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SYNTHESIS OF CERTAIN 1, 3,4-OXADIAZOLES, 1,2, 4-TRIAZOLES AND 1,3,4-THIADIAZOLES AS POTENTIAL CHEMOTHERAPEUTIC AGENTS

A. A. El-Emam*, M.A. Moustafa and M. M. El-Kerdawy

Department of Medicinal Chemistry, Faculty of Pharmacy, University of Mansoura, Mansoura, Egypt

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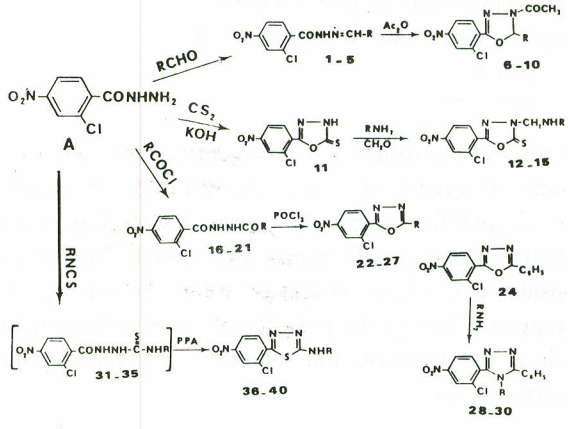
A series of five membered heterocyclics namely, 5-substituted-4-acetyl-2-(2-chloro-4-nitrophenyl)-1,3,4-oxadiazolines 6-10, 4-substitutedaminomethyl-2-(2-chloro-4-nitrophenyl)-1,3, 4-oxadiazoline-5-thiones 12-15, 2-substituded-5-(2-chloro-4-nitrophenyl)-1, 3, 4-oxadiazoles 22-27, 4-substituted-3-(2-chloro-4-nitrophenyl)-5-phenyl-1, 2, 4-triazoles 28-30, and 2-substitutedamino-5-(2-chloro-4-nitrophenyl)-1, 3, 4-thiadiazoles 36-40, were synthesized. Eight representative compounds were tested for their *invitro* antimicrobial activity against some pathogenic microorganisms, some of them were proved to be active.

Key words: Synthesis, Antimicrobial testing, 1,3,4-Oxadiazoles, 1,2, 4-Triazoles, 1,.

INTRODUCTION

A large number of 1,3,4-oxadiazoles have been reported to possess several biological activities such as bactericidal [1-3], fungicidal [4], analgesic, muscle relaxant and tranquilizing properties [5]. Several 1,2,4-triazoles have been proved to exhibit broad spectrum biological activities, the interesting ones being the tuberculostatic [6], fungicidal [7], bactericidal [8] and antiinflammatory activities [9]. In addition, some 1,3,4-thiadiazoles were early proved to be useful chemotherapeutic agents. The present paper, describes the synthesis of some 1,3,4-oxadiazoles, 1,2,4-triazoles and 1,3,4-thiadiazoles. The preliminary results of antimicrobial testing of some compounds are also reported.

2-Chloro-4-nitrobenzoylhydrazine **A** was condensed with some selected aldehydes in ethanol to obtain the corresponding anils 1-5, which upon treatment with acetic anhydride yielded the corresponding 5-substituted-4-acetyl-2-(2-chloro-4-nitrophenyl)-1, 3, 4-oxadiazolines 6-10. The method of Young and Wood [10] was adopted for the synthesis of the compound 2-(2-chloro-4-nitrophenyl)-1, 3, 4-oxadiazole-5-thione 11 by condensation of the hydrazide **A** with potassium hydroxide and carbon disulphide. Treatment of an ethanolic solution of compound 11 with formaldehyde solution and some primary amines at ambient temperature yielded the corresponding Mannich bases, 2-(2-chloro-4-nitrophenyl)-4-substituted aminomethyl-1, 3, 4-oxadiazoline-5-thiones 12-15. Interaction of **A** with some acid chlorides in pyridine yielded the corresponding N, N'-diacylhydrazines 16-21, which upon reflux with phosphorus oxychloride, by the method of Hayes *et. al.* [11] gave the corresponding 2,5-disubstituted-1, 3,4-oxadiazoles 22-27. The triazole derivatives, 4-substituted-3-(2-chloro-4-nitrophenyl)-5-phenyl-2, 1, 2, 4-triazoles 28-30, were prepared by prolonged heating of the compound 24, with appropriate primary amine in xylene. Attempted reaction of compound 24 with aniline or other aromatic amines failed to produce the corresponding triazole and the starting compound 24 was isolated unchanged. Treatment of **A** with some alkyl- or arylisothiocyanates in ethanol and subsequent treatment with polyphosphoric acid resulted in the formation of the respective 2-substitutedamino-5-(2-chloro-4-nitrophenyl)-1, 3, 4-thiadiazoles 36-40 via the formation of the unisolated intermediates 31-35.



Antimicrobial testing. The standardized disc method of Bondi *et al.* [12] was adopted for testing the preliminary antimicrobial activity of the compounds 7, 8, 11, 14, 24, 30, 36 and 39. Filter paper discs were moistened with the test compound solution in dimethylsulphoxide of specific concentration 10 mg/disc and carefully placed on an agar culture plates that have been previously inoculated separately with the microorganisms, *Staphylococcus*

aureus (S.A.)., *Escherichia coli* (E.C.) and *Candida albicans* (C.A.). The plates were incubated at 37° for 24 hours, and the diameter of the growth inhibition zone around the disc was measured to the nearest mm. The results of the antimicrobial activity of the tested compounds and the antibiotic Penicillin G (P.G.) and the antifungal antibiotic Mycostatin (M) both in concentration of 100 i.u./disc are shown in Table 1. The compounds 8, 11 and 14 were found

Table 1. The diameters of the inhibition zones (mm) exhibited by the compounds 7, 8, 11, 14, 24, 30, 36 and 39 each in concentration 10 mg/disc and the antibiotics penicillin G (P.G.) and mycostatin (M) each in concentration 100 i.u./disc.

Comp. No.	S.A.	E.C.	C.A.
Control*	§	§	§
7	§	§	§
8	19	§	§
11	20	§	§
14	16	§	§
24	§	§	§
30	21	19	§
36	§	§	§
39	§	§	§
P.G.	21	ϕ	ϕ
M	ϕ	ϕ	18

* Disc containing dimethylsulphox

* Disc containing dimethylsulphoxide only.

§ = Inactive

ϕ = Not tested.

to possess promising activity against *Staph. aureus*, compound 30 was found to be active against *Staph. aureus* and *E. coli* and no compound was found to possess marked activity against *C. albincans.* These results should not be considered as a final conclusion about the activity of these compounds due to the presence of other interfering factors such as the diffusion and solubility of the compounds in the agar media.

EXPERIMENTAL

All melting points are uncorrected, IR spectra were recorded on Pye-Unicam SP 1000 spectrophotometer in KBr (± in cm^{-1}) and PMR spectra were recorded in $CDCl_3$ on Varian EM-390 90 MHz instrument using TMS as the internal reference (chemical shift on δ ppm).

N-aryliden-N'-(chloro-4-nitrobenzoyl) hydrazines 1-5. The appropriate carbonyl compound (0.01 mole) was added to a hot solution of 2-chloro-4-nitrobenzoylhydrazine (0.01 mole) in ethanol (30 ml) and the mixture was heated under reflux for one hour. The solid separated on cooling was filtered, washed with ethanol and crystallized (Table 2).

5-Substituted-4-acetyl-2-(2-chloro-4-nitrophenyl)-1 3,4-oxadiazolines 6-10. The appropriate hydrazone 1-5 (1 g), was heated under reflux with acetic anhydride (5 ml) for 30 minutes. On cooling, the mixture was poured onto crushed ice (100 g) and stirred for 20 minutes. The separated solid was filtered, washed with water and crystallized (Table 2). The IR spectrum of compound 8 exhibited bands at 1680 (C=O), 1610 (C=N) and 1500 (NO_2). The PMR spectrum of compound 6 displayed signals at 7.5-8.3 (m, 6H, Ar-H), 7.3 (s, 1H, oxadiazoline-H) and 2.6 (s, 3H, $COCH_3$).

2-(2-chloro-4-nitrophenyl)-1, 3-4-oxadiazoline-5-thione 11. A mixture of 2-chloro-4-nitrobenzoylhydrazine (0.1 mole), potassium hydroxide (0.1 mole) and carbon disulphide (20 ml) in ethanol (20 ml) was heated under reflux on a steam bath until the evolution of hydrogen sulphide ceased (about 5 hours). The excess solvent was removed by distillation and the residue was stirred with water, filtered and the filtrate was acidified with dilute HCl. The precipitated solid was filtered, washed with water and crystallized (Table 2). The IR spectrum of this compound showed bands at 3380 (NH), 1630 (C=N), 1220 (C-O-C) and 1100 (C=S). The PMR spectrum exhibited signals at 8.9 (s, 1H, NH) and 8.1-7.8 (m, 3H, Ar-H).

4-Substitutedaminomethyl-2-(2-chloro-4-nitrophenyl) -1,3,4-oxadiazoline-5-thiones 12-15. To a ethanolic stirred mixture of compound 11 (0.01 mole) and formaldehyde solution (38%; 0.015 mole) (10 ml), a solution of ethanolic appropriate amine (10 ml) was added dropwise. The mixture was stirred for one hour at ambient temperature and left overnight. The separated crystalline product was filtered and recrystallized (Table 2). The IR spectrum of compounds 12-15 showed bands at 3250-3400 (NH), 1600-1650 (C=N), 1350-1380 (C=S) and 1220-1260 (C-O-C). The PMR spectrum of compound 13 showed signals at 7.8-7.3 (m, 8H, Ar-H and NH) and 4.6 (s, 2H, CH_2).

N-(2-Chloro-4-nitrobenzoyl)-N'-acylhydrazines 16-21. To a solution of 2-chloro-4-nitrobenzoylhydrazine (0.1 mole) in pyridine (100 ml), the appropriate acid chloride (0.1 mole) was added dropwise and the mixture was heated under reflux for 20 minutes. On cooling, the mixture was poured onto crushed ice (100 g) and the separated solid was filtered, washed and dried. The products were used for the next reaction without further purification.

Table 2. Crystallization solvents, melting points, yield percentages and molecular formulae of the synthesized compounds.

Comp. No.	R	Cryst. solv.	m.p. °C	Yield %	Molecular formula*
1	2-Thienyl	Ethanol	228	95	$C_{12}H_8ClN_3O_3S$
2		Acetic acid	231	92	$C_{12}H_7ClN_4O_5S$
3		Acetic acid	229	82	$C_{12}H_7ClN_4O_6$
4	*m*-$NO_2C_6H_4$-	Acetic acid	251	95	$C_{14}H_9ClN_4O_5$
5	*p*-BrC_6H_4-	Ethanol	188	95	$C_{14}H_9BrClN_3O_3$
6	2-Thienyl	Ethanol	134	48	$C_{14}H_{10}ClN_3O_4S$
7		Aqueous-ethanol	173	45	$C_{14}H_9ClN_4O_6S$
8		Aqueous-ethanol	177	35	$C_{14}H_9ClN_4O_7$
9	*m*-$NO_2C_6H_4$-	Ethanol	183	35	$C_{16}H_{11}BrClN_4O_6$
10	*p*-$NO_2C_6H_4$-	Aqueous-ethanol	152	55	$C_{16}H_{11}BrClN_3O_4$
11		Ethanol	192	82	$C_8H_4ClN_3O_3S$
12	C_6H_5-	Acetic acid	254	40	$C_{15}H_{11}ClN_4O_3S$
13	*p*-BrC_6H_4-	Ethanol	277	38	$C_{15}H_{10}Cl_2N_4O_3S$
14	*p*-ClC_6H_4-	Ethanol	276	40	$C_{15}H_{10}Cl_2N_4O_3S$
15	*p*-$NO_2C_6H_4$-	Ethanol	288	40	$C_{15}H_{10}ClN_5O_5S$
22	CH_3-	Ethanol	123	35	$C_9H_6ClN_3O_3$
23	$ClCH_2$	Water	119	35	$C_9H_5Cl_2N_3O_3$
24	C_6H_5-	Ethanol-benzene	187	45	$C_{14}H_8ClN_3O_3$
25	*p*-$NO_2C_6H_4$-	Benzene	230	48	$C_{14}H_7ClN_4O_5$
26	*m*-BrC_6H_4-	Ethanol	175	45	$C_{14}H_7BrClN_3O_3$
27	*p*-ClC_6H_4-	Xylene	255	48	$C_{14}H_7Cl_2N_3O_3$
28	*n*-C_4H_9-	Ethanol	173	28	$C_{18}H_{17}ClN_4O_2$
29	$C_6H_5CH_2$-	Ethanol	186	25	$C_{21}H_{15}ClN_4O_2$
30	$Et_2NCH_2CH_2$-	Dioxan	189	30	$C_{20}H_{22}ClN_5O_2$
36	C_2H_5-	Dioxan	222	65	$C_{10}H_9ClN_4O_2S$
37	*n*-C_4H_9-	Acetone	198	65	$C_{12}H_{13}ClN_4O_2S$
38	C_6H_{11}-	Acetic acid	207	60	$C_{14}H_{15}ClN_4O_2S$
39	C_6H_5-	DMF	300	65	$C_{14}H_9ClN_4O_2S$
40	$C_6H_5CH_2$-	Ethanol	218	50	$C_{15}H_{11}ClN_4O_2S$

* Satisfactory elemental analyses for C, H and S or N was obtained for all compounds.

2-Substituted-5-(2-chloro-4-nitrophenyl)-, 1,3, 4-oxadiazoles 22-27. A mixture of the appropriate N, N'-diacylhydrazine *16-21* (0.01 mole) and phosphorus oxychloride (10 ml) was heated under reflux for 6 hours. The mixture was distilled under reduced pressure and the residue was slowly added to cold water (100 ml). The separated solid was filtered and crystallized (Table 2).

4-Substituted-3-(2-chloro-4-nitrophenyl)-5-phenyl-1,2, 4-triazoles 28-30. To a solution of compound 24 (0.01 mole) in *p*-xylene (20 ml), appropriate primary amine (0.02 mole) was added and the mixture was heated under reflux for 12 hours. The orange crystalline products that separated on cooling were filtered, washed with *p*-xylene and crystallized (Table 2). The IR spectrum of compound 29 exhibited bands at 1650 (C=N–)and 1400 (CH_2). The PMR spectrum of the same compound displayed signals at 7.8-7.2 (m, 13H, Ar-H) and 3.8 (s, 2H, CH_2).

2-Substitutedamino-5-(2-chloro-4-nitrophenyl)-1,3, 4-thiadiazoles 36-40. To a hot solution of 2-chloro-4-nitrobenzoylhydrazine (0.01 mole) in ethanol (10 ml), the appropriate isothiocyanate (0.01 mole) was added and the mixture was heated under reflux for one hour. On cooling, crystalline products were separated 31-35. The mixture was then concentrated under reduced pressure. The residue

was mixed with polyphosphoric acid (8 ml) and the mixture was heated under reflux in an oil bath at 129o for one hour. After cooling to room temperature, the syrupy liquid was poured onto ice-cold water (50 g) and the precipitated solid was filtered, washed with water, dried and crystallized (Table 2).

REFERENCES

1. M. Y. Yousif, A.M. Ismaiel, A. A. El-Emam and M. M. El-Kerdawy, J. Chem. Soc. Pakistan, **8**, 183 (1986).
2. R. S. Gunnar, U.S. Pat., 3, 608, 862, (C. A. **73**, 14854, 1970).
3. M.A. Khalil, S.M. El-Khawass and M. G. Kassem, Sci. Pharm., **48**, 344 (1980).
4. B. N. Gosowami, J.C. S. Kataky, J. N. Baruah and S.C. Nath, J. Heterocyclic Chem., **21**, 205 (1984).
5. N. Soni, J. B. Barthwal, A.K. Saxena, K.P. Barbava and S. S. Parmar, *Ibid,* **19**, 29 (1982).
6. J. Lang and H. Tondys, Pol. Pharmacol Pharm. **27**, 211 (1975).
7. J. Wagner, J. Kamechi and S. Leistner, Pharmazie, **30**, 804 (1975).
8. A.K. Sengupta and A. A. Gupta, Indian J. Chem., **22B**, 263 (1983).
9. T..George, D. Mehta, R. Tahilramini, J. David and P. Tolwalker, J. Med. Chem., **14**, 335 (1971).
10. R.W. Young and K. H. Wood, J. Am. Chem., Soc., 77, 400 (1955).
11. F. N. Hayes, B. S. Rogers and D. G. Ott, J. Am. Chem. Soc., 77, 1850 (1955).
12. A..Bondi, E. H. Spaulding, E. D. Smith and C. C. Dietz, Am. J. Med. Sci., **214**, 2121 (1947).