yield.

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17. 10: Yellowish brown powder(EtOH+$CHCl_3$), mp 288°C, 65% yield,
11: Yellowish brown powder(EtOH+$CHCl_3$), mp 214°C, 68% yield,
12: Yellowish brown powder(EtOH+$CHCl_3$), mp 284°C, 60% yield,
13: Yellowish brown powder(EtOH+$CHCl_3$), mp 251°C, 63% yield,
14: Orange powder(EtOH+Acetone), mp 262°C, 58% yield,
15: Deep brown powder(EtOH+Benzene), mp 233°C, 50% yield,
16: Yellowish brown powder(EtOH+$CHCl_3$), mp 292°C, 68% yield,
17: Yellowish brown powder(EtOH+AcOH), mp 285°C, 65% yield,
18: Deep brown powder(EtOH+$CHCl_3$), mp 302°C, 85% yield,
19: Yellowish brown powder(EtOH+AcOH), mp 271°C, 61% yield.

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