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SYNTHESIS OF SOME SACCHARIN DERIVATIVES OF EXPECTED BIOLOGICAL ACTIVITY BASED ON N-(SACCHARINYL)-ACETIC ACID AZIDE

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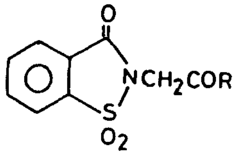
Azide 3 was prepared from the corresponding acid chloride 2. The base catalyzed decomposition with aromatic amines, aminobenzoic acids and/or hydrazines afforded the corresponding anilides 4a–f and/or hydrazides 5a–d via azido group displacement. Compounds 5c and 5d were refluxed in Ac_2O to give 1,3,4-oxadiazole derivatives 6a and 6b. Lewis acid catalyzed decomposition of azide 3 with anhyd. $AlCl_3$ in dry aromatic substrates gave the corresponding ketones 7a–c. Also, the reaction of azide 3 with glycine gave 9.

Key words: Saccharin, acetic acid azide.

The reported pharmaceutical properties[1-4] (anxiolytic agent, enzyme inhibitors and analgesic agent) of saccharin and its derivatives promoted my interest for the synthesis of saccharin derivatives containing CH_2CONH, $CH_2NHCONH$, CH_2CO, oxadiazole and imidazole moieties.

In the present investigation N-(saccharinyl)-acetic acid azide (3) was prepared by the action of aq. NaN_3 in acetone on N-(saccharinyl)-acetic acid chloride (2).

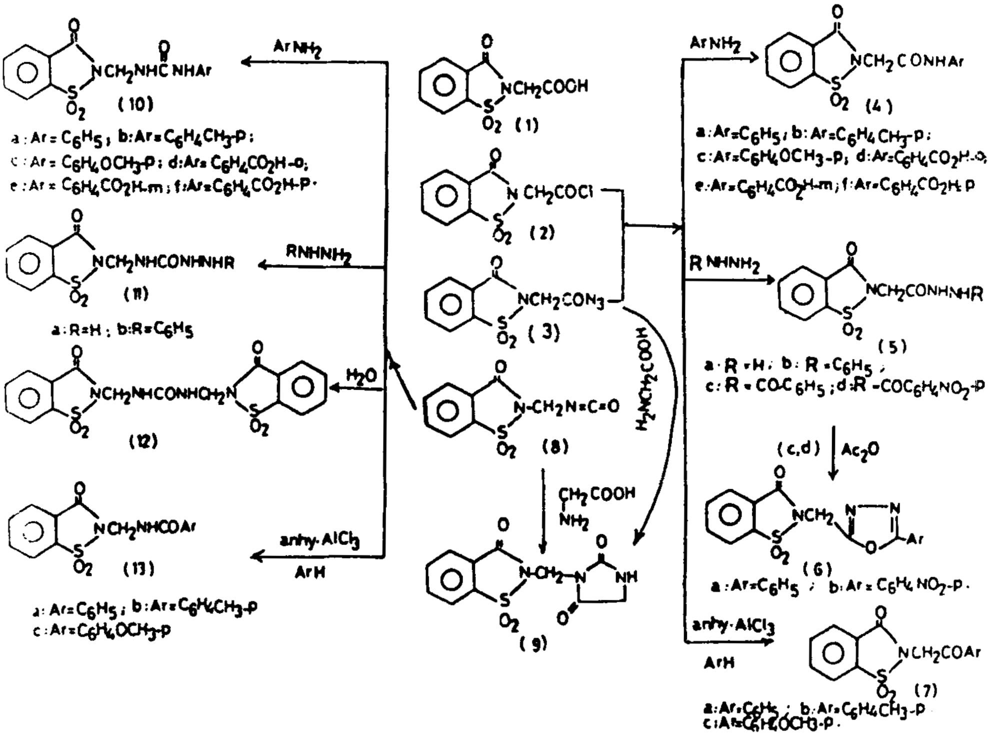


1: R = OH, 2: R = Cl, 3: R = N_3

The structure of 3 was supported by IR spectra which showed νN_3 at 2170 cm^{-1}, νCO of acid azide at 1710 cm^{-1}, νSO_2 at (1320 cm^{-1} and 1120 cm^{-1}) and νCO of cyclic imide at 1730 cm^{-1}.

The base-catalyzed decomposition reaction of 3 with aromatic amines and/or aminobenzoic acids afforded the corresponding N-(saccharinyl)-acetanilides (4a–f). Similarly the title azide 3 underwent base catalyzed decomposition with hydrazine hydrate, phenylhydrazine, benzoylhydrazine and *p*-nitrobenzoyl hydrazine to give the corresponding N-(saccharinyl)-acetic acid hydrazides (5a–d). The structures of 4a–f and 5a–d were established by (i) Direct comparison (m.m.p) with authentic specimens prepared by the reaction of N-(saccharinyl)-acetyl chloride (2) with the above mentioned aromatic amines, aminobenzoic acids and/or hydrazines. This showed that the reaction took place via the azide group displacement. (ii) IR spectra revealed absorption bands at 3350–3200 cm^{-1} (νNH), 1680–1640 cm^{-1} (νCO of anilides and/or hydrazides), 1750–1730 cm^{-1} (νCO of cyclic imide), 1350–1300 cm^{-1} and

1160–1120 cm^{-1} (νSO_2). (iii) Mass spectra: m/z (relative abundance %) compound 4b, 330 (11.5) (M^+), 197 (3.7), 196 (24), 183 (16.2), 141 (7.6), 133 (31.8), 105 (37.4), 91 (27.9), 77 (66), 65 (13.7), 57 (100), 51 (23.11); compound 4e, 360 (3.8) (M^+), 197 (6), 183 (52), 168 (6.7), 163 (15), 140 (8.9), 119 (45.7), 104 (39.9), 91 (47), 76 (100), 65 (28.3), 57 (51); compound 5b, 331 (5.6) (M^+), 259 (3.1), 196 (4.7), 135 (6.6), 120 (8.9), 119 (9.4), 105 (7.5), 91 (18.5), 77 (54.9), 76 (19.5), 65 (16.2), 57 (100).



Moreover, it was found that when compound 5c and/or 5d was refluxed with acetic anhydride, it was easily cyclized to give 2-phenyl-5-(N-methyl saccharin)-1,3,4-oxadiazole (6a) and 2-(*p*-nitrophenyl)-5-(N-methyl saccharin)-1,3,4-oxadiazole (6b) respectively. The structure of 6a and 6b was supported by: (i) IR spectra which revealed absorption bands at 1740–1730 cm^{-1} (νCO of cyclic imide), 1320–1310 cm^{-1} and 1150–1130 cm^{-1} (νSO_2), 1630–1620 cm^{-1} (νCN) and 1070–1060 cm^{-1} (νC—O—C of ether). (ii) Mass spectra: m/z (relative abundance %) compound 6a, 341 (0.01) (M^+), 285 (0.02), 224 (0.24), 206 (0.1), 196 (0.84), 183 (0.14), 182 (0.1), 168 (0.5), 141 (7), 117 (0.44), 105 (100), 77 (42); compound 6b, 386 (0.13) (M^+), 224 (6.64), 206 (1.77), 196 (8.9), 183 (7.4), 182 (4.01), 162 (1.4), 150 (100), 141 (1.14), 140 (1.1), 134 (7.5), 104 (56.65), 77 (14.95). In accordance with ions produced under electron impact, the fragmentation of compounds 6a and 6b was generally found to follow the general fragmentation pattern anticipated for oxadiazoles.[5–8]

Lewis acid-catalyzed decomposition of azide 3 with anhyd. $AlCl_3$ in aromatic substrates was found to give the corresponding aroyl-N-methyl-saccharin (7a–c). The structure of 7 was established by: (i) Direct comparison (m.m.p) with authentic specimens prepared by the reaction of 2 with the same aromatic substrates in the presence of anhyd. $AlCl_3$. (ii) IR spectra displayed the bands attributed to the presence of CO of ketone at (1710 cm^{-1}), CO of cyclic imide at (1730 cm^{-1}) and SO_2 at (1320 and 1110 cm^{-1}). (iii) Mass spectra of 7b gave molecular ion at m/z (relative abundance %) 315 (0.2) (M^+), 273 (0.11), 224 (0.12), 206 (100), 183 (0.15), 178 (6.7), 163 (2.4), 141 (0.3), 140 (0.3), 139 (1.6), 99 (0.6), 91 (0.4), 77 (0.6), 76 (1.1), 75 (1.2), 57 (0.5).

Moreover, it was found that azide 3 and/or isocyanate 8 reacted with glycine to give 1-(N-methyl saccharin)-imidazole-2,5-dione (9). The structure of 9 was identified by (i) IR which showed bands due to νCN at 1625 cm^{-1}, νCO of two different imide at 1740 cm^{-1}, 1710 cm^{-1}, 1680 cm^{-1} and νSO_2 at (1310 cm^{-1} and 1130 cm^{-1}. (ii) ^{1}H NMR spectrum showed signals at (δ ppm). 5.85 (s, 2H, CO—CH_2—NH), 6.6 (s, 2H, N—CH_2—), 7.8 (m, 4H, Ar H) and 9.1 (s, 1H, NH). (iii) Mass spectra showed molecular ion at m/z (relative abundance %) 295 (0.03) (M^+), 238 (0.21), 210 (2.86), 196 (100), 168 (0.3), 104 (39), 76 (33.7).

On the other hand, when N(saccharinyl)-acetyl isocyanate (8) was allowed to react with aromatic amines and/or aminobenzoic acids, it gave the corresponding N-aryl-N'-(saccharinylmethyl)ureas (10a–f). The structures of 10a–f were confirmed by IR spectra which showed bands due to νCO of N,N'-diaryl urea at 1670–1640 cm^{-1}, νCO of cyclic imide at 1740–1720 cm^{-1}, νNH at 3300–3120 cm^{-1} and νSO_2 at (1340 –1310 and 1150–1120 cm^{-1}).

Also isocyanate 8 reacted with hydrazine hydrate and/or phenyl hydrazine to give N-aryl-N'-(saccharinylmethyl)semicarbazides (11a and b). The structures of 11a and 11b was proved by IR spectra which showed νCO of semicarbazide at 1680–1660 cm^{-1}, νCO of cyclic imide at 1750–1730 cm^{-1}, νNH at 3320–3250 cm^{-1} and νSO_2 at (1340–1320 and 1150–1130 cm^{-1}).

Treatment of isocyanate 8 with few drops of distilled water in refluxing benzene yields sym. N,N'-di(saccharinylmethyl) urea (12). The structure of 12 was supported by: (i) IR spectra which showed bands due to νCO of urea at 1680 cm^{-1}, νNH at 3400–3350 cm^{-1}, νCO of cyclic imide at 1720 cm^{-1}, and νSO_2 at (1340 and 1150 cm^{-1}). (ii) Mass spectra gave unstable molecular ion which cannot be detected but it showed molecular ions corresponding to N-(saccharinyl)-acetyl isocyanate, saccharinylmethyl amine and other ions in accordance with the general fragmentation pattern, m/z (relative abundance), 238 (3.5), 212 (1.7), 210 (2.7), 197 (8.3), 196 (41.9), 183 (100), 168 (7.4), 141 (12.5), 140 (11.6).

Lewis acid catalyzed reactions of N-(saccharinyl)-acetyl isocyanate (8) with anhyd. $AlCl_3$ in aromatic substrates was found to give N-aroyl-saccharinylmethyl amine (13a–c). The structure of 13a–c was proved by: (i) IR spectra which showed νNH at 3350–3250 cm^{-1}, νCO of anilides at 1680–1650 cm^{-1}, νCO of cyclic imide at 1750–1720 cm^{-1} and νSO_2 at (1340–1315 and 1160–1120 cm^{-1}). (ii) Mass spectra: m/z (relative abundance %) compound 13a, 316 (2.8) (M^+), 196 (5.7), 183 (100), 168 (7.7), 163 (15.5), 141 (5.6), 140 (18.5), 120 (13.5), 119 (49.1), 105 (27.3), 91 (30.2), 77 (38.5) 75 (12.6), 65 (22.6), 57 (47.4).

EXPERIMENTAL

All melting points are uncorrected. IR spectra in KBr were on Shimadzu 470 spectrometer. ^{1}H NMR spectra were measured on Varian EM-390-90 MHz spectrometer using TMS as internal reference. Mass spectra were recorded on HP Model: MS 5988 at 70 eV.

TABLE I

Physical data of various compounds prepared

Compd. No.	M.P °C*	Yield (%)	Mol.Formula (M.wt)	Analysis Calc.(%) (found) C	H	N
1	184-186^a	55	$C_9H_7NO_5S$	44.81	2.9	5.81
			(241)	(44.86	2.85	5.73)
2	233-235^b	78	$C_9H_6Cl\ NO_4S$	41.62	2.31	5.39
			(259.5)	(41.53	2.27	5.28)
3	105-107^a	65	$C_9H_6N_4O_4S$	40.6	2.26	21.05
			(266)	(41.1	2.22	21.1)
4 a	149-151^c	49	$C_{15}H_{12}N_2O_4S$	56.96	3.8	8.86
			(316)	(56.78	3.75	8.9)
4 b	182-184^c	64	$C_{16}H_{14}N_2O_4S$	58.18	4.24	8.48
			(330)	(58.21	4.16	8.40)
4 c	191-193^c	72	$C_{16}H_{14}N_2O_5S$	55.49	4.05	8.09
			(346)	(55.41	4.10	8.01)
4 d	152-154^c	49	$C_{16}H_{12}N_2O_6S$	53.33	3.33	7.77
			(360)	(53.28	3.21	7.81)
4 e	164-166^c	68	$C_{16}H_{12}N_2O_6S$	53.33	3.33	7.77
			(360)	(53.21	3.17	7.65)
4 f	143-145^c	45	$C_{16}H_{12}N_2O_6S$	53.33	3.33	7.77
			(360)	(53.38	3.23	7.69)
5 a	242-244^a	49	$C_9H_9N_3O_4S$	42.35	3.53	16.47
			(255)	(42.30	3.51	16.42)
5 b	182-184^c	47	$C_{15}H_{13}N_3O_4S$	54.38	3.93	12.69
			(331)	(54.33	3.97	12.62)
5 c	228-230^a	61	$C_{16}H_{13}N_3O_5S$	53.48	3.62	11.70
			(359)	(53.43	3.66	11.74)
5 d	162-164^c	77	$C_{16}H_{12}N_4O_7S$	47.52	2.97	13.86
			(404)	(47.57	2.95	13.82)
6 a	205-208^c	61	$C_{16}H_{11}N_3O_4S$	56.30	3.23	12.32
			(341)	(56.18	3.20	12.25)
6 b	145-147^c	82	$C_{16}H_{10}N_4O_6S$	49.74	2.59	14.51
			(386)	(49.66	2.51	14.47)
7 a	185-187^c	38	$C_{15}H_{11}NO_4S$	59.80	3.65	4.65
			(301)	(59.86	3.61	4.69)
7 b	123-125^c	67	$C_{16}H_{13}NO_4S$	60.95	4.13	4.44
			(315)	(60.89	4.11	4.31)
7 c	201-203^c	53	$C_{16}H_{13}NO_5S$	58.01	3.93	4.23
			(331)	(57.66	3.79	4.33)
9	220-222^a	55	$C_{11}H_9N_3O_5S$	44.75	3.05	14.24
			(295)	(44.63	2.91	14.30)
10 a	119-121^d	71	$C_{15}H_{13}N_3O_4S$	54.38	3.93	12.69
			(331)	(54.27	3.97	12.72)
10 b	110-112^d	64	$C_{16}H_{15}N_3O_4S$	55.65	4.35	12.17
			(345)	(55.67	4.31	12.11)
10 c	205-207^c	72	$C_{16}H_{15}N_3O_5S$	53.19	4.16	11.63
			(361)	(53.13	4.12	11.67)

TABLE I (*Continued*)

Compd. No.	M.P °C*	Yield (%)	Mol.Formula (M.wt)	Analysis Calc.(%) (found) C	H	N
10 d	98-100^{d}	60	$C_{16}H_{13}N_3O_6S$ (375)	51. 2 (51.15	3.47 3.41	11.2 11.16)
10 e	195-197^{d}	82	$C_{16}H_{13}N_3O_6S$ (375)	51.2 (51.23	3.47 3.44	11.2 11.25)
10 f	210-212^{e}	75	$C_{16}H_{13}N_3O_6S$ (375)	51.2 (51.27	3.47 3.49	11.2 11.22)
11a	213-215^{c}	72	$C_9H_{10}N_4O_4S$ (270)	40 (40.17	3.7 3.8	20.74 20.77)
11b	218-220^{c}	35	$C_{15}H_{14}N_4O_4S$ (346)	52.02 (52.11	4.05 4.10	16.18 16.25)
12	224-226^{d}	55	$C_{17}H_{14}N_4O_7S_2$ (450)	45.33 (45.30	3.11 3.15	12.44 12.49)
13a	232-234^{c}	71	$C_{15}H_{12}N_2O_4S$ (316)	56.96 (56.91	3.8 3.78	8.86 8.79)
13b	185-187^{c}	69	$C_{16}H_{14}N_2O_4S$ (330)	58.18 (58.12	4.24 4.21	8.48 8.43)
13c	191-193^{c}	57	$C_{16}H_{14}N_2O_5S$ (346)	55.49 (55.42	4.05 4.01	8.09 8.11)

* The compounds recrystallized from (a) xylene, (b) toluene,(c)ethanol,(d) benzene+ ethanol, (e) diethyl ether.

N-(saccharinyl)-acetic acid (1): A mixture of sodium saccharin (0.01 mole) and chloroacetic acid (0.012 mole) in xylene was refluxed for 6 hr. The product was filtered hot and the filtrate was allowed to cool. The solid product was crystallized from xylene (cf. Table I).

N-(saccharinyl)-acetic acid chloride (2): N-(saccharinyl)-acetic acid (0.01 mole) was refluxed with excess thionyl chloride for 2 hr, the excess thionyl chloride was distilled off and the residual solid product was crystallized from dry toluene to give 2 (cf. Table I).

N-(saccharinyl)-acetic acid azide (3): A solution of NaN_3 (0.015 mole) in the least amount of water was added dropwise into a cold solution of 2 (0.01 mole) (ice-bath) in dry acetone (50 ml) under stirring. The reaction mixture was stirred for an additional half hour, and then poured into ice-cold water. The resulting solid was crystallized from dry ether to give 3 (cf. Table I).

N-(saccharinyl)-acetanilides (4a–f) and N-(saccharinyl)-acetic acid hydrazides (5a–d): Azide 3 and/ or acid chloride 2 (0.01 mole) in dry benzene was treated with aromatic amines, aminobenzoic acid or the appropriate hydrazine (0.015 mole). The reaction mixture was refluxed for 1 hr, then cooled to room temperature. The solid product was filtered and crystallized from a suitable solvent to give 4a–f or 5a–d (cf. Table I; yields are reported for 3 only).

Action of acetic anhydride on 5c and 5d: Formation of 2-Phenyl-(6a) and 2-(p-nitrophenyl)-(6b) 5-(N-methyl saccharin)-1,3,4-oxadiazole: Compound 5a and/or 5b (0.01 mole) was heated in acetic anhydride (10 ml) for $\frac{1}{2}$ hr. The reaction mixture was cooled and poured on ice-cold water. The solid product separated was filtered and crystallized from ethanol to give 6a and/or 6b (cf. Table I).

Action of aromatic substrates on azide 3 and/or acid chloride 2 in the presence of anhyd. $AlCl_3$: Formation of aroyl-N-methyl saccharin (7a–c): Anhyd. $AlCl_3$ (0.03 mole) was added with stirring to 3 and/or 2 (0.01 mole) in dry aromatic substrate at room temperature. The reaction mixture was stirred for an additional 1 hr and the resulting complex was decomposed with ice-water/cold dil. HCl. The solvent was steam-distilled and the residual solid filtered and crystallized from ethanol to give 7a–c (cf. Table I).

Action of glycine on azide 3 and/or isocyanate 8: Formation of 9: A mixture of azide 3 and/or isocyanate 8 (0.01 mol) (prepared by refluxing azide 3 in dry toluene for one hour), glycine (0.01 mole) and few drops of pyridine in dry toluene was refluxed for 3 hr. The excess solvent was removed and the solid residue was washed with water, and then crystallized from xylene to give 9 (cf. Table I).

N-aryl-N'-(saccharinyl methyl)-urea (10a–f) and N-aryl-N'-(Saccharinyl methyl)-semicarbazides (11a and b): A solution of 8 (0.01 mole) in dry benzene was treated with aromatic amines, aminobenzoic acids or the appropriate hydrazine (0.015 mole). The reaction mixture was refluxed ½ hr, cooled and the solid product filtered and crystallized from a suitable solvent to five 10a–f, 11a and 11b (cf. Table I).

Hydrolysis of 8 with water: formation of 12: A solution of 8 (0.01 mole) in dry benzene was treated with a suitable amount of distilled water (1 ml). The reaction mixture was refluxed for 1 hr. The solid product formed was filtered and crystallized from a mixture of benzene and ethanol to give 12 (cf. Table I).

N-aroyl-saccharinyl methyl amine (13a–c): Anhyd. AlCl$_3$ (0.03 mole) was added to 8 under stirring in dry aromatic substrate at room temperature. The reaction mixture was stirred for an additional 1 hr. The resultant complex formed was decomposed with ice-cold dil. HCl. The solvent was steam-distilled and the residual solid filtered and crystallized from ethanol to give 13a–c (cf. Table I).

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