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Synthesis & Characterization of Saccharine Derivatives

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Abstract
The formation of saccharine derivatives [1-15] is obtained by reaction of saccharine with carbonyl –containing compounds (ketone, aldehyde , ester , di ester) or with amide compounds (alkyl di amine , Aryl di amine), some of steps involved mannich reaction and aldol reaction to synthesis of new open chain compounds which represented (amides , alkene , sulphone derivatives , amines derivatives, esters , ethers) .
All newly synthesized compounds [1-16] were characterized by (elemental analysis , FT.IR , H.NMR)-spectroscopic analysis & melting points .
Keyword: saccharine , sulphone, aldol reaction , alkylation , mannich reaction.

Introduction :
Saccharin is a synthetic organic compound that testes hundreds of times sweeter that sucrose & is used as a calorie free sweetener ,saccharine has the chemical formula $C_7H_5NO_3S$, white crystalline powder which is not soluble in water , stable when heated , even in the presence of acids , also does not react chemically with other food ingredients [1-3] , & stores , it is available commercially in three forms : the acid & the sodium , & the calcium salts .
Saccharine has several names (benzo sulfinide ,ortho –benzo sulfimide , 3 – benzisothiazolinone -1 , 1-dioxide), while trade names include (saxin , sweet , sucrosa , sakarin , Necta sweet)[4,5] .
Most of sulfur compounds have wide ranging pharmacological applications [6,7] , also sulfone compounds & saccharine used starting material in the chemical synthesis of a rang of drugs & other chemical compounds[8-14] .

Experimental:
- ❖ All chemicals used were supplied from BDH & Merck - company , purity 99.98 % .
- ❖ All measurements were carried out by :

1 – Melting points : electro thermal 9300 , melting point engineering LTD , U.K
2 – FT . IR spectra : fourrier transform infrared shimadzu 8300 – (FT . IR), KBr disc was performed by CO.S.Q.Iraq .
3 – H.NMR-spectra and (C.H.N) – analysis : in Malaysia .

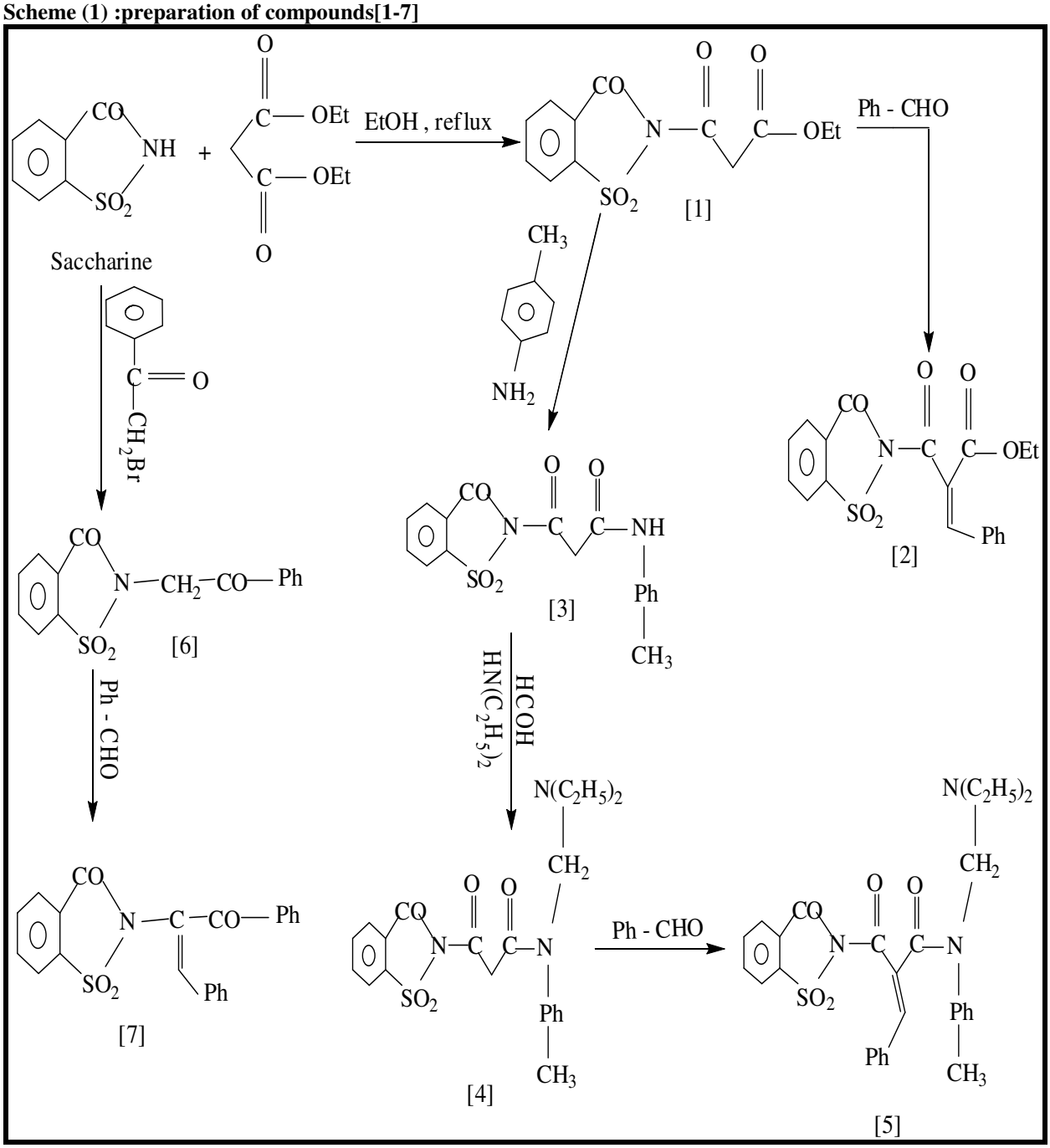
Synthesis of compounds [1-5] :
A mixture of saccharine (0.1mole , 18 g) with diethyl malonoate (0.1 mole , 16 g) were heated in presence of ethanol for (3hrs) to produce compound[1] , which (0.1 mole , 29 g) reacts with one of {benzaldehyde (0.1 mole , 10 g), P-methyl aniline (0.1 mole , 10 g)} to give compounds [2,3] respectively . (0.1mole , 35 g) from compound [3] treated with formaldehyde (0.1 mole , 3 g) & (0.1 mole , 7g) of diethyl amine by mannich reaction to produce compound [4] ,which (0.1 mole , 44 g) reacts with benzaldehyde (0.1 mole , 10 g) to yield compound [5] .

Synthesis of compounds [6-9] :
(0.1 mole , 18 g) of saccharine reacts with 2 –phenyl 1 –bromo ethanone (0.1 mole , 19.8 g) to produce compound [6] , which reacts with benzaldehyde in presence of ethanol to yield compound [7] , while (0.1 mole , 18 g) of saccharine reacts with ethyl ethanoate (0.1 mole , 8 g) by refluxing for (4hrs) in presence of ethanol to yield compound [8] , which (0.1 mole , 22.5 g) reacts with (0.1 mole , 10.6 g) of benzaldehyde in presence of ethanol to give compound [9] .

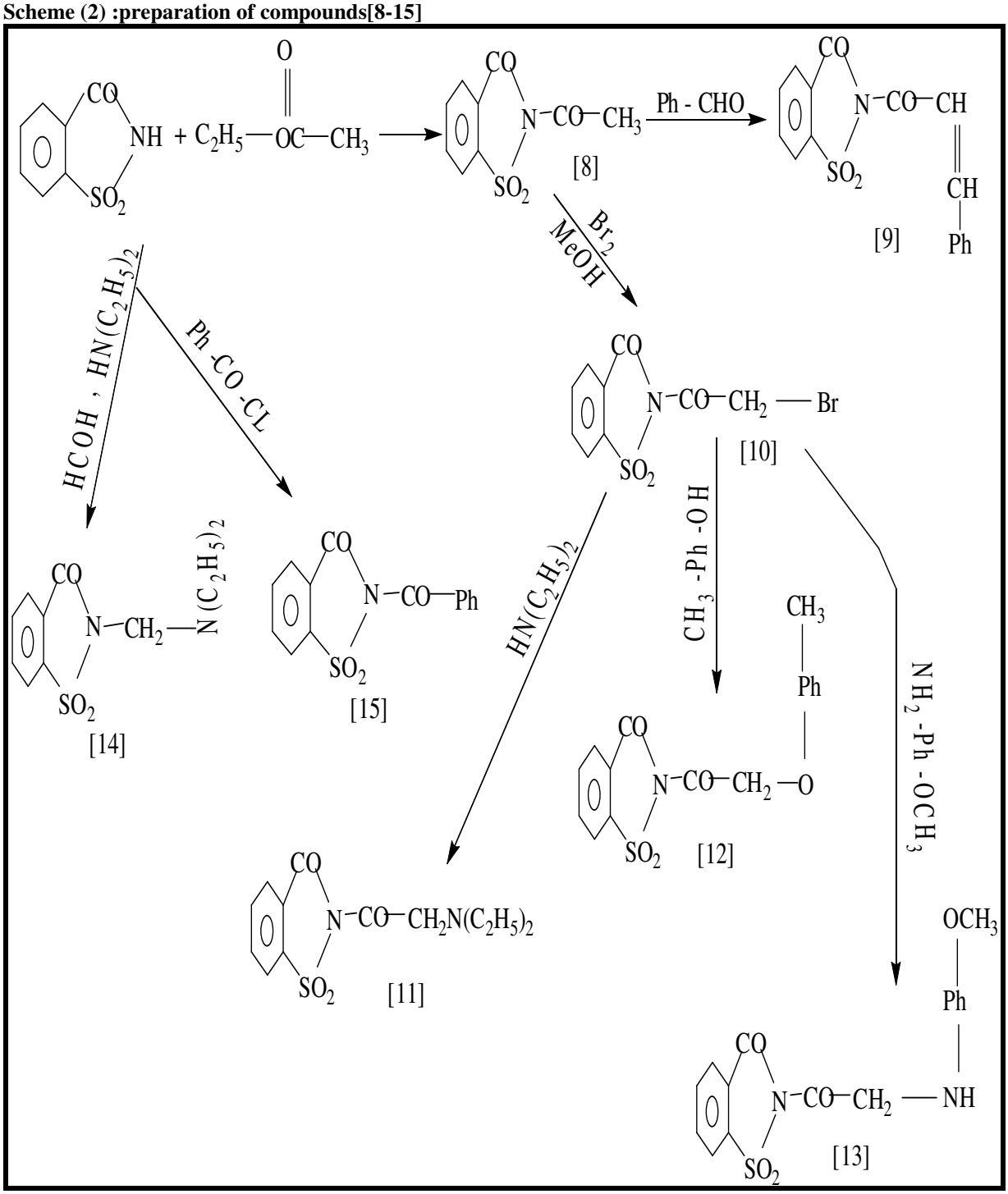
Synthesis of compounds [10-13] :
A mixture of (0.1 mole , 22 g) of compound [8] with (0.1 mole , 10 g) of bromine were reacted to yield compound [10] , which (0.1 mole , 27 g) reacts with one of { diethyl amine (0.1 mole , 7.3 g) , P –methyl phenol (0.1 mole , 10 g) , P –methoxy aniline (0.1 mole , 12 g)} in presence of ethanol to produce compounds [11,12,13] respectively .

Synthesis of compounds [14.15] :
A mixtyre of saccharine (0.1 mole , 18 g) with one of {benzoyl chloride (0.1 mole , 14 g) , diethyl amine (0.1 mole , 7.3 g)} were reacted with reflux for (5hrs) to yield compounds [14,15] respectively .

Scheme (1) :preparation of compounds[1-7]



Scheme (2) :preparation of compounds[8-15]



Results & Discussion :

This study describes the synthesis of new saccharine derivatives [1-15] via reaction of saccharine with different compounds to yield target compounds .

The formatted compounds [1-15] have been characterized by their melting points & spectroscopic methods (FT.IR , H.NMR , (C.H.N)-analysis) .

Their FT.IR –spectrum , table (1) & figure (1-4) showed an absorption bands at (1685-1698) cm^{-1} due to (-CO-N-) carbonyl of amide in compounds [1-5 , 8, 10-13 , 15] , & bands at (1735,1755)cm^{-1} due to (-CO-Eth)carbonyl of ester [15] in compounds [1-2] , absorption bands at (3070 -3085)due to (CH=CH) alkene . in compounds [2,5, 7-9] , absorption bands at (2920-2960) cm^{-1} due to (CH) aliphatic in compounds [1-6 , 8 , 10-14] , absorption bands at (1160-1140)cm^{-1} due to (C–O–C) ether in compounds [12,13] , absorption bands at (1720)cm^{-1} due to (-CO-) carbonyl of ketone in compound [6] .

And other bands[14,15] are summarized in table (1) . .

Their H.NMR –spectra showed signals at ∫ (4.2 - 4.85)due to (COOEt) ester in compounds [1,2] , signals at ∫ (10.2 -10 -12) due to protons of amide (N-CO-CH_2) in compounds [3-5, 8 , 10-13] , signals at ∫ (3.1 – 3.88) due to protons of amine ($N(C_2H_5)_2$) in compounds [4,5,11,14] , signal at ∫ (2.15 – 2.69) due to (C=CH) alkene in compounds [2,5,7,9] , & others signals of functional groups[14,15] show in the following , table (2).

Their (C.H.N) –analysis & melting points , it was found from compared the calculated data with experimentally data of these compounds , the results were compactable , the data of analysis , M.F & melting points are listed in table (3) .

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Table (1): FT.IR –data (cm^{-1}) of compounds [1-15].

Comp. No.	$IR_{(KBr)}$ (Importance Groups)
[1]	((-CO-N)) carbonyl of amide :1698 ,(SO_2–N) sulphone : 1340 , (-CO-O-)carbonyl of ester : 1755 , (CH) aliphatic : 2940 .
[2]	(-CO-N) amide :1698, (SO_2)sulphone :1325 ,(-CO-O-)ester :1735 ,(C=CH) alkene:3080 .
[3]	((-CO-N)) amide : 1690, (SO_2) sulphone : 1350 , (CH) aliphatic : 2940 .
[4]	((-CO-N)) amide : 1695, (SO_2) sulphone : 1355 , (CH) aliphatic : 2960 .
[5]	(-CO-N)amide :1690, (SO_2)sulphone :1377 ,(C=CH) alkene :3070 ,(CH)aliphatic : 2920 .
[6]	((-CO-N)) amide : 1690, (SO_2) sulphone : 1350 (-CO-) carbonyl of ketone : 1720 .
[7]	((-CO-N)) amide : 1685, (SO_2) sulphone : 1355 , (C=CH) alkene :3080 .
[8]	((-CO-N)) amide : 1688, (SO_2) sulphone : 1350 , (CH) aliphatic : 2960 .
[9]	((-CO-N)) amide : 1686, (SO_2) sulphone : 1330 , (CH=CH) alkene :3085 .
[10]	(C-Br) :870 , ((-CO-N)) amide : 1695 , (SO_2) sulphone : 1355 .
[11]	(-CO-N) amide : 1686, (SO_2) sulphone : 1344 .
[12]	(C–O–C) ether :1133 ,(-CO-N)amide :1690, (SO_2) sulphone :1350 ,(CH) aliphatic :2985 .
[13]	(C–O–C) ether :1140 ,(NH) amine :3320 ,(-CO-N) amide:1695 , (SO_2) sulphone :1355 .
[14]	(CH) aliphatic :2955 , (-CO-N) amide : 1696 , (SO_2) sulphone : 1360 .
[15]	(-CO-N) amide : 1695 , (SO_2) sulphone : 1378 .

Table (2) : H.NMR –data (∫ $_{PPm}$) of compounds [1-15] .

Comp. No.	H.NMR (Important peaks)
[1]	4.2 (2H , CH_2 –COO) protons of ester two signals 4.5 , 4.85 (-$COOCH_2CH_3$) protons of ester .
[2]	2.15 (1H , C=CH) proton of alkene , two signals 4.18 , 4.26 ($COOC_2H_5$) protons of ester .
[3]	10.2 ((CH_2-CO-N-)) protons of amide , 10.8 (-CO-NH-) proton of amide , 1.03 (-CH_3) protons of methyl group .
[4]	10.3 (-N-CO-CH_2) protons of amide , 1.4 (CH_3) protons of methyl group , 3.1 (N –CH_2 –N) , 3.8 (-$N(C_2H_5)_2$).
[5]	2.69 (C=CH) proton o alkene , 0.85 (CH_3) , 3.55 (N –CH_2 –N) , 3.82 ($N(C_2H_5)_2$).
[6]	12.4 (CH_2-CO-) protons of ketone .
[7]	2.3 (C=CH) proton of alkene .
[8]	10.03 ((-N-CO-CH_2) protons of amide .
[9]	2.44 (-CO-CH=CH) proton of chalgone .
[10]	2.9 (CH_2 –Br) .
[11]	10.12 (CH_2-CO-N-) amide , 3.851 ($N(C_2H_5)_2$).
[12]	3.99 (CH_2 –O-) protons of ether , 0.95 (CH_3) .
[13]	3.5 (CH_2NH) protons of amine , 3.91 (-OCH_3) protons of ether .
[14]	3.88 (N –CH_2 –N) , 3.37 ($N(C_2H_5)_2$).
[15]	7.24 (Ph-) protons of phenyl group .

Table (3) : physical properties & (C.H.N) –analysis of compounds [1-15] .

Comp. No.	M.F	M.P (C°)	%	Name of compounds	Calc. / Found.		
					C%	H%	N%
[1]	$C_{12}H_{11}NO_6S$	170	88	3-saccharine-3–one–ethyl propanoate .	48.48 48.39	3.703 3.673	4.713 4.662
[2]	$C_{19}H_{15}NO_6S$	183	86	3-saccharine-3–one–2-styrene –ethyl propanoate .	59.22 59.18	3.896 3.801	3.636 3.571
[3]	$C_{17}H_{14}N_2O_5S$	189	89	3-saccharine-3–one–1–(4–methyl aniline) propanone .	56.98 56.91	3.91 3.86	7.821 7.721
[4]	$C_{22}H_{25}N_3O_5S$	200	85	3-saccharine-3–one–N–diethyl–N –methyl amine–N–(4–methyl benzene) –propane amide .	59.59 59.51	5.643 5.553	9.48 9.391
[5]	$C_{29}H_{27}N_3O_5S$	215	88	3-saccharine-3–one–N–diethy–N –methyl amine–N–(4–methyl benzene)–2–styrene–propane amide .	65.78 65.72	5.103 5.99	7.939 7.873
[6]	$C_{15}H_{11}NO_4S$	178	89	2–saccharine-1–phenyl ethanone .	59.8 59.6	3.654 3.616	4.651 4.542
[7]	$C_{22}H_{15}NO_4S$	192	88	2–saccharine-2–styrene-1–phenyl ethanone .	67.86 67.81	3.856 3.774	3.598 3.524
[8]	$C_9H_7NO_4S$	168	86	Acetyl saccharine .	48.0 47.96	3.111 3.09	6.222 6.198
[9]	$C_{16}H_{11}NO_4S$	190	87	3–phenyl-1–saccharine-1–one-2 –propene .	61.34 61.28	3.514 3.443	4.472 4.433
[10]	$C_9H_6NO_4SBr$	196	87	2–saccharine-2–one–ethyl bromide .	38.98 38.89	2.166 2.09	5.054 5.00
[11]	$C_{13}H_{16}N_2O_4S$	212	85	2–saccharine–N ,N –diethyl amine ethanone .	52.70 52.64	5.405 5.331	9.459 9.411
[12]	$C_{16}H_{13}NO_5S$	225	89	2–saccharine-1–(4–methyl phenyl) acrtyl ether .	58.06 58.00	3.927 3.812	4.22 4.16
[13]	$C_{16}H_{14}N_2O_5S$	237	86	2–saccharine-1–(anidine) ethanone .	55.49 55.41	8.092 8.031	4.04 4.00
[14]	$C_{12}H_{16}N_2O_3S$	166	88	1–saccharine–N ,N–diethyl amine methylene .	53.73 53.69	5.97 5.913	10.447 10.39
[15]	$C_{14}H_{10}NO_4S$	160	87	Benzoyl saccharine .	58.33 58.24	3.472 3.42	4.861 4.792

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