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Studies on 1,3,4-Oxadiazoles: Preparation and Antimicrobial Activity of 2-Aryl-5-(*p*-Nitroso Thymoxy Methyl)-1,3,4-Oxadiazole

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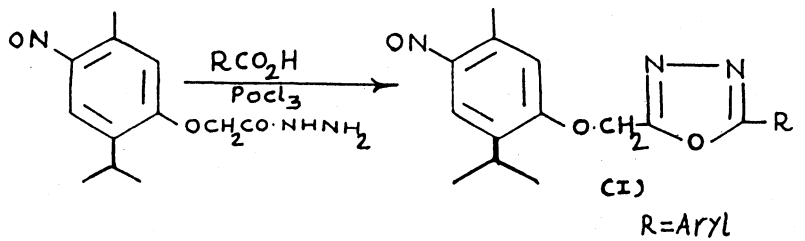
Certain new 1,3,4-oxadiazole derivatives having thymol moiety have been synthesised by reaction of the 4-nitrosohydrazinocarbonylmethyl thymol with different aromatic acids in phosphorous oxychloride. These compounds have been characterised by spectral data and are evaluated for antimicrobial activity. Some of them are found to be having moderate to good activity as compared to standard drugs.

INTRODUCTION

Several 2,5-disubstituted-1,3,4-oxadiazole derivatives possess wide spectrum of biological properties[1]. 1,3,4-Oxadiazole possesses potent therapeutic properties[2, 5]. Thymol derivatives are also well known therapeutic agents[6–9]. We have combined the two structures having thymol moiety and synthesised 2-aryl-5-(*p*-nitroso thymoxy methyl)-1,3,4-oxadiazoles of type (I).



2,5-Disubstituted-1,3,4-oxadiazoles of type (I) were prepared by the reaction of different aromatic acids on phosphorous oxychloride with 4-nitroso hydrazino carbonyl-methyl thymol[10]. The latter was prepared by the nitrosation of thymol in ethanol and hydrochloric acid. Sodium nitrite at 0°C yielded *p*-nitroso thymol followed by the reaction with ethyl chloroacetate giving *p*-nitroso carbethoxy-methyl thymol. This one reaction with hydrazine hydrate afforded *p*-nitroso hydrazino carbonyl-methyl thymol. The products were tested for antibacterial and antifungal activity.

EXPERIMENTAL

Melting points were determined in open capillary tube and are uncorrected. The structures of the compounds were established on the basis of their elemental analyses and spectral data. IR spectra (KBr) were recorded on a Shimadzu IR-435 spectrophotometer and PMR spectra were recorded in $CDCl_3$ on Hitachi R-1200 (60 MHz) using TMS as internal reference; chemical shifts are expressed in δ(ppm).

4-Nitroso carbethoxymethyl thymol (a)

A mixture of 4-nitroso thymol[10] (0.01 M), ethylchloroacetate (0.01 M) in dry acetone 20 mL and anhydrous K_2CO_3 (2 g) was refluxed on water bath for 6 h. The content was cooled, poured on crushed ice, filtered and recrystallised from ethanol, m.p. 48°C, yield 75%.

4-Nitroso hydrazino carbonyl-methyl thymol (b)

A mixture of (a) (0.01 mL) and hydrazino hydrate (0.015 M) in ethanol (25 mL) was refluxed on water bath for 5 h. The content was cooled, poured on ice water, filtered and recrystallised from ethanol, m.p. 164°C, yield 65%.

IR ν_{max} cm^{-1}: 2965 (ν_{asym}(CH)), 2855 (ν_{asym}(C—H)), 3035 (ν(C—H)), 1600, 1565, 1500 (ν(C=C)), 1640 (ν(C=O)), 1625 (N—H def + ν(C—N), 3300 (ν_{asym}(NH)), 3200 (ν_{asym}(NH)).

2-(*p*)-Methoxyphenyl-5-(*p*-nitroso thymoxy methyl)-1,3,4-oxadiazoles (IIi)

A mixture of (b) (0.01 M) and *p*-methoxybenzoic acid (0.01 M) in phosphorous oxychloride (5 mL) was refluxed for 5–6 h. The content was cooled and poured on crushed ice, made basic by sodium bicarbonate solution and the resulting solid was filtered, dried and recrystallised from DMF, m.p. 286°C, yield 65%. IR: ν_{max} (cm^{-1}): 2970 (ν_{asym}(C—H)), 2860 (ν_{sym}(C—H)), 3040 (ν(C—H)), 1610, 1570, 1519 (ν(C=C), ν(C—NO)), 1100 (ν(C—O—C)), 1610 (ν(C=N)). PMR $CDCl_3$. δ: 1.243–1.297 (d, 6*H*, $(CH_3)_2$ – CH), 2.452 (S, 3H + 2H, CH_3 + OCH_2), 3–3.6 (m, 1H, $(CH_3)_2$ – C*H*), 3.902 (S, 3H, OCH_3), 6.6–8.3 (6H, m, Ar—H).

Similarly other 1,3,4-oxadiazoles were prepared and physical constants are recorded in Table-1.

Antimicrobial Activity

All the compounds were screened for their antibacterial activity against gram-positive *S. citrus*, *B. mega* and gram-negative *E. coli*, *S. typhosa* and antifungal activity against *A. niger*. The zone of inhibition was measured in mm and recorded in Table-1. The activity was compared with known chosen standard drugs *viz.* ampicillin, chloramphanicol, norfloxacin and griseofulvin at the same concentration i.e. 50 μg.

In case of antibacterial activity, from the experimental data it has been observed that 1,3,4-oxadiazoles of type IIa–n were found to possess moderate activity against *B. mega* and *S. typhosa*. However, compounds such as IIa, IIc,

TABLE-1
ANTIMICROBIAL ACTIVITY OF 2-ARYL-5-(4-NITROSO THYMOXYMETHYL)-1,3,4-OXADIAZOLES.

Comp. No.	R	m.f.	m.p. (°C)	Antibacterial activity zone of inhibition in mm				Antifungal activity zone of inhibition in mm
				S. citrus	*B. mega*	*E. coli*	*S. typhosa*	*A. niger*
IIa	C_6H_5	$C_{19}H_{19}N_3O_3$	361	20	14	24	12	13
IIb	2—ClC_6H_4	$C_{19}H_{18}N_3O_3Cl$	278	21	15	20	14	14
IIc	3—ClC_6H_4	$C_{19}H_{18}N_3O_3Cl$	288(d)	20	13	21	13	12
IId	4—ClC_6H_4	$C_{19}H_{18}N_3O_3Cl$	300	19	12	23	14	15
IIe	3,5(—$OH)_2C_6H_3$	$C_{19}H_{19}N_3O_5$	257	18	14	20	12	13
IIf	3,4(—$NO_2)_2C_6H_3$	$C_{19}H_{29}N_5O_5$	271	20	13	19	13	14
IIg	2—OCH_3—C_6H_4	$C_{20}H_{21}N_3O_4$	300	21	14	19	14	16
IIh	3—OCH_3—C_6H_4	$C_{20}H_{21}N_3O_4$	271	20	11	18	15	12
IIi	4—OCH_3—C_6H_4	$C_{20}H_{21}N_3O_4$	286	21	13	21	12	11
IIj	3—NO_2—C_6H_4	$C_{19}H_{18}N_4O_5$	273	20	14	21	13	12
IIk	C_6H_5CH=CH	$C_{21}H_{21}N_3O_3$	278	21	12	23	14	14
III	2—CH_3—C_6H_4	$C_{20}H_{21}N_3O_3$	228	18	13	21	12	13
IIm	3—CH_3—C_6H_4	$C_{20}H_{21}N_3O_3$	242	20	12	22	13	12
IIn	4—CH_3—C_6H_4	$C_{20}H_{21}N_3O_3$	234	20	14	18	15	15
	Ampicillin (50 µg)		—	22	17	24	17	—
	Chloramphanicol (50 µg)		—	24	26	24	25	—
	Norfloxacin (50 µg)		—	33	23	26	28	—
	Griseofulvin (50 µg)		—	—	—	—	—	23

% yield varied from 60 to 75.

IId, IIe, IIf, IIg, IIh, IIi, IIj, IIk, IIl, IIm, IIn exhibited remarkable activity against *S. citrus* and *E. coli* but were less active than the standard drugs *viz.* ampicillin and chloramphenicol.

In case of antifungal activity compounds of type (I) showed moderate activity against *A. niger* but were less active in comparison with known chosen standard griseofulvin.

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