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SYNTHESIS OF SCHIFF BASES BASED ON BENZYLIDENE AND DIMETHYLCARBAMOYLMETHYLENE DERIVATIVES AND THEIR MICROBIOLOGICAL EVALUATIONS

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ABSTRACT

Four biologically active Schiff bases of benzylidene derivatives (6-9), namely, 4-Hydroxy-3-methoxy-benzylidene-phenylamine (6), 4-Hydroxy-3-methoxy-benzylidene-2-methyl-phenylamine(7), 4-Hydroxy-3-methoxy-benzylidene-4-methyl-phenylamine (8) and 4-Hydroxy-3-methoxy-benzylidene-imino-phenylamine (9), were prepared. Also, with the aim of developing new compounds contain both of phenoxy and amide groups together in their skeletons in intent to possess a broad biological effects, six novel dimethylcarbamoylmethylene derivatives (15-20), namely, [N-(2-methylphenyl)]-carbamoylmethylene-2-methyl-phenoxide(15), [N-(2-methylphenyl)]-carbamoyl-methylene-3-methyl-phenoxide (16), [N-(2-methylphenyl)]-carbamoyl- methylene-4-methyl-phenoxide (17), [N-(4-methylphenyl)]-carbamoylmethylene-2-methyl-phenoxide (18), [N-(4-methyl-phenyl)]-carbamoylmethylene-3-methyl-phenoxide (19) and [N-(4-methylphenyl)]-carbamoylmethylene-4-methyl-phenoxide (20), were synthesized. All compounds were purified by crystallization and recrystallization resulted in pure crystals. The physical constants, melting points, R_f values in different solvents systems were recorded. Both of IR spectrum and MS spectrum of these compounds were in full agreement with their assigned chemical structures.

The bacteriological efficiency of the new synthesized compounds was evaluated on three microorganisms, one of useful bacteria (*Sarcina urea*), one pathogenic bacteria (*Staphylococcus aureus*) and one useful yeast (*Saccharomyces cerevisiea*).

The Propagation of the *S. cerevisiea* was accelerated by both of (9) and (6), which mean that the absence of the substitution at ortho- or para- positions with methyl group has good effect on the yeast. On the other hand, the survival of the *S. cerevisiea* was inhibited by both of (7) and (8). Also, the Proliferation of the *S. aureus* was inhibited by (9), (6) and (7). This means that these compounds could be used as germicidals. Both of (6) and (9), which have no methyl group at ortho- or para-positions were activated the proliferation of the *S. urea.* Both of (8) and (7) were also activated the *S. urea* but in ratio less than the two latter compounds.

The survival of the *S. urea* was activated by all of the dimethylcarbamoyl-methylene derivatives (15-20), specially the compounds (16), (17) and (18). Also, the propagation of the yeast, *S. cerevisiea,* was also activated by all the derivatives (15-20) and the maximum activation were observed by each of (15), (16) and (18). These derivatives (15-20) were represented a highly germicidal effect towards the pathogenic bacteria *S. aureus.* Both of (15) and (19) reflect the maximum germicidal activity. It could be concluded that the substitution by the methyl group in the phenyl ring (anilide) at para- or ortho-positions with the substitution in the phenoxide ring at ortho- or meta-positions by methyl group, which represented by (18), (16) and (15), were reflected the highly biological activation. This means that these compounds could be use to accelerate the stimulation of the nitrogen fixers bacteria group in their growth media and also accelerate the fermentation process in the industrial processes.

INTRODUCTION

The *Sarcina urea* is one of the asymbiotic nitrogen fixation bacteria, which play an important role in enhancing legumes production. *Saccharomyces cerevisiea* play an important role in the initial stages of organic matter decomposition in the surrounding media Bab`Eva & Chernov (1982). The pathogenic bacteria, *Staphylococcus aureus*, cause wound infections; it also causes toxic shock syndrome, brain abscesses, acute endocarditis, food poisoning, scaled skin syndrome, carbuncles, impetigo and other skin conditions (Brickner et al., 1996 and Heritage *et al.*, 1996). Clearly, there is an urgent need for the discovery and development of new agents effective against the emerging and currently problematic gram-positive pathogens (Silver & Bostian, 1993). This growing problem of multidrug resistance has recently rekindled interest in the search for new antibiotic structural classes that inhibit or kill by novel mechanisms.

Aldehydes and ketones react with primary amines to form Schiff bases (they are also called aldimines, azomethines and imines). Schiff bases are important in many biochemical reactions because many enzymes use an $-NH_2$ group of an amino acid to react with an aldehyde or ketone to form an imine linkage. Schiff bases are well known to have pronounced biological activities. Their ready synthesis and myriad properties have contributed greatly to their popularity and to the study of many biological systems.

New series of 4-fluorobenzyl benzylidene thiazolidineones, 3-aryl-5-benzylidene-2-phenyl-4-imidazolone, N-benzyl-N-phenoxyethylamines, 1-(2,4-dichlorophenoxyacetyl)-2-(2-hydroxybenzylidene/naphthylidene) hydrazin, new Schiff bases bearing methoxy and azo groups and N-benzyl(heptyl)-3-benzyl(heptyl)amino-4-hydroxybutanamides, were synthesized by Oda *et al.* (1994), Oza *et al.* (1994), Halve & Goyal,.(1996), Metri *et al.* (1996) and Tlekhusezh *et al.* (1996). The titled compounds showed acceptable both of antibacterial against *S. aureus, Escherichi coli* and *Candida albicans* and other bacteria and also have antifungal activities

The synthesis of new (N-heteroaryl) arylmethanamines and their Schiff bases and the antimicrobial activities against *Candida sp.* and antiviral activities against some plant pathogenic fungi were reported by Fioravanti *et al.* (1997). The antibacterial of Schiff base 1-(3,4-dihydroxybenzylidene)thio-semicarbazone was studied by Zhu *et al.* (1997). The 5-oximidazolyl-aminopyrazole-4-carboxaldehydes reacted with arylamines to afford corresponding Schiff bases which exhibited significant antibacterial and antifungal activities (Biplab *et al.,* 1998). The synthesis of new chloro-benzylidene substituted derivatives and their antimicrobial activity were reported by Kiek-Kononowick *et al.* (1998). It had the best antibacterial activities against *S. aureus*.

The amide derivatives were widely synthesized due to their highly biological activities. They were utilized as anticonvulsant, antiobesity drugs, antitumour and they also useful in therapeutic treatment of epilepsy and Alzheimer's disease (Safwat *et al.*, 1988 and John, 1993).

The synthesis of the phenoxy and amide derivatives which showed significant antibacterial, antifungal and insecticidal activity properties were synthesized by Kumaran & Kulkarni (1994), Oda *et al.* (1994), Brickner *et al.* (1996), Tlekhusezh *et al.* (1996) and Kamel *et al.* (1997).

EL-Malt *et al.* (1997) synthesized some [N-(substituted phenyl)]-carbamoylmethylene-substituted phenoxide, which have aphicidial activity against the *Brevicornye brassicae L*. and in the same time, the predator *Coccinella undecimpunctata aegyptiaca* was more tolerant to these compounds. Certain aromatic amides of 4-[(2-naphthalenyl)-methyl] benzamides derivatives were prepared by Agnes *et al.* (1998), which showed good pesticidal activity. EL-Malt *et al.* (1998) synthesized five promethean compounds of [N-(substituted-phenyl)]-carbamoylmethylene-1-naphthoxide derivatives, which either activated or inhibited the *S. cerevisiea*, also some of them could be served as a germicidal agent against the pathogenic bacteria *S. aureus*. Eighteen new hydrazones have been synthesized by Ersan *et al.* (1998), which possessed significant moderate activity against *Candida* species. Peter *et al.* (1998) prepared the N-phenyl-□-fluoroalkenamides, which showed good pesticidal activities particularly against insects and acarids. Five cyanoamidino-substituted thiocarbamides were synthesized by Tayade (1998), and all compounds were effective against *S. aureus.* Shirodkar & Gandhi (1998) synthesized certain pharmacologically active 3-aryl-5-mercapto-4-(4-pyridinecarboxamido)-4H-1,2,4 triazoles derivative. Certain novel oxadiazole and arylacetamide derivatives were synthesized by Oza *et al.* (1998), which showed moderate antimycobacterial activity against *Mycobacterium tuberculosi*s.

The present investigation was carried out with the aim of developing new benzylidene derivatives (6-9) and dimethylcarbamoylmethylene derivatives (15-20) which contain both of phenoxy and amide groups together in their skeletons in intent to possess a broad biological effects.

Four Schiff bases of benzylidene derivatives (6-9), namely, 4-Hydroxy-3-methoxy-benzylidene-phenylamine (6), 4-Hydroxy-3-methoxy-benzylidene-2-methyl-phenylamine (7), 4-Hydroxy-3-methoxy-benzylidene-4-methyl-phenylamine (8) and 4-Hydroxy-3-methoxy-benzylidene-imino-phenylamine (9), were synthesized. Also, six novel dimethylcarbamoyl-methylene derivatives (15-20), namely, [N-(2-methylphenyl)]-carbamoylmethylene-2-methyl-phenoxide (15), [N-(2-methylphenyl)]-carbamoyl-methylene-3-methyl-phenoxide (16), [N-(2-methylphenyl)]-carbamoylmethylene-4-methyl-phenoxide (17), [N-(4-methylphenyl)]-carbamoylmethylene-2-methyl-phenoxide (18), [N-(4-methyl-phenyl)]-carbamoylmethylene-3-methyl-phenoxide (19) and [N-(4-methylphenyl)]-carbamoyl-methylene-4-methyl-phenoxide (20), were also synthesized.

For screening the biological activity of the synthesized compounds, three microorganisms, one of useful bacteria, *Sarcina urea*, which fix the nitrogen in the soil asymbiotically, one pathogenic bacteria, *Staphylococcus aureus*, and one of the useful yeast, *Saccharomyces cerevisiea*, which use for the industrial fermentation processes, were used.

MATERIALS AND METHODS

General:-

All chemicals were analytical grade and were used without further purification. All solvents used were distilled before used. Thin Layer Chromatography was fulfilled on Merck aluminium sheets silica gel 60_{F254}. Development of chromatograms was accomplished in two solvent systems: cyclohexane : petroleum ether : isopropanol (2:1:1 v/v/v) [SS1] and 1,4-dioxane : hexane (1:2 v/v) [SS2]. Spots were visualised by exposing to short-wavelength (Desag 245 /366 nm) ultraviolet light. Compounds showed fluorescent blue spots. Melting points were determined in open capillary tubes. Mass spectra were determined on a Finnigan spectrophotometer, Model SSQ 7000 single-focusing instrument with a chamber voltage of 70eV. Infrared spectrum were measured in KBr and recorded on an FT/ IR-300E Jasco Spectrometer. It was performed by Central scientific services unit of the National Research Centre, Giza, Egypt.

The Schiff bases of Benzylidene derivatives (6-9):

The benzylidene derivatives (6-9) were prepared according to

Fioravanti et al. (1997).

4-Hydroxy-3-methoxy-benzylidene-phenylamine (6):

The aniline (2) (4.65 g; 4.55 ml, 0.05 mol.) was added to the solution of 2-methoxy-4-formyl-phenol (1) (7.6 g, 0.05 mol) in 30 ml of absolute methanol. The mixture was heated in a water bath for 6 hours. The reaction mixture was concentrated. The solid separated was filtered, washed with cooled distilled water and dried. The solid was recrystallized in absolute ethanol, to afford 9.88 g (87%) of pure (6), m.p. (147-148°C), R_f, 0.76, for SS1.

4-Hydroxy-3-methoxy-benzylidene-2-methyl-phenylamine (7):

To a solution of 10.7 g (10.72 ml, 0.1 mol) of 2-methyl-aniline (3) in 30 ml of absolute methanol, 15.2 g (0.1 mol) of (1) was added and stirred well. The reaction mixture was heated and refluxed for 6 hours in a water bath. After cooling, the reaction mixture was concentrated. The precipitate was washed many times with cooled distilled water until free from colors and dried. The crude product was recrystallized from a mixture of ethanol and petroleum ether (2:1,v/v), this gave 19.28g(80%) of (7), m.p. (78-79°C), R_f, 0.73, for SS1.

4-Hydroxy-3-methoxy-benzylidene-4-methyl-phenylamine (8):

To a solution of 4-methyl-aniline (4) (10.7g, 0.1 mol.) in 30 ml of absolute ethanol, 15.2 g (0.1 mol.) of (1) was added. The reaction mixture was heated and refluxed for 6 hours and then treated and worked up as described above, affording 22.41g (93% yield) of (8), m.p.(110-111°C), R_f, 0.74, for SS1.

4-Hydroxy-3-methoxy-benzylidene-imino-phenylamine (9):

The phenylhydrazine (5) (10.81g; 9.85 ml, 0.1 mol.) was added to the solution of 15.2g (0.1 mol) of (1) in 30 ml of anhydrous ethanol. The mixture was heated in a water bath for 6 hr. After cooling to ambient temperature the

reaction was concentrated, washed with cooled distilled water and dried. The resulted solid was recrystallized in absolute ethanol, to afford 21.54 g (89%) of pure (9) ,m.p. (103-104°C), R_f, 0.72, for SS1.

□-chloroacetyl chloride:

□-chloroacetyl chloride was prepared according to EL-Malt and Hafez (1996).

[N-(substituted-methylphenyl)]-carbamoylmethylene chloride derivatives (10-11):

They were prepared according to EL-Malt *et al.* (1997). Recrystallisation in absolute ethanol afforded 3.11g (85%) of [N-(2-methyl-phenyl)]-carbamoyl-methylene chloride (10) (m.p. 105-106°) and 3.26g (89%) of [N-(4-methyl-phenyl)]-carbamoylmethylene chloride (11) (m.p. 155-156°).

Preparation of potassium polyethylene glycolate:

Potassium polyethylene glycolate (KPEG) was prepared according to EL-Malt *et al.* (1998).

The Dimethylcarbamoylmethylene derivatives (15-20):

The Dimethylcarbamoylmethylene derivatives (15-20) were prepared according to EL-Malt *et al.* (1997).

[N-(2-methylphenyl)]-carbamoylmethylene-2-methyl-phenoxide (15):

The [N-(2-methylphenyl)]-carbamoylmethylene chloride (10) (1.01 g ;0.006 mol.) in 25 ml of cyclohexane was added to the solution of 10 ml of KPEG and 0.648 g (0.63 ml, 0.006 mol) of 2-methyl-phenol (12). The mixture was heated at 75°C for 3.5 hr. After cooling to ambient temperature the reaction was acidified with 10% hydrochloric acid, the organic phase was washed with distilled water and dried upon filter-paper. The white solid was recrystallized in absolute ethanol, to afford 1.19 g (88%) of (15) (m.p. 84-85°C). R_f, 0.72 and 0.61 for SS1 and SS2 respectively.

[N-(2-methylphenyl)]-carbamoylmethylene-3-methyl-phenoxide (16):

To a solution of 10 ml of KPEG, 0.648 g (0.62 ml, 0.006 mol) of 3-methyl-phenol (13) was added and stirred well. To this mixture 1.01 g (0.006 mol) of (10) in a 25 ml of cyclohexane was added and the reaction mixture was stirred vigorously. The reaction mixture was heated and refluxed for 3 hours. After cooling, hydrochloric acid 10% was added slowly to neutralized the reaction mixture. The precipitate was washed many times with distilled water until free from acid and dried. The crude product was recrystallized from a mixture of benzene and petroleum ether (2:1, v/v), this gave 1.26 g (93%) of pure (16) (m.p. 74-75°C). R_f, 0.69 and 0.58 for SS1 and SS2 respectively.

[N-(2-methylphenyl)]-carbamoylmethylene-4-methyl-phenoxide (17):

The (10) (1.01 g;0.006 mol.) in 25 ml of cyclohexane was added to the solution of 10 ml of KPEG and 0.648 g (0.006 mol) of 4-methyl-phenol (14). The mixture was heated at 75°C for 3 hr. After cooling to ambient temperature the reaction was acidified with 10% hydrochloric acid, the organic phase was

washed with distilled water and dried. The white solid was recrystallized in absolute ethanol, to afford 1.11g (82%) of (17) (m.p. 86-87°C). R_f, 0.68 and 0.57 for SS1 and SS2, respectively.

[N-(4-methylphenyl)]-carbamoylmethylene-2-methyl-phenoxide (18):

To a solution of 10 ml of KPEG, 0.648 g (0.63 ml, 0.006 mol) of 2-methyl-phenol (12) was added and stirred vigorously. To this mixture 1.01 g (0.006 mol) of [N-(4-methylphenyl)]-carbamoylmethylene chloride (11) in a 25 ml of cyclohexane was added and the reaction mixture was stirred. The reaction mixture was heated and refluxed for 3 hours, allowed to cool to room temperature, then acidified with 10% hydrochloric acid, washed with redistilled water and dried. The residue was recrystallized in absolute ethanol, to afford analytically pure material 1.15 g (85%) of (18) (m.p. 80-81°C). R_f, 0.70 and 0.59 for SS1 and SS2 respectively.

[N-(4-methylphenyl)]-carbamoylmethylene-3-methyl-phenoxide (19):

To a solution of (11) (1.01 g,0.006 mol.) in 25 ml of cyclohexane, 0.648 g (0.62 ml, 0.006 mol.) of 3-methyl-phenol (13) was added and 10 ml of KPEG. The reaction mixture was heated and refluxed for 2.5 hours and then treated and worked up as described above, affording 1.16 g (86% yield) of (19) (m.p. 68-69°C). R_f, 0.67 and 0.56 for SS1 and SS2 respectively.

[N-(4-methylphenyl)]-carbamoylmethylene-4-methyl-phenoxide (20):

To a solution of 10 ml of KPEG, 0.648 g (0.006 mol) of 4-methyl-phenol (14) was added and stirred vigorously. To this mixture 1.01 g (0.006 mol) of (11) in a 25 ml of cyclohexane was added and the reaction mixture was stirred. The reaction mixture was heated and refluxed for 3 hours, allowed to cool to room temperature, then acidified with 10% hydrochloric acid, washed with redistilled water and dried upon filter-paper. The residue was recrystallized in absolute ethanol, to afford analytically pure material 1.23 g (91%) of (20) (m.p. 95-96°C). R_f, 0.71 and 0.60 for SS1 and SS2 respectively.

Bioassay for the bacteriological activity:-

Microorganisms:

The microorganisms (*Sarcina urea, Saccharomyces cerevisiea* and *Staphylococcus aureus*) used in this investigation were obtained from the Microbiological Resources Center (Cairo MIRCEN), Faculty of Agriculture, Ain Shams University, Cairo, Egypt.

Media:

All bacteria species were grown in nutrient glucose agar medium (Dowson, 1957).

Bacteriological evaluations (Disk Diffusion Assay):

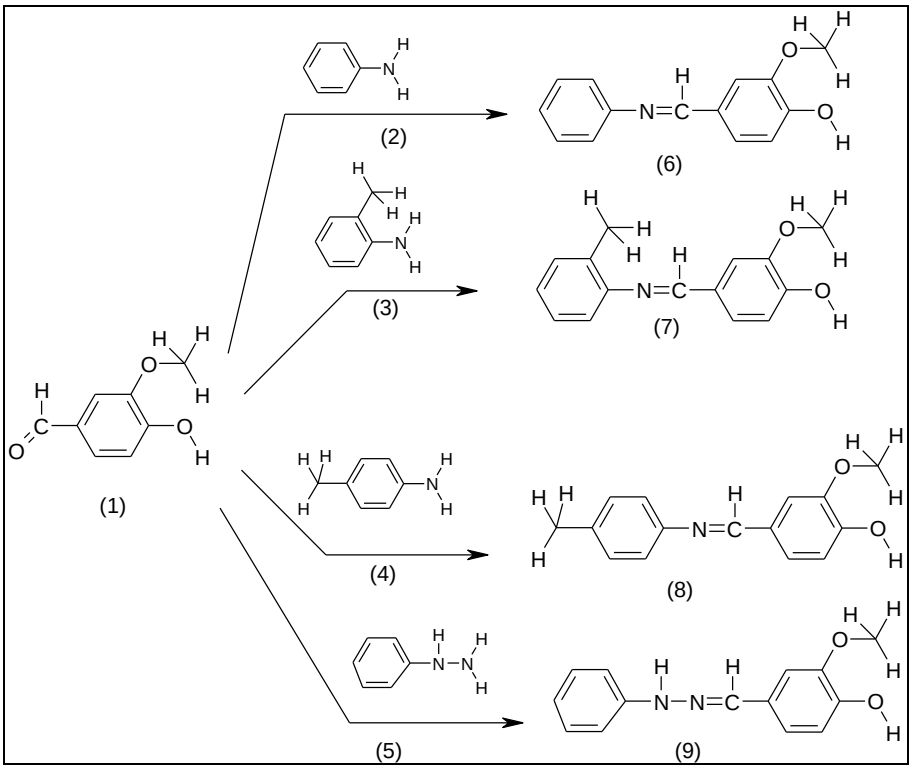
Filter paper disks (Whatman No.1, 9 mm diameter) containing aliquots of 50 □l of the prepared compounds solutions (40 mg/ml acetone) were applied to the surface of agar plates which were previously inoculated with standard amounts of 48 hr old culture of test organisms (Thornberry,1950 and Jain and Kar,1971). The plates were kept in a refrigerator at 4°C for 4 hr. to

permit the diffusion of the compounds in the agar, before organisms were sufficiently dense to allow for accurate measurement of the zone inhibition or activation. These plates were then incubated at 28°C and the diameter of the inhibition zone (mm) was recorded after 24-48 hr. Control disks were impregnated with 50 □l of acetone.

RESULTS AND DISCUSSION

The Schiff bases of Benzylidene derivatives (6-9):

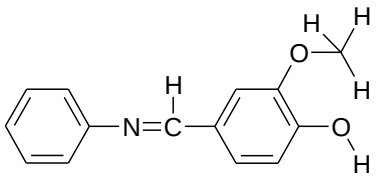
By the reaction of 2-methoxy-4-formyl-phenol (1) with the aniline (2), 2-methyl-aniline (3), 4-methylaniline (4) and phenylhydrazine (5) in the presence of alcohole, four compounds of the benzylidene derivatives (6-9) were synthesized (Scheme 1).



Scheme (1)

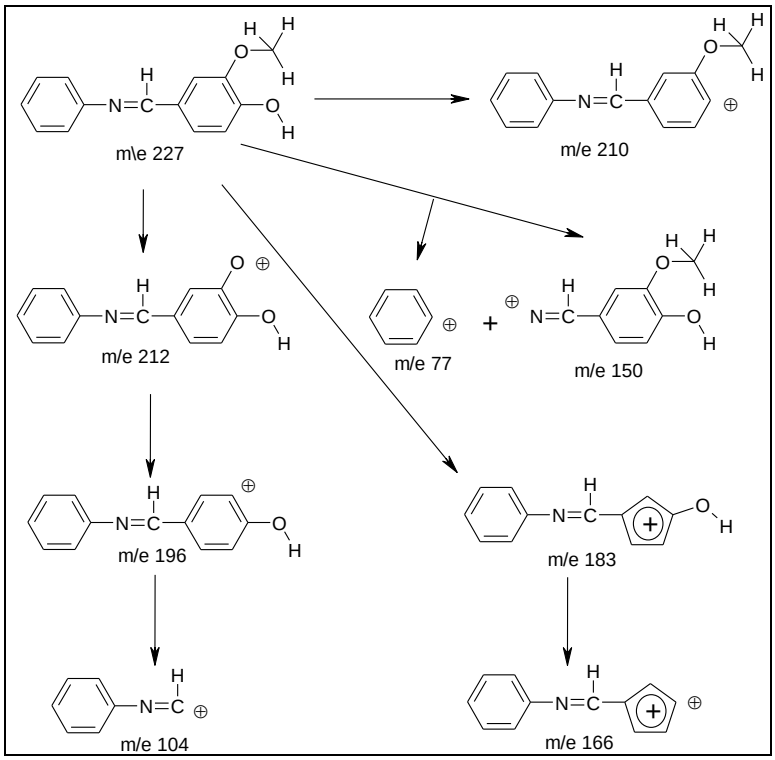
4-Hydroxy-3-methoxy-benzylidene-phenylamine (6):

The Infrared spectrum (I.R.) of the prepared and pure (6) showed, ν_{max} (KBr) 1585 (-C=C-), 904 (=C-H), 2950 (Ar-H), 1621 (-N=CH-), 742 & 811 (5&2 *adjacent* Ar-*H*), 3100 (*Intramolecular* OH) and 1352 Cm-1 (C-N) (Fig. 1).



(6)

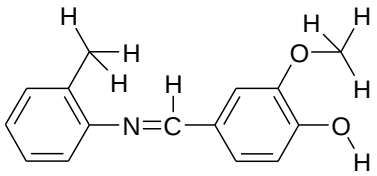
The Mass Spectra showed a molecular ion peak ($M^{\oplus}$) at m/e 227 corresponding to the molecular formula $C_{14}H_{13}NO_2$ (Figure 2). The compound gave the fragments peaks at m/e 210 [$M^{\oplus}$-17 (OH)], m/e 212 [$M^{\oplus}$-15 (CH_3)], m/e 196 [$M^{\oplus}$-31 (O+CH_3)], m/e 104 [$M^{\oplus}$-123 (O+CH_3+OH+Ph)], m/e 183 [$M^{\oplus}$-44 (CH_3+CO)], m/e 166 [$M^{\oplus}$-61 (CH_3+CO+OH)], m/e 150 [$M^{\oplus}$-77 (Ph)] and m/e 77 [$M^{\oplus}$-150 (OCH_3+OH+N+CH+Ph)]. This fragmentation can be illustrated as follows in scheme (2).



Scheme (2)

4-Hydroxy-3-methoxy-benzylidene-2-methyl-phenylamine (7):

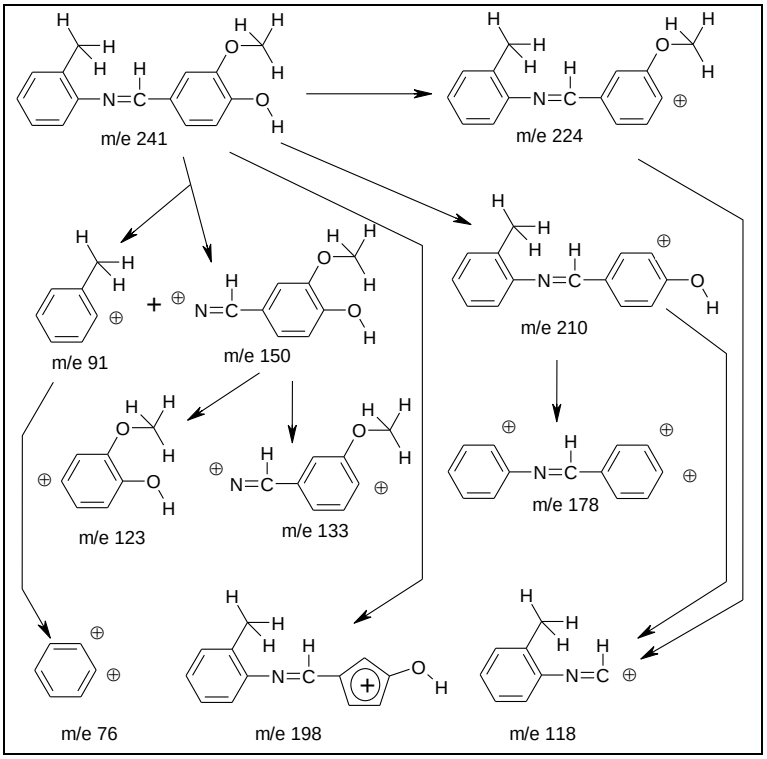
The Infrared spectrum (I.R.) of the prepared and pure (7) showed, ν_{max} (KBr) 1585 (-C=C-), 943 (=C-H), 3000 (Ar-H), 1623 (-N=CH-), 761 & 820 (4&2 *adjacent* Ar-*H*), 3050 (*Intramolecular* OH), 2950 (CH_3) and 1360 Cm-1 (C-N) (Fig. 1).



(7)

The Mass Spectra showed a molecular ion peak ($M^{\oplus}$) at m/e 241 corresponding to the molecular formula $C_{15}H_{15}NO_2$ (Figure 2). The compound gave the fragments peaks at m/e 224 [$M^{\oplus}$-17(OH)], m/e 118 [$M^{\oplus}$-123 (OH+OCH_3+Ph)], m/e 210 [$M^{\oplus}$-31 (OCH_3)], m/e 178 [$M^{\oplus}$-63 (OCH_3+OH+CH_3], m/e 91 [$M^{\oplus}$-150 (Ph+OCH_3+OH+N+CH)], m/e 150 [$M^{\oplus}$-91 (Ph+CH_3)], m/e 133 [$M^{\oplus}$-108 (Ph+CH_3+OH)], m/e 123 [$M^{\oplus}$-118 (Ph+CH_3+N+CH], m/e 76 [$M^{\oplus}$-165 (CH_3+N+CH+Ph+OCH_3+OH)] and m/e 198 [$M^{\oplus}$-43 (CH_3+CO)]. (Scheme 3).

Figure (1): The I.R. spectrum of the substituted Schiff bases derivatives (6-9)

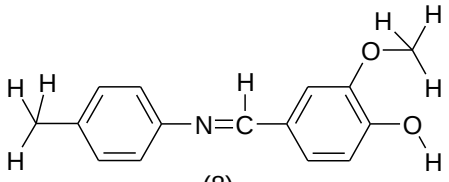


Scheme (3)

4-Hydroxy-3-methoxy-benzylidene-4-methyl-phenylamine (8):

The I.R. of the prepared and pure (8) showed, ν_{max} (KBr) 1589 (-C=C-), 937 (=C-H), 3050 (Ar-H), 1623 (-N=CH-), 865 (2 *adjacent* Ar-*H*), 3100 (*Intramolecular* OH), 2938 (CH_3) and 1350 Cm-1 (C-N) (Fig. 1).

The Mass Spectra showed a molecular ion peak ($M^{\oplus}$) at m/e 241 corresponding to the molecular formula $C_{15}H_{15}NO_2$.



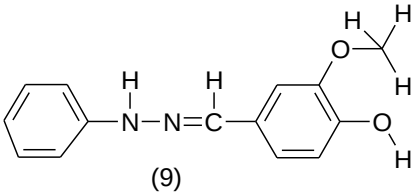
(8)

The Mass Spectra showed a molecular ion peak ($M^{\oplus}$) at m/e 241 corresponding to the molecular formula $C_{15}H_{15}NO_2$ (Figure 2). The compound gave the fragments peaks at m/e 224 [$M^{\oplus}$-17(OH)], m/e 118 [$M^{\oplus}$-123 (OH+OCH_3+Ph)], m/e 210 [$M^{\oplus}$-31 (OCH_3)], m/e 178 [$M^{\oplus}$-63 (OCH_3+OH+CH_3], m/e 91 [$M^{\oplus}$-150 (Ph+OCH_3+OH+N+CH)], m/e 150 [$M^{\oplus}$-91 (Ph+CH_3)], m/e 133 [$M^{\oplus}$-108 (Ph+CH_3+OH)], m/e 123 [$M^{\oplus}$-118 (Ph+CH_3+N+CH], m/e 76 [$M^{\oplus}$-165 (CH_3+N+CH+Ph+OCH_3+OH)] and m/e 198 [$M^{\oplus}$-43 (CH_3+CO)]. (Scheme 3).

Figure (2): The M.S. spectrum of the substituted Schiff bases derivatives (6-9)

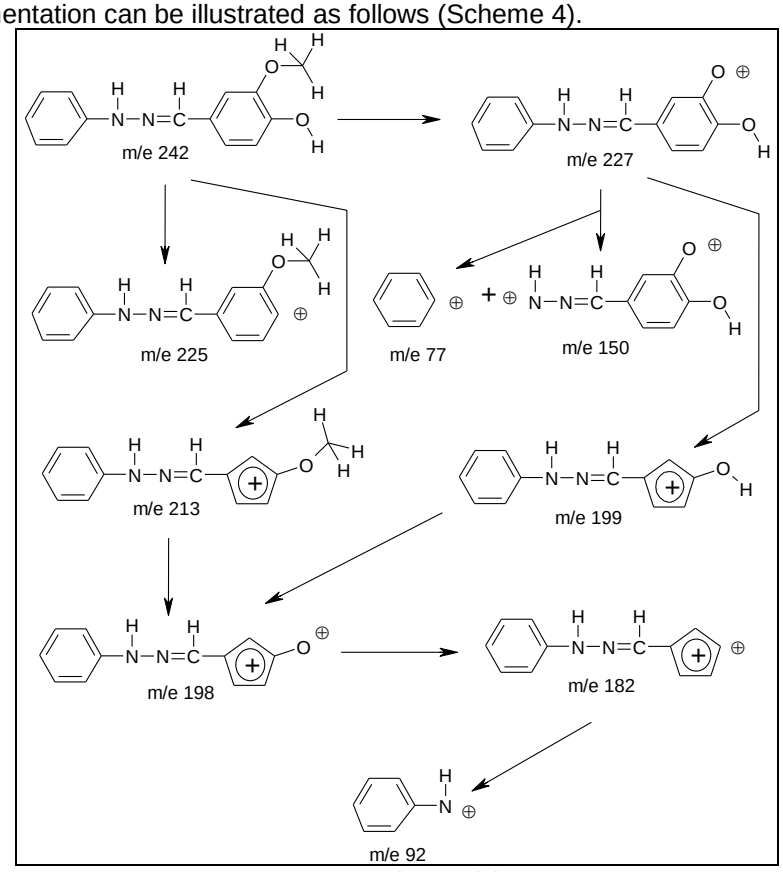
4-Hydroxy-3-methoxy-benzylidene-imino-phenylamine (9):

The I.R of the prepared and pure (9) showed, ν_{max} (KBr) 1589 (-C=C-), 914 (=C-H), 3050 (Ar-H), 1600 (-N=CH-), 3450 (Ar-NH-R), 748 & 860 (5&2 *adjacent* Ar-*H*), 3313 (*Intramolecular* OH), 2950 (CH_3) and 1351 Cm-1 (C-N) (Fig. 1).



(9)

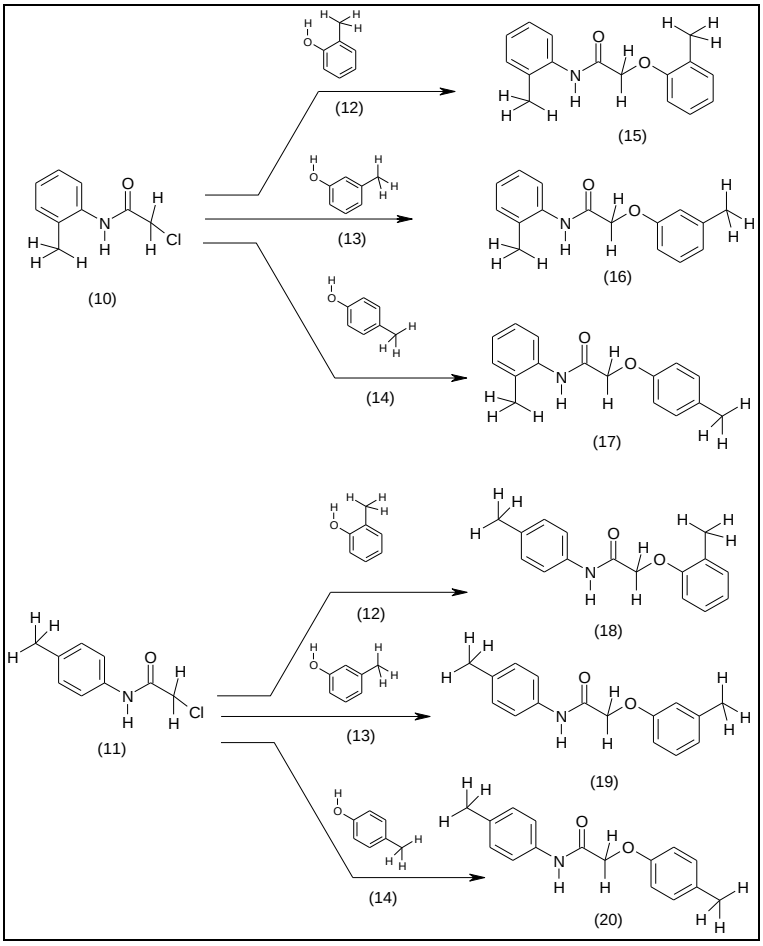
The Mass Spectra (MS) showed a molecular ion peak ($M^{\oplus}$) at m/e 242 corresponding to the molecular formula $C_{14}H_{14}N_2O_2$ (Figure 2). The compound gave the fragments peaks at m/e 227 [$M^{\oplus}$-15 (CH_3)], m/e 77 [$M^{\oplus}$-165 (Ph+OCH_3+OH+CH+N+NH)], m/e 150 [$M^{\oplus}$-92 (Ph+CH_3)], m/e 199 [$M^{\oplus}$-43 (CH_3+CO)], m/e 213 [$M^{\oplus}$-29 (H+CO)], m/e 198 [$M^{\oplus}$-44 (H+CO+CH_3)], m/e182 [$M^{\oplus}$-60 (H+CO+CH_3+O)] and m/e 92 [$M^{\oplus}$-150 (Ph+OCH_3+OH+CH+N)]. This fragmentation can be illustrated as follows (Scheme 4).



Scheme (4)

The Dimethylcarbamoylmethylene derivatives (15-20):

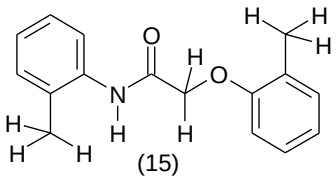
Six novel compounds of the Dimethylcarbamoylmethylene derivatives (15-50) were synthesized by the reaction of the [N-(substituted methylphenyl)]-carbamoylmethyl chloride (10-11) derivatives with the substitutted-methylphenol (12-14) in the presence of phase transfer catalysis. The synthesis steps were indicated in Scheme (5). The synthesis mechanism of carbamoylmethylene derivatives involves a nucleophilic backside attack of the phenolic ion (substituted-phenol derivatives) on the alkyl halide ([N-(substituted methylphenyl)]-carbamoylmethylene chloride).



Scheme (5)

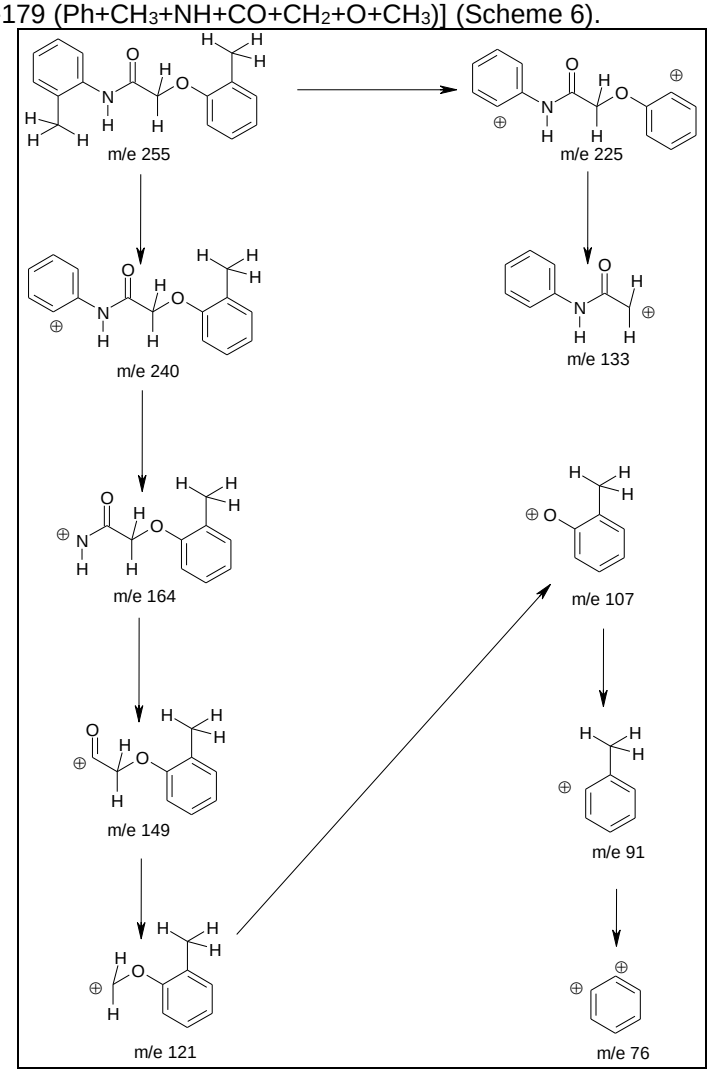
[N-(2-methylphenyl)]-carbamoylmethylene-2-methyl-phenoxide (15):

The I.R of the prepared and pure (15) showed, ν_{max} (KBr) 1589 (-C=C-), 862 (=C-H), 3025 (Ar-H), 3409 (-NH-), 1687 (-CO-), 1290 (C-N *aromatic*), 1457 (-CO-CH_2- *sym*. *stretching*), 757 (4 *adjacent* Ar-*H*) and 2906 Cm^{-1} (s) (CH_3) (Fig.3).



(15)

The Mass spectra represents a molecular ion peak ($M^{\oplus}$) at m/e 255 corresponding to the molecular formula $C_{16}H_{17}NO_2$. The compound gave the fragments peaks at m/e 240 [$M^{\oplus}$-15 (CH_3)], m/e 225 [$M^{\oplus}$-30 (CH_3+CH_3)], m/e 164 [$M^{\oplus}$-91 (Ph+CH_3)], m/e 149 [$M^{\oplus}$-106 (Ph+ CH_3+NH)], m/e 133 [$M^{\oplus}$-122 (CH_3+CH_3+O+Ph)], m/e 121 [$M^{\oplus}$-134(Ph+CH_3+NH+CO)], m/e 107 [$M^{\oplus}$-148 (Ph+CH_3+NH+CO+CH_2)], m/e 91 [$M^{\oplus}$-164 (Ph+CH_3+NH+CO+CH_2+O)] and m/e 76 [$M^{\oplus}$-179 (Ph+CH_3+NH+CO+CH_2+O+CH_3)] (Scheme 6).

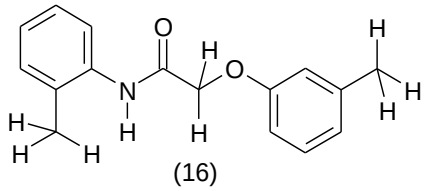


Scheme (6)

Figure (3): The I.R. spectrum of the Dimethylcarbamoylmethylene derivatives (15-20).

[N-(2-methylphenyl)]-carbamoylmethylene-3-methyl-phenoxide (16):

The I.R of the prepared and pure (16) showed, ν_{max} (KBr) 1587 (-C=C-), 937 (=C-H), 3048 (Ar-H), 3359 (-NH-), 1670 (-CO-), 1290 (C-N *aromatic*), 1415 (-CO-CH_2- *sym*. *stretching*), 819&757 (3&4 *adjacent* Ar-*H*) and 2915 Cm^{-1} (s) (CH_3) (Fig.3).

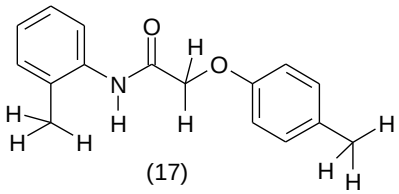


(16)

The Mass spectra (Fig. 4) represents a molecular ion peak ($M^{\oplus}$) at m/e 255 corresponding to the molecular formula $C_{16}H_{17}NO_2$. The compound gave the fragments peaks at m/e 240 [$M^{\oplus}$-15 (CH_3)], m/e 164 [$M^{\oplus}$-91 (Ph+CH_3)], m/e 149 [$M^{\oplus}$-106 (Ph+CH_3+NH)], m/e 121 [$M^{\oplus}$-134(Ph+CH_3+NH+CO)], m/e 225 [$M^{\oplus}$-30(CH_3+CH_3)], m/e 133 [$M^{\oplus}$-122(CH_3+CH_3+O+Ph)], m/e 107 [$M^{\oplus}$-148 (Ph+CH_3+NH+CO+CH_2)], m/e 91 [$M^{\oplus}$-164 (Ph+CH_3+NH+CO+CH_2+O)] and m/e 76 [$M^{\oplus}$-179 (Ph+CH_3+NH+CO+CH_2+O+CH_3)], respectively.

[N-(2-methylphenyl)]-carbamoylmethylene-4-methyl-phenoxide (17):

The I.R of the prepared and pure (17) showed, ν_{max} (KBr) 1589 (-C=C-), 939 (=C-H), 3100 (Ar-H), 3363 (-NH-), 1681 (-CO-), 1290 (C-N *aromatic*), 1400 (-CO-CH_2- *sym*. *stretching*), 819&752 (2&4 *adjacent* Ar-*H*) and 2910 Cm^{-1} (s) (CH_3) (Fig.3).

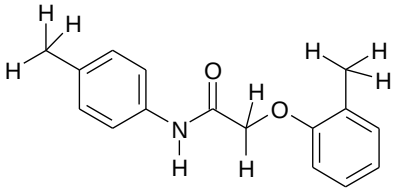


(17)

The Mass spectra (Fig. 4) represents a molecular ion peak ($M^{\oplus}$) at m/e 255 corresponding to the molecular formula $C_{16}H_{17}NO_2$. The compound gave the fragments peaks at m/e 240 [$M^{\oplus}$-15 (CH_3)], m/e 225 [$M^{\oplus}$-30 (CH_3+CH_3)], m/e 164 [$M^{\oplus}$-91 (Ph+CH_3)], m/e 149 [$M^{\oplus}$-106 (Ph+ CH_3+NH)], m/e 133 [$M^{\oplus}$-122 (CH_3+CH_3+O+Ph)], m/e 121 [$M^{\oplus}$-134(Ph+CH_3+NH+CO)], m/e 107 [$M^{\oplus}$-148 (Ph+CH_3+NH+CO+CH_2)], m/e 91 [$M^{\oplus}$-164 (Ph+CH_3+NH+CO+CH_2+O)] and m/e 76 [$M^{\oplus}$-179 (Ph+CH_3+NH+CO+CH_2+O+CH_3)], respectively.

[N-(4-methylphenyl)]-carbamoylmethylene-2-methyl-phenoxide (18):

The I.R of the prepared and pure (18) showed, ν_{max} (KBr) 1592 (-C=C-), 919 (=C-H), 3050 (Ar-H), 3353 (-NH-), 1670 (-CO-), 1292 (C-N *aromatic*), 1406 (-CO-CH_2- *sym*. *stretching*), 860&742 (2&4 *adjacent* Ar-*H*) and 2910 Cm^{-1} (s) (CH_3) (Fig.3).

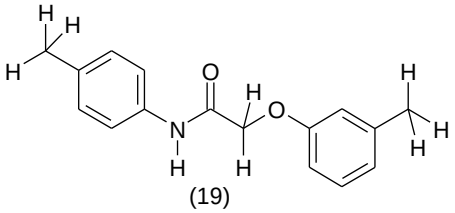


(18)

The Mass spectra represents a molecular ion peak ($M^{\oplus}$) at m/e 255 corresponding to the molecular formula $C_{16}H_{17}NO_2$. The compound gave the fragments peaks at m/e 240 [$M^{\oplus}$-15(CH_3)], m/e 164 [$M^{\oplus}$-91($Ph+CH_3$)], m/e 149 [$M^{\oplus}$-106($Ph+CH_3+NH$)], m/e 121 [$M^{\oplus}$-134($Ph+CH_3+NH+CO$)], m/e 225 [$M^{\oplus}$-30 (CH_3+CH_3)], m/e 133 [$M^{\oplus}$-122(CH_3+CH_3+O+Ph)], m/e 107 [$M^{\oplus}$-148 ($Ph+CH_3+NH+CO+CH_2$)], m/e 91 [$M^{\oplus}$-164($Ph+CH_3+NH+CO+CH_2+O$)] and m/e 76 [$M^{\oplus}$-179 ($Ph+CH_3+NH+CO+CH_2+O+CH_3$)], respectively (Fig.4).

[N-(4-methylphenyl)]-carbamoylmethylene-3-methyl-phenoxide (19):

The I.R of the prepared and pure (19) showed, ν_{max} (KBr) 1594 (-C=C-), 935 (=C-H), 3025 (Ar-H), 3351 (-NH-), 1673 (-CO-), 1290 (C-N *aromatic*), 1406(-CO-CH_2- *sym*. *stretching*), 821&779 (2&3 *adjacent* Ar-*H*) and 2911 Cm^{-1} (s) (CH_3) (Fig.3).

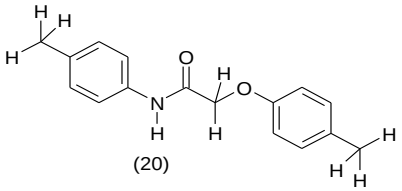


(19)

The Mass spectra (Fig 4) represents a molecular ion peak ($M^{\oplus}$) at m/e 255 corresponding to the molecular formula $C_{16}H_{17}NO_2$. The compound gave the fragments peaks at m/e 240 [$M^{\oplus}$-15(CH_3)], m/e 164 [$M^{\oplus}$-91($Ph+CH_3$)], m/e 149 [$M^{\oplus}$-106($Ph+CH_3+NH$)], m/e 121 [$M^{\oplus}$-134($Ph+CH_3+NH+CO$)], m/e 225 [$M^{\oplus}$-30(CH_3+CH_3)], m/e 133 [$M^{\oplus}$-122(CH_3+CH_3+O+Ph)], m/e 107 [$M^{\oplus}$-148($Ph+CH_3+NH+CO+CH_2$)], m/e 91 [$M^{\oplus}$-164($Ph+CH_3+NH+CO+CH_2+O$)] and m/e 76 [$M^{\oplus}$-179($Ph+CH_3+NH+CO+CH_2+O+CH_3$)], respectively.

[N-(4-methylphenyl)]-carbamoylmethylene-4-methyl-phenoxide (20):

The I.R of the prepared and pure (20) showed, ν_{max} (KBr) 1594 (-C=C-), 815 (=C-H), 3042 (Ar-H), 3328 (-NH-), 1670 (-CO-), 1290 (C-N *aromatic*), 1405 (-CO-CH_2- *sym*. *stretching*), 857 (2 *adjacent* Ar-*H*) and 2910 Cm^{-1} (s) (CH_3) (Fig.3).



(20)

Figure (4): The M.S. spectrum of the Dimethylcarbamoylmethylene derivatives (15-20).

The Mass spectra (Fig. 4) represents a molecular ion peak ($M^{\oplus}$) at m/e 255 corresponding to the molecular formula $C_{16}H_{17}NO_2$. The compound gave the fragments peaks at m/e 240 [$M^{\oplus}$-15 (CH_3)], m/e 225 [$M^{\oplus}$-30(CH_3+CH_3)], m/e 164 [$M^{\oplus}$-91 (Ph+CH_3)], m/e 149 [$M^{\oplus}$-106(Ph +CH_3+NH)], m/e 133 [$M^{\oplus}$-122 (CH_3+CH_3+O+Ph)], m/e 121 [$M^{\oplus}$-134 (Ph+CH_3+NH+CO)], m/e 107 [$M^{\oplus}$-148 (Ph+CH_3+NH+CO+CH_2)], m/e 91 [$M^{\oplus}$-164 (Ph+CH_3+NH+CO+CH_2+O)] and m/e 76 [$M^{\oplus}$-179 (Ph+CH_3+NH+CO+CH_2+O+CH_3)], respectively.

The Bacteriological evaluations:-

Evaluation of the biological activity of the various new synthesized chemical compounds towards some microorganisms (three gram positive strains) was performed by measuring the inhibition zone using disk diffusion assay as a parameter for antibacterial activity and also the activation zones. The results were indicated in Tables (1 and 2).

The Schiff bases of Benzylidene derivatives (6-9):

The Propagation of the *Saccharomyces cerevisiea* was accelerated by both of 4-Hydroxy-3-methoxy-benzylidene-imino-phenylamine (9) and the 4-Hydroxy-3-methoxy-benzylidene-phenylamine (6), which mean that the absence of the substitution at ortho- or para- positions with methyl group has good effect on the yeast. On the other hand, the survival of the *S. cerevisiea* was inhibited by both of 4-Hydroxy-3-methoxy-benzylidene-2-methyl-phenylamine (7) and 4-Hydroxy-3-methoxy-benzylidene-4-methyl-phenylamine (8).

Also, the Proliferation of the *Staphylococcus aureus* was inhibited by 4-Hydroxy-3-methoxy-benzylidene-imino-phenylamine (9), 4-Hydroxy-3-methoxy-benzylidene-phenylamine (6) and 4-Hydroxy-3-methoxy-benzylidene-2-methyl-phenylamine (7). This means that these compounds could be used as germicidals.

Table (1): Effect of benzylidene derivatives on certain microorganisms.

Microorganism	The tested synthesized compounds			
	6	7	8	9
Sarcina urea	++	+	+	++
Staphylococcus aureus	13*	16*	10*	19*
Saccharomyces cerevisiea	+++	15*	13*	+++

***= Width of inhibition zone (mm)** **+= Activation**

Both of 4-Hydroxy-3-methoxy-benzylidene-phenylamine (6) and 4-Hydroxy-3-methoxy-benzylidene-imino-phenylamine (9) which have no substitution with methyl group at ortho- or para-positions activated the proliferation of the *Sarcina urea.*

The 4-Hydroxy-3-methoxy-benzylidene-4-methyl-phenylamine (8) and 4-Hydroxy-3-methoxy-benzylidene-2-methyl-phenylamine (7) also activated the *Sarcina urea* but in ratio less than the two latter compounds.

Dimethylcarbamoylmethylene derivatives:-

In respect to the asymbiotic nitrogen fixers bacteria, the survival of the *Sarcina urea* was activated by all of the synthesized dimethylcarbamoyl-methylene derivatives. The highly activation was carried out by [N-(2-methylphenyl)]-carbamoylmethylene-3-methyl-phenoxide (16), [N-(2-methylphenyl)]-carbamoylmethylene-4-methyl-phenoxide) (17) and [N-(4-methylphenyl)]-carbamoylmethylene-2-methyl-phenoxide (18).

The propagation of the yeast, *Saccharomyces cerevisiea,* was also activated by all the carbamoylmethylene phenoxide derivatives. The maximum activation was observed by both of [N-(2-methylphenyl)]-carbamoylmethylene-3-methyl-phenoxide (16) and [N-(4-methylphenyl)]-carbamoylmethylene-2-methyl-phenoxide (18).

Table (2): Effect of substituted dimethylcarbamoylmethylene derivatives on certain microorganisms.

Microorganism	**The tested synthesized compounds**					
	15	16	17	18	19	20
Sarcina urea	+	++	++	++	+	+
Staphylococcus aureus	10*	7*	6*	8*	10*	8*
Saccharomyces cerevisiea	++	++	+	++	+	+

***= Width of inhibition zone (mm)** **+= Activation**

All the carbamoylmethylene phenoxide derivatives were represented by a highly germicidal effect towards the pathogenic bacteria *Staphylococcus aureus.* Both of [N-(2-methylphenyl)]-carbamoylmethylene-2-methyl-phenoxide (15) and [N-(4-methylphenyl)]-carbamoylmethylene-3-methyl-phenoxide (19) reflected the maximum germicidal activity.

It could be concluded that the substitution by the methyl group in the phenyl ring (anilide) at para- or ortho-positions with the substitution in the phenoxide ring at ortho-, meta- or para-position by methyl group, which represented by [N-(4-methylphenyl)]-carbamoylmethylene-2-methyl-phenoxide (18), [N-(2-methylphenyl)]-carbamoylmethylene-2-methyl-phenoxide) (15) and [N-(2-methylphenyl)]-carbamoylmethylene-3-methyl-phenoxide (16) were reflected the highly biological activation. This means that it could be use these compounds to accelerate the stimulation of the nitrogen fixers bacteria group in its growth media and also accelerate the fermentation process in the industrial processes.

Summarizing the considered results of these new compounds. It could be concluded that (16), (17) and (18) compounds could be use to accelerate the stimulation of the nitrogen fixers bacteria group (*Sarcina urea*)in its growth media. Also, it could be recommended to mix these compounds with the inoculum which mixed with the seeds before planting. Each of the (15), (16) and (18) compounds could be used to enhanced the propagation of the *Saccharomyces cerevisiea.* In addition, (7) and (8), could be used to stop or inhibit the fermentation process in some manufacture systems required that.

The compounds (7) and (9) could be served as a germicidal agents against the pathogenic bacteria *Staphylococcus aureus.*

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تخليق بعض قواعد شف المشتقة من البنزاميد و كذلك مشتقات الدامثايل كرباموبل ميثيلين وتقييم تأثيرها ميكروبيولوجياً

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تم تخليق أربعة مركبات من Schiff bases من البنزايلدين (9-6) هي: 4-هيدروكسي-3-ميثوكسي-بنزايلدين-فينايل امين (6) ،4-هيدروكسي-3-ميثوكسي-بنزايلدين-2-ميثايل-فينايل امين (7) ؛ 4-هيدروكسي-3-ميثوكسي-بنزايلدين-4-ميثايل-فينايل امين (8) ،4-هيدروكسي-3-ميثوكسي-بنزايلدين-آزو-فينايل امين (9). كما هدفت الدراسة إلى تخليق مركبات جديدة تحتوى على كل من مجموعتي الفينوكسي والأميد معا في نفس السلسلة المخلقة بهدف زيادة نشاطها وفاعليتها وتأثيرها الحيوي، وتم تخليق ستة مشتقات من [ن-(مستبدل ميثايل فينايل)]-كرباموبل ميثيلين-فينوكسيد (20-15)، وهي: [ن-(2-ميثايل فينايل)]-كرباموبل ميثيلين-2-ميثيل-فينوكسيد (15) ،[ن-(2-ميثايل فينايل)]-كرباموبل ميثيلين-3-ميثيل-فينوكسيد (16)، [ن-(2-ميثايل فينايل)]-كرباموبل ميثيلين-4-ميثيل-فينوكسيد (17) ، [ن-(4-ميثايل فينايل)]-كرباموبل ميثيلين-2-ميثيل-فينوكسيد (18) ، [ن-(4-ميثايل فينايل)]-كرباموبل ميثيلين-3-ميثيل-فينوكسيد (19) ، [ن-(4-ميثايل فينايل)]-كرباموبل ميثيلين-4-ميثيل-فينوكسيد (20).جميع المركبات المحضرة تم تنقيتها بطرق البلورة وأعاده البلورة ،وبعد الحصول على المركبات في صورة بلورات نقية ، أمكن تقدير ثوابتها الطبيعية مثل درجة الانصهار و قيم ال R_f في نظم مذيبات مختلفة، كما أمكن التعرف عليها وإثبات تركيبها الكيميائي بواسطة التحليل الطيفي بالأشعة تحت الحمراء و طيف الكتلة.

تم دراسة التقييم البيولوجي لتأثير تلك المركبات على الكائنات الحية الدقيقة، أستخدم ثلاثة أنواع مختلفة، نوع من البكتريا النافعة هي *Sarcina urea* وهى من البكتريا المثبتة للنتروجين لاتكافليا ، وكذلك نوع من البكتريا الممرضة هي *Staphylococcus aureus* ، ونوع مفيد من الخمائر هي *Saccharomyces cerevisiea* التى لها الكثير من الاستخدامات الصناعية. وتم قياس تأثير المركبات المحضرة عيها عن طريق قياس مدى تنشيطها أو تثبيطها لنموات تلك الكائنات الحية الدقيقة باستخدام طريقة ال Disk diffusion assay.

بدراسة التأثير البيولوجي لها على ال *S. cerevisiea* وجد أن نموات الخميرة زادت بدرجة كبيرة خاصة مع المركبان (9) و (6)-مما يعنى أن غياب الاستبدال على الوضع أورثو أو بارا بالميثايل يعطى تأثير منشط جيد. من ناحية أخرى – فقد حدث تثبيط لنمو الخميرة مع كل من المركبان (7) و (8). تم حدوث تثبيط شديد لنموات البكتريا الممرضة بواسطة كل من المركبات: (9), (6) و (7). يمكن القول بأن يمكن استخدام تلك المركبات كمبيدات جرثومية. كل من المركبان: (6) و (9) واللذان يحتويان على استبدال على الوضع بارا بالميثايل أو وجود ذرة هيدروجين في نفس الوضع دون وجود استبدالات أخرى أعطى تأثير منشط جيد لنمو بكتريا *S. urea* وهى من البكتريا المثبتة للنتروجين لاتكافليا في التربة. المركبان : (8) و (7) –نشطا نمو بكتريا *S. urea* و لكن بدرجة اقل من المركبان السابقان.

تم دراسة النشاط البيولوجي لمركبات مشتقات الكرباموبل فينوكسيد على البكتريا النافعة هي *S. urea* ، وأظهرت جميع المركبات تنشيط كبير لنمو تلك البكتريا. أكثر تنشيط سجل كان لكل من (16) , (17) و (18). كما أظهرت دراسة التأثير البيولوجي لها على الخمائر وهى *S. cerevisiea* أنها نشطت النموات. كان اكثر تنشيط لوحظ لكل من(15) و (16) و (18). جميع مشتقات الكرباموبل فينوكسيد أظهرت فعاليتها كمبيدات جرثومية تجاه *S. aureus* وهى بكتريا ممرضة، كان أقصى تأثير ابادى لكل من (15) و (19).

من النتائج السابقة يمكن التكهن بالعلاقة بين التركيب الكيميائي للمركبات المحضرة ونشاطها البيولوجي، فقد وجد أن وجد الاستبدالات من مجاميع الميثيل على حلقة الأنيليد في الوضع بارا أو الوضع أرثو جنبا إلى جنب مع وجود استبدالات بمجاميع الميثايل على الأوضاع ميتا أو أرثو على حلقة الفينوكسى- يعطى أعلى نشاط بيولوجي -وهذا ممثل بالمركبات (18) , (16) و (15) . من جميع النتائج السابقة لهذه المركبات الجديدة المحضرة – يمكن استخلاص أنه يمكن استخدام كل من المركبات (16) , (17) و (18) تنشيط نموات البكتريا المثبتة للنتروجين لتكافليا في التربة (*S. urea*) وذلك في بيئات النمو الخاصة بها ومضاعفة أعدادها. أيضاً, يمكن القول بأن يمن خلط تلك المركبات مع اللقاحات البكتيرية للبذور التى سيتم زراعتها. كل من (16) و (18) يمكن استخدامها لتحسين نمو الخميرة (*S. cerevisiea*). المركبات (15), (19) يمكن استخدامها كمبيدات جرثومية تجاه *S. aureus* وهى بكتريا ممرضة.