Synthesis of Some Substituted Carbamodithioic Acid Esters and Their Antimicrobial Activities

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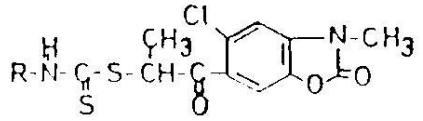
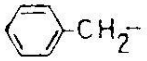
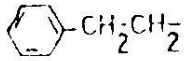
Summary: In this study seven new dithiocarbamate derivatives have been prepared by the reaction of 3-methyl-5-chloro-6-(2- bromopropionyl)-2-benzoxazolinone and substituted potassium dithiocarbamate derivatives. Their structures have been elucidated by UV, IR, NMR, MS and elementary analysis. The compounds synthesized have been assayed for their antifungal and antibacterial activities against various microorganisms.

Introduction

It is well known that the esters of N-substituted carbamodithioic acid derivatives have been reported to have various pharmacological activities such as antibacterial, antifungal, antiviral, herbicide, and tuberculostatic [1-11]. These pharmacological activities are more pronounced in N-monosubstituted dithiocarbamic acid esters than the N,N- disubstituted carbamodithioic acid derivatives because of the labile nature of hydrogen atom attached to the nitrogen atom.

In this paper, we aimed to determine the contribution of benzoxazolone ring and various alkyl substituents on nitrogen atom of dithiocarbamate structure to antimicrobial activity. We synthesized seven new compounds the formula of which are given below and screened their antibacterial and antifungal activities.



Compound	R
I	CH_3
II	C_2H_5
III	(n)C_3H_7
IV	(n)C_4H_9
V	(n)C_5H_{11}
VI	
VII	

Material and Methods

Methylamine, ethylamine, propylamine, butylamine, pentylamine, benzylamine, phenethyl amine and 5-chloro-2-benzoxazolinone were purchased from Merck and Aldrich. Potassium salts of substituted dithiocarbamic acids and 3-methyl-5-chloro-6-(2-bromopropionyl)-2-benzoxazolinone were prepared as reported [12-15].

Melting points of the compounds have been determined with Thomas Hoover capillary melting point apparatus and the values given are uncorrected. UV spectra were obtained with Hitachi 220S spectrophotometer using methanol as solvent at 5.10^{-5}M concentration. IR spectra were recorded with Perkin Elmer 457 IR Grating spectrophotometer employing KBr pellets. NMR spectra were recorded with Bruker 200 MHz using deuterium chloroform as solvent and tetramethylsilane as internal standart. Mass spectra were recorded on Brucker. Elemental analysis of the compounds have been performed at Mainz West Germany.

3-Methyl-5-chloro-6-2-(N-substituted dithiocarbamoylthio) propionyl-2-benzoxazolinones

In order to synthesize these compounds, equimolar amounts of 3-methyl-5-chloro-6-(2-bromopropionyl)-2-benzoxazolinone and corresponding potassium dithiocarbamate derivative were refluxed in methanol for two hours. Then the solution was evaporated to dryness under diminished pressure. The precipitate formed was washed with water and dried. They were crystallized from appropriate solvents as given in Table-1. Spectal properties of the compounds are given in Table-2.

Microbiology

The compounds synthesized were screened for their antibacterial and antifungal properties against various bacteria and yeast-like fungi by the dilution method [16-18]. The results are seen in Table-3.

Table-1: Empirical formula, molecular weight, melting point, % yield and UV characteristics of the compounds I-VII.

Compound	Empirical formula	M.W.	m.p. (°C)	Crystal. Solv.	% Yield	UV (λ_{max}MeOH log ϵ)
I	$C_{13}H_{13}ClN_2O_3S_2$	344	153	isopropanol	87.44	279:4.21
II	$C_{14}H_{15}ClN_2O_3S_2$	358	158	isopropanol	84.12	281:4.29
III	$C_{15}H_{17}ClN_2O_3S_2$	372	145	methanol	79.91	281:4.26
IV	$C_{16}H_{19}ClN_2O_3S_2$	386	160	isopropanol	84.10	281:4.35
V	$C_{17}H_{21}ClN_2O_3S_3$	400	149	methanol	80.60	280:4.41
VI	$C_{19}H_{17}ClN_2O_3S_3$	420	187	methanol	83.55	281.4.26 212:4.03
VII	$C_{20}H_{19}ClN_2O_3S_2$	434	91	isopropanol	75.53	281:4.09 243:4.11 215:3.90

Table-2: Spectral and elemental analysis of the compounds I-VII.

Com-pound	IR (cm^{-1})	NMR (ppm)	Mass m/z (70 eV)	Analysis Calc. %	Found %
I	3350 (N-H), 1745 (C=O, lac) 1680 (C=O, ket) 1195 (C=S)	1.21 (3H, d, CH_3CH-) 2.82 (3H, d, CH_3NHCS) 3.36 (3H, s, N-CH_3) 4.26 (1H, q, CH-CH_3) 5.70 (1H, NH, broad) 7.60 - 7.70 (2H, m, benzoxazolone H^4, H^7)	344, 326, 212, 211, 210 (% 100), 182, 126, 99, 97, 91, 76, 74, 73, 59, 55	C:45.28 H: 3.80 N: 8.12	45.11 3.65 8.39
II	3300 (N-H) 1745 (C=O, lac), 1680(C=O, ket.) 1190 (C=S)	0.80 (3H, t-CH_3CH_2) 1.20 (3H, d, CH_3CH) 3.30 (2H, q, CH_2CH_3) 3.35 (3H, s, N-CH_3) 4.30 (1H, q, $CHCH_3$) 5.65 (1H, NH, broad) 7.60 - 7.80 (2H, m, benzoxazolone H^4, H^7)	358, 342, 212, 211, 210 (% 100), 184, 182, 126, 99, 97, 91, 88, 55	C:46.86 H: 4.21 N: 7.81	46.69 4.09 8.00
III	3300 (N-H) 1745 (C=O, lac.) 1680 (C=O, ket.) 1180 (C=S) 3.35	0.69 (3H, t, CH_3CH_2) 1.21 (3H, d, CH_3CH-) 1.56 (2H, m, CH_2CH_3) (3H, s, N-CH_3) 3.79 (2H, t, -CH_2-N) 4.35 (1H, q, $CHCH_3$) 5.60 (1H, NH, broad) 7.50-7.80 (2H, m, benzoxazolone H^4, H^7)	372,356, 212, 211, 210 (% 100), 126, 102, 99, 97, 77, 76, 75, 74, 73, 57, 55	C;48.32 H: 4.60 N: 7.,51	48.09 4.58 7.59
IV	3250 (N-H) 1745 (C=O, lac.) 1680 (C=O, ket.) 1180 (C=S)	0.66 (3H, T, CH_3CH_2) 1.20 (3H, d, CH_3CH) 1.40 1.70 (4H, m, $CH_3CH_2CH_2$) 3.00, 1H, NH, broad) 3.35 (3H, S, N-CH_3) 3.52 (2H, t, -CH_2-) 4.27 (1H, q, $CHCH_3$) 7.50-7.90 (2H, m, benzoxazolone H^4, H^7)	371, 212, 211, 210 (% 100), 184, 182, 126, 116, 99, 97, 77 76, 75, 74, 73, 57, 55	C: 49.67 H: 4.95 N: 7.24	49.51 4.87 7.15
V	3380 (N-H) 1750 (C=O, lac) 1680 (C=O, ket.) 1170 (C=S)	0.76 (3H, t, CH_3CH_3) 1.20 (3H, d, CH_3CH) 1.41 1.70 (6H, m, -$CH_2CH_2CH_2$-) 3.00 (12H, NH, broad) 3.36 (3H,s, N-CH_3) 3.56 (2H, t, -CH_2N-) 4.28 (1H, q, $CHCH_3$) 7.60-7.90 (2H, m, benzoxazolone H^4, H^7)	400, 364, 212, 211 210 (% 100), 182, 130, 129, 126, 73, 72.43	C: 50.93 H: 5.28 N: 6.99	51.01 5.16 6.85
VI	3290 (N-H) 1740 (C=O, lac.) 1680 (C=O, ket.) 1160 (C=S) 740, 690 (mono subs.benzene)	1.25 (3H, d, CH_3CH) 3.00 (1H, NH, broad) 3.32 (3H, s, N-CH_3) 3.41 (2H, s, CH_3NH) 4.34 (1H, q, $CHCH_3$) 6.90-8.00 (7H, m, benzoxazolone H^4,H^7 and phenyl protons)	404, 212, 211, 210, 156, 149, 126, 92, 91(%100), 76, 75	C: 54.21 H: 4.07 N: 6.66	54.44 4.13 6.45

Table-2: continued.

Com-pound	IR (cm^{-1})	NMR (ppm)	Mass m/z (70 eV)	Analysis Calc. %	Found %
VII	3300 (N-H) 1745 (C=O, lac.) 1680 (C=O, ket.) 1165 (C=S) 740, 690 (mono subs. benzene)	1.24 (3H, d, CH_3CH) 2.89 (2H, t, Ph-CH_2) 3.35 (3H,s, N-CH_3) 3.74 (2H, t, CH_2NH) 4.32 (1H, q, $CHCH_3$) 5.69 (1H, NH, broad) 7.00-8.10 (7H, m, benzoxazolone H^4, H^7 and phenyl protons).	212, 211, 210 (% 100) 182, 164, 126, 97, 91 76, 63, 51	C: 55.23 H: 4.40 N: 6.44	55.01 4.18 6.36

s: singlet, d: doublet, t:triplet, q:quartet, m: multiplet, lac. : lactam, ket.: ketone

Table-3: Antimicrobial activity of the compounds I-IV (MIC: μg/ml)

Com-pound	A	B	C	D	E	F	G	H
I	>400	>400	>400	>400	200	200	100	150
II	>400	>400	>400	>400	>400	300	300	200
III	>400	200	>400	300	100	150	100	50
IV	>400	300	>400	300	200	200	150	200
V	>400	>400	>400	>400	200	200	150	150
VI	>400	>400	>400	>400	100	300	300	300
VII	>400	>400	>400	>400	25	50	50	50

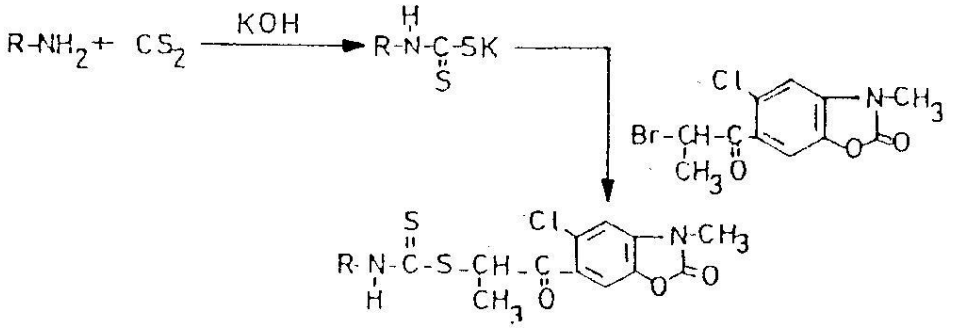
A: Staphylcoccus faecalis, B: Staphylococcus aureus, C: Pseudomanosaeruginosa D: Escherichia coli; E. Candida parapsilosis, F: Candida albicans, G: Canadida pseudotropicalis, H: Candida stellatoidea.

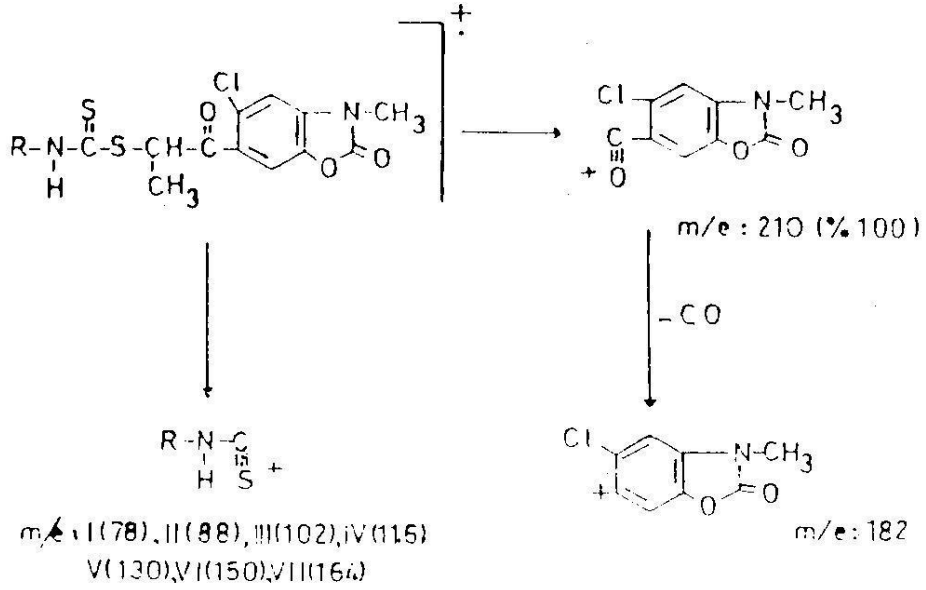
Results and Discussion

To synthesize compound, 3-methyl-5-chloro-6-(2-bromopropionyl)-2- benzoxazolinone and N-disubstituted dithiocarbamate derivatives prepared by the reaction of aliphatic amines with carbon disulphide and potassium hydroxide were heated in methanol (Scheme-1).

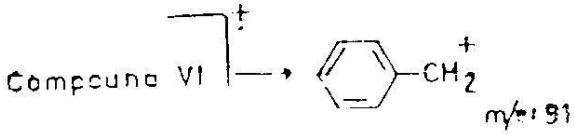
3-methyl-5-chloro-6-(2-bromopropionyl)-2-benzoxazolinone used in this reaction was prepared by heating 3-methyl-5-chloro-2- benzoxazolinone and 2-bromopropionic acid in polyphosphoric acid [15].

All spectral data are in accordance with literature [19-27]. In UV spectrum, intensive absorption bands can be seen about 280 and 245 nm. All compounds exhibited the characteristic bands of their respective chromophores. In IR spectrum, C=O streching (lactam), C=O streching (ketone), C=S streching and C-H bending vibration bands are at expected positions. In NMR spectrum, protons in structure correspond to the chemical shift and integral values. The protons in N-CH_3 group have been seen approximately at 3.35 ppm in all compounds. H^7 and H^4 protons of benzoxazolinone ring are between 7.50 and 7.80 ppm. In mass spectrum, molecular ion peak were not seen in compounds IV, VI, VII. The base peaks of compound I, II, III, IV, V, VI are at m/z: 210. The fragmentation can be explained as follows (Scheme-2).





The base peak of compound VI formed at m/z : 91 due to tropilium formation (Scheme-3).



In addition, since all compounds have one chlorine atom, M + 2 ion peaks (m/z: 212, 184) are observed in their spectra. The elemental analysis of the compounds synthesized also confirmed their structure.

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