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Synthesis of Imidazolidines, Saccharins and Chromone Bearing Imidazolidine Ring

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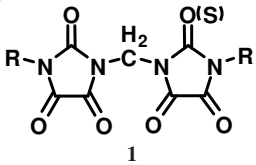
As a part of a research program related to the synthetic study of pharmacologically and agrochemically interesting imidazolidines, we synthesized imidazolidines **8**, **9**, **10**, saccharins **12**, **13** and chromone **17** bearing imidazolidine-2,4,5-trione or 2-thioxoimodazolidine-4,5-dione rings.

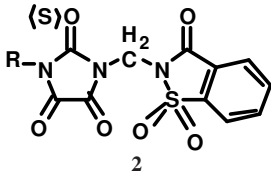
Key Words: Imidazolidines, Saccharin, Chromone, Herbicide, Fungicide.

INTRODUCTION

There are several examples of naturally occurring and synthetic imidazolidine-2,4-dione (hydantoin) derivatives exhibiting various biological activities, such as antitumor[1], anti-arrhythmic[2], anticonvulsant and herbicidal activity[3], inhibition of glycogen phosphorylase[4] and aldose reductase[5] and neuro-transmission[6] effects. Numerous imidazolidine-2,4,5-triones are known for their herbicide, plant growth regulator and in a minor part, fungicide properties[7]. Polymers containing imidazolidine 2,4,5-trione(parabanic) rings are known as highly thermally stable polymers with improved chemical resistance in organic solvents[8-13]. Recently, many marine imidazol alkaloids have been isolated from sponges and their antitumor and antibacterial activities have also been found[14,15]. As a part of a research program related to the synthetic study of pharmacologically and agrochemically interesting imidazolidines[16], we chose to associate imidazolidine-2,4,5-trione **1** bearing imidazolidine-2,4,5-trione or 2-thioxo imidazolidine-4,5-dione rings as an active component for the desired property. Also in order to obtain new agrochemicals, we report the synthesis of the new saccharin **2** and chromone **3** derivatives containing 2,4,5-imidazolidinetrione group or 2-thioxo imidazolidine-4,5-dione.



1



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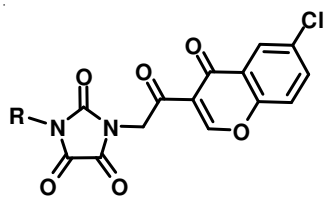
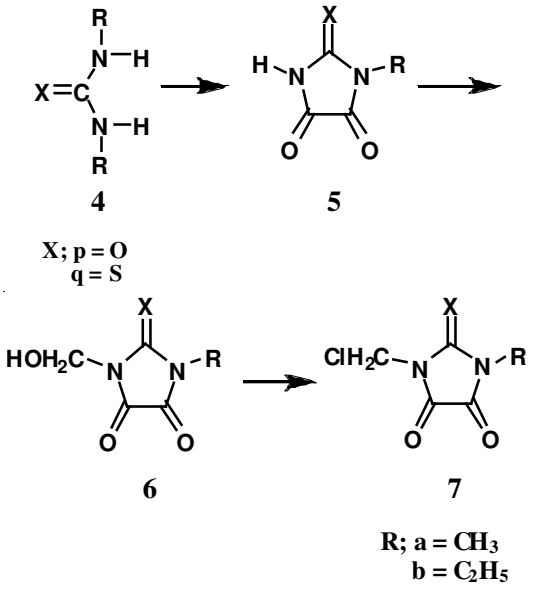


3

The basic-catalyzed condensation between imidazolidine-2,4,5-triones **5** and paraformaldehyde (**Scheme-I**) in aqueous solution allowed us a mixture of the expected N-hydroxy-methyl derivatives **6** and **5**. However, the instability of **6** made its isolation very difficult.

The use of column chromatography as a method of purification failed, whatever the eluent or support (silica gel, alumina) used, because the R_f value is the same for the two compounds. For this reaction, the next chlorination step, using a large excess of thionyl chloride, was realized starting directly from a mixture of **6** and **5**. The chlorinated precursors **7** were easily isolated by column chromatography (silica gel, CH_2Cl_2) and the product has a much higher R_f value than the starting material. 1-Chloromethyl-2-thioxo-imidazolidine-2,4-diones **7q** was obtained by the same methods as the reactions of imidazolidine-2,4,5-triones **5q** (Table-1).

1-Ethyl-3-((3-methyl-2,4,5-trioxoimidazolidin-1-yl)-methyl-imidazolidine-2,4,5-trione **8**, 1-ethyl-3-((3-ethyl-4,5-dioxo-2-thioxoimidazolidin-1-yl)methyl)imidazolidine-2,4,5-trione **9** and 3,3'-methylene *bis*(1-ethyl-2-thioxoimidazolidine-4,5-dione) **10** were obtained in good yields as shown in Table-2. The typical experimental procedure for **8** is as follows: To a solution of 1-chloromethyl-3-methyl-imidazolidine-2,4,5-trione **7pa** (2.0 g, 1.13×10^{-2} mol) in dry THF (15 mL) under



Reagents and reaction conditions; (I) benzene, rt, COClClCO, (II) $(CH_2O)_n$, K_2CO_3, (III) $SOCl_2$

Scheme-I: Synthesis of 1-chloromethyl-imidazolidine-2,4,5-triones **7p** and 1-chloromethyl-2-thioxo-imidazolidine-4,5-diones **7q** by using N-substituted ureas 4

TABLE-1
PHYSICAL DATA FROM 2,4,5-IMIDAZOLIDINETRIONES **5** TO 1-CHLOROMETHYL-3-PHENYL-2-THIOXO-IMIDAZOLIDINE-4,5-DIONE **7**

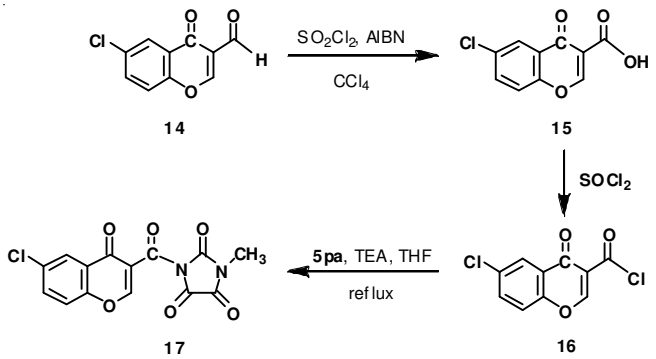
Entry	Reactant	Product	Yield* (%)	m.p. (ºC)
1	**4pa**	**5pa**	92	146-147
2	**4pb**	**5pb**	85	121-123
3	**5pa**	**7pa**	62	149-150
4	**5pb**	**7pb**	81	83-84
5	**4qa**	**5qa**	60	104-105
6	**4qb**	**5qb**	70	77-79
7	**5qa**	**7qa**	45	97-100
8	**5qb**	**7qb**	50	89-90

*Isolated yields.

nitrogen at room temperature was added solution of 1-ethyl-imidazolidine-2,4,5-trione **5pb** (1.47 g, 1.04×10^{-2} mol) and triethylamine (0.4 mL) in dry THF (15 mL). The reaction mixture was stirred at room temperature for 0.5 h. After 0.5 h, the reaction mixture was refluxed at 60-65 ºC for 7 h. The reaction mixture was cooled again to room temperature and THF (75 mL) was added. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel eluted with only CH_2Cl_2, to provide the **8** as a white crystalline solid (1.6 g, 62 %). Yields of the product **8-10** synthesized by the reaction of **7pa**, **7qb** with **5pb** or **5qb** like the previous reaction are show in Table-2. In the development of new agrochemical, we chose to associate benzisothiazole **2** or chromone group **3** as a new structure in which each part would serve as an active component for the desired property. The typical experimental procedure for 1-ethyl-2-thioxo-3-(1,1,3-trioxo-1,3-dihydro-1^6-benzo[d]isothiazol-2-ylmethyl)-imidazolidine-4,5-imidazolidine-4,5-dione **12** is as follows: To a solution of 1-ethyl-2-thioxo-imidazole-4,5-dione **3qb** (1 g, 4.8 mmol) in dry THF (10 mL) under nitrogen at room temperature was added solution of saccharin **11** (1.5 g, 8.2 mmol) and triethylamine (1.1 mL) in dry THF (10 mL). The reaction mixture was stirred at room temperature for 0.5 h. After 0.5 h, the mixture was refluxed at 55-60 ºC for 5 h. The reaction mixture was cooled again to room temperature and THF (30 mL) was added. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel eluted with only CH_2Cl_2, to provide the 12 as a yellow crystalline solid (1.68 g, 49 %).

Compound **2pb** was synthesized in good yield (54 %) as a yellow crystalline solid.

Chromone (or 1,4-benzopyrone) is a derivative of benzopyran with a substituted ketogroup on the pyran ring. The new imidazolidine with a chromone group was synthesized by three reaction steps from 6-chloro-3-carboxylic chromone **14**.

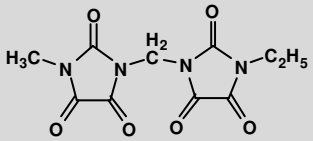
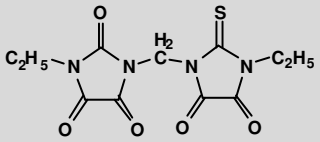
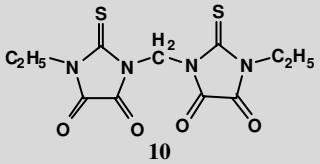
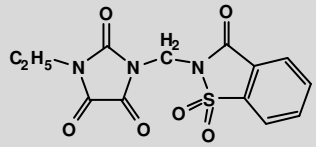
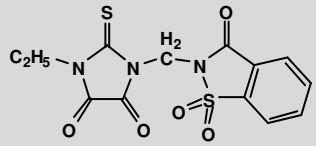
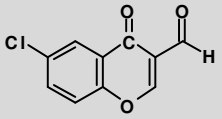
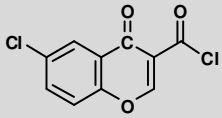
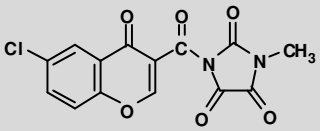


Compound **17** was synthesized by the reaction of **5pa** and **16** formed through oxidation and chlorination steps in good yield (55 %). The experimental procedure for compound **17** is as follows: To a solution of N-methyl-2,4,5-imidazolidinetrione **5pa** (0.3 g, 2.0×10^{-4} mol) in dry THF (10 mL) under nitrogen atmosphere at room temperature the solution of 6-chloro-3-carbochloric chromone **16** (0.5 g, 2.0×10^{-4} mol) and TEA (1.3 mL) in dry THF (5 mL) were added. The reaction mixture was stirred at room temperature for 0.5 h. After 0.5 h, the reaction mixture was refluxed at 55-60 ºC for 3 h. The reaction mixture was cooled again to room temperature and THF (50 mL) was added. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel eluted with only CH_2Cl_2, to provide compound **17** as a yellow crystalline solid (0.18 g, 55 %). Biological tests for the phytocides, herbicides and insecticides of the new imidazolidines **8**, **9**, **10**, **12**, **13**, **15**, **16**, **17** are in progress.

1-Ethyl-3-[(3-methyl-2,4,5-trioxoimidazolidin-1-yl)methyl]imidazolidine-2,4,5-trione (8): Yield 70 %, m.p. 126-129 0ºC; ^{1}H NMR (200 MHz, DMSO) δ 5.21 (s, 2H), 3.51 (d, *J* = 7.08 Hz, 2H), 2.92 (s, 3H), 1.12 (t, *J* = 7.02 Hz, 3H); ^{13}C NMR (50 MHz, DMSO) δ 156.8, 156.1, 152.5, 40.4, 33.7, 12.9; GC/MS m/z 282 (M^+).

1-Ethyl-3-[(3-ethyl-4,5-dioxo-2-thioxoimidazolidin-1-yl)methyl]imidazolidine-2,4,5-trione (9): Yield 72 %, m.p.

TABLE-2
PHYSICAL DATA OF SYNTHESIZED COMPOUNDS (**8, 9, 10, 12, 13, 15, 16, 17**)

Entry	Reactant 1	Reactant 2	Product	Yield* (%)	m.p. (ºC)
1	**7pa**	**5pb**	 **8**	70	126-129
2	**7pb**	**5qb**	 **9**	72	162-163
3	**7qb**	**5qb**	 **10**	74	149-151
4	**7pb**	**5qb**	 **12**	54	182-183
5	**7qb**	**5qb**	 **13**	49	157-158
6	**14**	SO_2Cl_2, AIBN	 **15**	76	225-226
7	**15**	$SOCl_2$	 **16**	86	158-159
8	**16**	**5pa**	 **17**	55	220-221

*Yields are isolated yields.

162-163 ºC; ^{1}H NMR (200 MHz, DMSO) δ 5.53 (s, 2H), 3.80 (d, *J* = 7.01 Hz, 2H), 3.51 (d, *J* = 6.93 Hz, 2H), 1.11 (t, *J* = 7.10 Hz, 6H); ^{13}C NMR (50 MHz, DMSO) δ 180.1, 156.7, 156.0, 154.9, 154.7, 152.4, 43.6, 36.6, 33.8, 12.9, 12.5; GC/MS m/z 312 (M^+).

3,3'-Methylenebis(1-ethyl-2-thioxoimidazolidine-4,5-dione) (10): Yield 74 %, m.p. 149-151 ºC; ^{1}H NMR (200 MHz, DMSO) δ 5.82 (s, 2H), 3.81 (d, *J* = 7.09 Hz, 4H), 1.12 (t, *J* = 6.95 Hz, 6H); ^{13}C NMR (50 MHz, DMSO) δ 180.2, 154.8, 47.0, 36.7, 12.4; GC/MS m/z 328 (M^+).

2-[3-Ethyl-2,4,5-imidazolidinetrionyl]methyl]-1,2-benzisothiazol-3-one-1,1-dioxide (12): R_f: 0.4 (TLC eluent; only CH_2Cl_2) yield: 54 %, m.p. 182-183 ºC IR (KBr, ν_{max}, cm^{-1}): 2981, 2885, 1746, 1425, 1340, 1293, 1251, 1180, 1115 mass, m/z: 337 ([M^+], (2), 273 (8), 223 (4), 196 (100), 174 (15), 169 (14), 132 (20) ^{1}H NMR (200 MHz, acetone-d_6): δ 1.18-1.28 (t, 3H, CH_3),3.64-3.75 (q, 2H, CH_2), 5.70 (s, 2H, N-CH_2-N), 8.02-8.22 (m, 4H, phenyl).

2-[(3-ethyl-2-thio-4,5-imidazolidinedionyl)methyl]-1,2-benzisothiazol-3-one-1,1-dioxide (13): R_f: 0.3 (TLC eluent; 100 % CH_2Cl_2) yield: 49 %, m.p. 156.5-159 ºC, IR (KBr, ν_{max}, cm^{-1}): 1780, 1740, 1720, 1390, 1330, 1280, 1240, 1175 mass, m/z: 353 ([M^+]) ^{1}H NMR (200 MHz, acetone-d_6): δ 1.17 (t, 3H, -CH_2), 3.99-4.06 (q, 2H, -CH_2), 6.04 (s, 2H, N-CH_2-N), 8.05-8.20 (m, 4H, phenyl).

6-Chloro-3-carboxylic chromone (15): R_f : 0.5 (TLC eluent; *n*-hexane:ethylacetate = 2:1 v/v) yield: 76 %, m.p.: 225-227 ºC, ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.4-8.3 (m, 4H), 9.0 (s, 1H), 13.3 (s, 1H).

6-Chloro-3-carbochloric chromone (16): R_f: 0.2 (TLC eluent; *n*-hexane:ethylactate = 5:1 v/v) yield: 86.3 %, m.p.: 158-159 ºC, ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.4-8.5 (m, 4H), 8.9 (s, 1H) 16.

1-(6-Chloro-4-oxo-4*H*-chromone-3-carbonyl)-3-methyl-imidazoline-2,4,5-trione (17): R_f: 0.45 (TLC eluent; *n*-hexane:ethylacetate = 1:1 v/v) yield: 55 %, m.p.: 220-225 ºC, ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.2 (s, 3H), 7.4-8.5 (m, 4H), 8.9 (s, 1H).

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