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SYNTHESIS AND REACTIONS OF BENZOFURANYL-L-ASCORBIC ACID ANALOGUES

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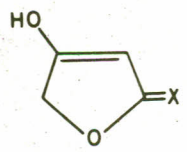
Substituted benzofuranyl analogues of dehydro-L-ascorbic acid were prepared. The reaction of 2-formyl-3-5- or 3,7-dimethylbenzofurane with glyoxal afforded 4(3,5- or 3,7-dimethylbenzofuran-2-yl)-2-hydroxytetronimides [4], that formed monoacyl derivatives [6]. Oxidation of the tetronimides (4) with nitrous acid yielded the corresponding 4-(3, 5- or 3,7-dimethylbenzofuran-2-yl)-2, 3-dixobutyrolactones (7). With acyl- or arylhydrazines, compound (7) gave the corresponding bis-acyl- (12) or bis-aryl-hydrazones (13). Treatment of (4) with an excess of arylhydrazines in aqueous acetic acid gave the methane derivatives (10), whereas with *o*-phenylenediamine under similar conditions they gave the methylquinoxalines (11). Reaction of (7)with *o*-phenyl-enediamine afforded the quinoxalinone derivatives (14), whereas with *o*-phenylenediamine and (*p*-chlorobenzoyl) hydrazine gave the product (15).

Key words: Synthesis; L-Ascorbic analogues.

INTRODUCTION

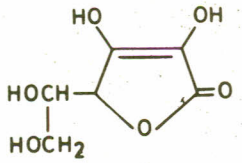
The tetronic acid nucleus I is found in many naturally occurring compounds that possess interesting biological activities [1]; an example is ascorbic acid II. Many of the derivatives of tetronic acid I were proved to be effective as analgesic [2], hypnotic [3] and antibacterial [4] agents.

In the present investigation and in continuation of our work [5-11] on the synthesis of L-ascorbic acid analogues, some derivatives of tetronimide III, which is an isoester of tetronic acid, were prepared; namely 4-[3,5- or 3, 7-dimethylbenzofuran-2-yl]-2-hydroxytetronimides (4, Table 1). They give the colour reactions characteristic for the tetronimide nucleus [12]. The described tetronimides (4) were prepared using the methods discribed in the literature [5-11]. A mechanism similar to that postulated for the aryl analogues [13] may be involved.



I : X = O

III: X = NH



II

Such conditions were found to be most favourable for the formation of the tetronimide derivatives (4) but not for ring enlargment [14-16]. Among the aldehydes used were 3,5-dimethyl-2-formylbenzofuran [17] and 3, 7-dimethyl-2-formylbenzofuran [17]. On the other hand, 2-formylpyridine and 1-formylnaphthalene gave unsuccessful results. This was attributed to the decrease of the partial positive charge on the carbonyl of the aldehydic group by the high electron donating ability of the pyridine or naphthalene rings, and thus failed to produce the corresponding tetronimides. The infrared (ir) spectrum of the tetronimides (4) showed absorption bands at 1710-1715 cm^{-1} for C=O group, 3350-3400 cm^{-1} indicating (OH) group, 2940-3000 cm^{-1} corresponds for NH group, 1630 cm^{-1} for -C=C-C=N group, 1210 cm^{-1} due to -C-O-C and at 1550 cm^{-1} for NH and C-H coupling. These (ir) data proves the tautomerization of the enediol (4) to the hydroxycarbonyl compound (5). Furthermore, in the PMR spectra of (4), the two methyl group protons appeared as two singlets at δ 1.92-2.21, the CH proton of the furanone nucleus as a singlet at 4.64, the hydroxyl protons and the aromatic protons as a multiplet at 5.5-7.1 in addition to the imino proton at 9.4 ppm.

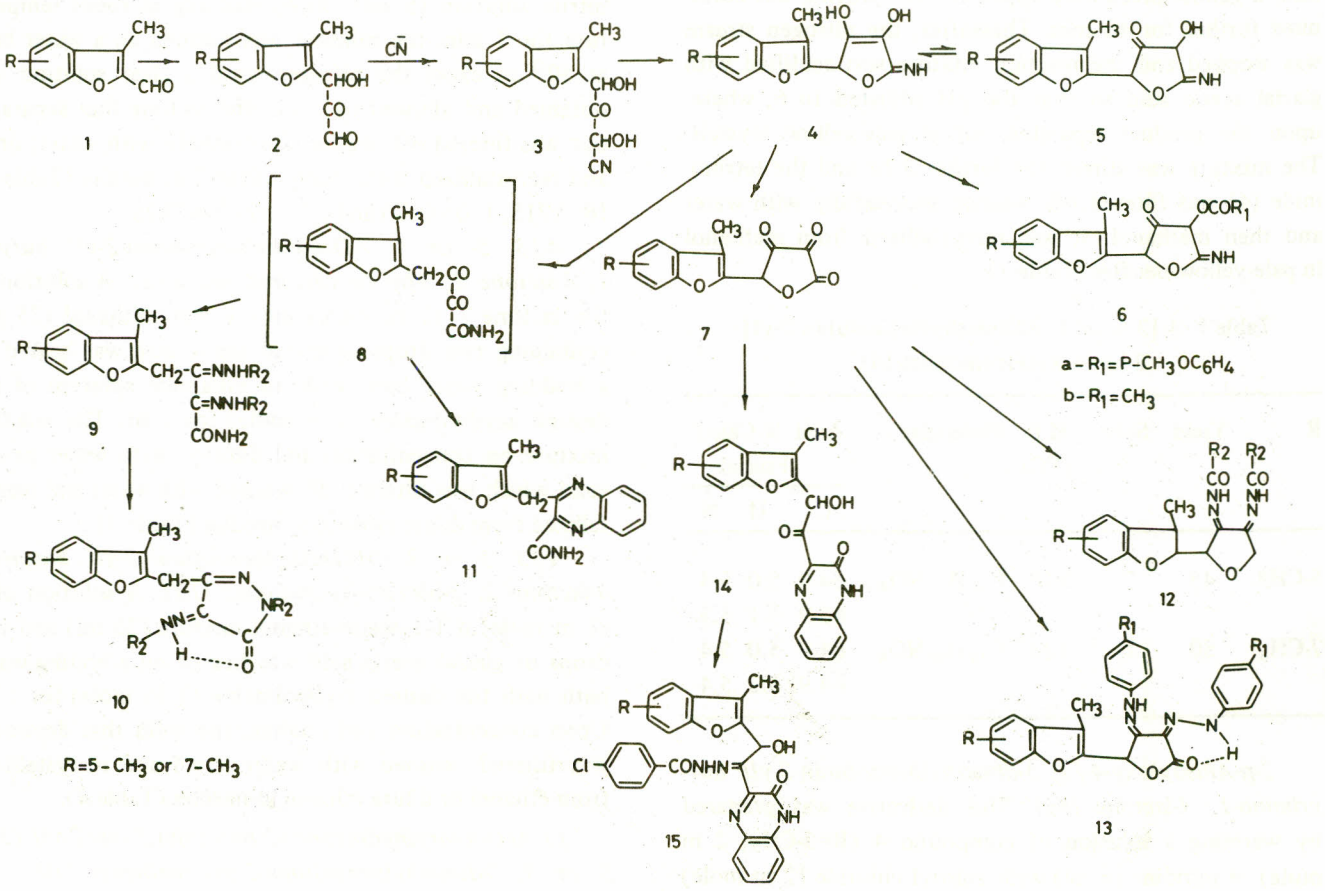
Acylation of tetronimides (4) with acyl chlorides gave the monoacyl derivatives; 2-acyloxy-4-(3, 5- or 3, 7-dimethylbenzofuran-2-yl)-tetronimides (6), which may result from (4) or one of their tautomers. Their (ir) spectra exhibited a band at 1740 due to acyl C=O, ν C=O at 1715, ν NH at 3380 and ν C=N at 1640cm^{-1}.

Treatment of (4) with nitrous acid brought about simultaneous hydrolysis of the imino group and oxidation of enediol group to give 2, 3-dioxo-4-[3,5- or 3,7-dimethylbenzofuran-2-yl] butyro-1, 4-lactones (7, Table 2), the aryl analogues of dehydro-L-ascorbic acid. Their (ir) spectra showed two carbonyl absorption bands at 1705, 1715 cm^{-1} and the lactone carbonyl band at 1775 cm^{-1}.

Lactones (7) reacted readily with acylhydrazines to give the corresponding 4-[3,5- or 3, 7-dimethylbenzofuran-2-yl] butyro-1, 4-lactone 2, 3-bis (acylhydrazones) (12, Table 3). Their (ir) spectra exhibited carbonyl absorption bands in the region of 1670-1710 cm^{-1}. With arylhydrazines, lactones (7) gave the corresponding 4-[3, 5 or 3-7 dimethyllenzo furan-2-yl] butyro-1, 4-Lactone 2, 3-bis (arylhydrazones) 13, (Table 4) which were characterized by their (ir) data.

The (ir) spectra of (13) showed a band at 1715 due to lactone carbonyl group instead of the carbonyl frequencies (1705, 1715 cm^{-1}) observed in (7). The appearance of lactone carbonyl band at a lower frequency (1715 cm^{-1}) in (13) compared to that(1775 cm^{-1}) in (7) could be attributed to hydrogen bonding between the lactone carbonyl and the imino group of the hydrazone residue on C-2. Similar hydrogen bonding has been observed in bis-hydrazones of L-ascorbic acid and its analogues [18].

Treatment of the tetronimides (4) with an excess of arylhydrazines in aqueous acetic acid resulted in the formation of organge coloured products; 3-(3, 5- or 3, 7-dimethylbenzofuran-2-yl-methyl)-1-aryl-4-arylhydrazono-2-pyrazolin-5-ones (10, Table 5). With an excess of *o*-phenylenediamine under the same conditions compound (4) gave 2-carboxamido-3-(3,5- or 3, 7-dimethylbenzofuran-2-yl) methylquinoxalines (11, Table 6). The (ir) spectra of the pyrazolinone derivatives (10) exhibited absorption due to (CON) at 1660-1670 cm^{-1}, NH at 3380 cm^{-1} but another carbonyl group and hydroxyl group bands were not appeared in their spectral regions. Further evidence for the absence of the hydroxyl group was obtained from the failure of the acylation of (10) under conditions similar to that of (4) and consequently they were formulated as (10). Comparison of this reaction with the reaction sequence 7 → 13 indicated that for the formation of (10), hydrolysis accompanied by the deoxygenation of the tetronimide (4) occurred primarily affording a deoxygenated intermediate of possible structure (8) (not isolated). This was followed by the reaction of (8) with arylhydrazines to give the corresponding *bis*-arylhydrazones (9), that underwent cyclization to (10) by nucleophilic attack of the nitrogen pair of electrons of the hydrazones (9) on the carbonyl group followed by the loss of ammonia. Another series of heterocyclic compounds resulting from the 5-furanone nucleus was achieved by reaction of *o*-phenylenediamine. Reaction of (7) with an equimolar proportion of *o*-phenylenediamine gave a quinoxaline derivative, namely, 1-hydroxyl-1-(3, 5- or 3, 7-dimethylbenzofuranyl)-



2-(2quinoxalinone-3-yl) ethanes (14). Its (ir) revealed a band at 1665 cm^{-1} due to (OCN) of the 2-quinoxalinone ring, whereas the reaction of equivalent amounts of the lactone (7) and *o*-phenylenediamine, followed by *p*-chlorobenzoylhydrazine, gave the mono-hydrazone (15).

EXPERIMENTAL PROCEDURE

Melting points were taken in open glass capillaries and are uncorrected. IR spectra were recorded in KBr pellets on a Pye-Unicam SP 1025 infrared spectrophotometer, and PMR spectra in $CDCl_3$ on a Varian 100 instrument using tetramethylsilane as internal standard. Microanalysis were performed in the Chemistry Department, Faculty of Science, Cairo University, Cairo, Egypt.

4-[3, 5- or 3, 7-Dimethylbenzofuran-2-yl]-2-hydroxytetronimides (4). A cooled solution of potassium cyanide (0.26 mole) in 2N sodium carbonate solution (400 ml) was treated in one lot with glyoxal sodium hydrogen sulphite monohydrate (0.15 mole) under a nitrogen atmosphere. To the resulting solution, a solution of 3, 5- or 3, 7-dimethyl-2-formylbenzofuran [17] (0.01 mole) in 1, 4-dioxane (50 ml) was added in one portion under stirring. After 15 min. a yellow precipitate appeared. The stirring was continued further for 40 min. Thereafter, the nitrogen stream was stopped and the reaction mixture was acidified with glacial acetic acid so that the pH adjusted to 6, whereupon the product separated out in pale-yellow crystals. The mixture was stirred for further 3 hr and the tetronimide (4) was filtered off, washed successfully with water and then methanol. It was recrystallized from methanol in pale-yellow needles (Table 1).

Table 1. 4-[3,5- or 3, 7-Dimethylbenzofuran-2-yl]-2-hydroxytetronimides (4)

R	Yield	Solv.	M.P. (°C)	Molecular	Anal. % Calc./ Found		
					C	H	N
5-CH3	45	E	118	$C_{12}H_{13}NO_4$	64.9	5.0	5.4
					65.9	5.1	5.3
7-CH_3	50	E	124	$C_{14}H_{13}NO_4$	64.9	5.0	5.4
					64.9	5.2	5.4

2-p-Anisoyloxy-4-[3, 5-dimethylbenzofuran-2-yl] butyrimino-1, 4-lactone (6a). This derivative was prepared by warming a solution of compound 4 (R=5-CH_3; 2 m mole) in pyridine (6 ml) with anisoyl chloride (2 m mole) for 10 min. on a boiling water bath, and then keeping the mixture for 5 hr at room temperature. The mixture was poured into ice-cold, 2M sulphuric acid (25 ml) and the crude product was treated with saturated sodium hydrogen carbonate solution (25 ml), filtered off, washed with water and recrystallized from benzene-methanol mixture in colourless needles, yield, 65 %, m.p. 156°, Anal.Calc. for $C_{22}H_{18}NO_6$: C, 67.4, H, 4.6 ; N, 3.6. Found: C, 67.3 ; H, 4.7 ; N, 3.5.

2-Acetyloxy-4-[3, 7-dimethylbenzofuran-2-yl] butyriminolactone (6b). A mixture of 4 (2 m mole) and acetic anhydride (2 ml) was heated on a boiling water bath for 15 min, the reaction mixture kept at room temperature for 2 hr. and poured into ice-cold saturated sodium hydrogen carbonate solution. The acetate (6b) thus separated, was filtered off, washed several times with water, dried and recrystallized from benzene-methanol mixture in colourless needles, m.p. 204° (yield 60 %).

Anal.Calc. for $C_{16}H_{15}NO_5$: C, 63.8; H, 5.0; N, 4.7. Found: C, 63.8; H, 4.8; N, 4.7.

4-[3, 5- or 3, 7-Dimethylbenzofuran-2-yl]-2, 3-dioxobutyro-1, 4-lactones (7). A suspension of 4 (3 m mole) in acetone (5 ml) and 2M sulphuric acid (8 ml) was cooled below 10° and treated dropwise with aqueous 10 % sodium nitrite solution (5 ml). After standing at room temperature for 5 min, the mixture was warmed on a water bath at 50° to expel the nitrogen until a clear solution was obtained and allowed to cool. The lactone that separated out was filtered off, washed successively with water, dried and recrystallized from dilute ethanol in needles (Table 2). IR: 1715, 1705 (CO) and 1775 cm^{-1} (COO).

4-[3, 5- or 3, 7-Dimethylbenzofuran-2-yl] butyro-1, 4-lactone 2, 3-bis (acylhydrazones) (12). A solution of the lactone 7 (1 m mole) in 1.1 water-ethanol (25 ml) containing two drops of glacial acetic acid was heated on a boilding water bath with an ethanolic solution of the desired acylhydrazine (2 m mole) for 2 hr. The reaction mixture on concentration and dilution with water gave a solid which was filtered off, washed with water and recrystallized from dilute ethanol in needles (Table 3).

4-[3, 5- or 3, 7-Dimethylbenzofuran-2-yl] butyro-1, 4-lactone 2, 3-bis-(arylhydrazones) (13). A solution of 7 (1 m mole) in 1:1 water-ethanol mixture (25 ml) and two drops of glacial acetic acid was heated on a boiling water bath with the desired arylhydrazine (2 m mole) for 2 hr. Upon concentration and cooling, the solid that deposited was filtered, washed with water, dried and recrystallized from ethanol or dilute ethanol in needles (Table 4).

[1-Aryl-4-(arylhydrazono)-2-pyrazolin-5-one-2-yl]-(3, 5- or 3, 7-dimethylbenzofuran-2-yl) methanes (10). A

Table 2. 4-(3, 5- or 3, 7-Dimethylbenzofuran-2-yl)-2, 3-dioxobutyro-1, 4-lactones (7)

R	M.P. (°C))	Yield	Solv.	Molecular Formula	Anal. % Calc. / Found C	H	KBr ν_{max} (cm^{-1})
5-CH_3	92	40	E-W	$C_{14}H_{10}O_5$	65.1	3.9	1770(COO; 1710, 1695(CO)
					65.0	4.0	
7-CH_3	65	45	E-W	$C_{14}H_{10}O_5$	65.1	3.9	1770(COO); 1710, 1695(CO)
					65.3	4.1	

Table 3. 4(3,5- or 3,7-Dimethylbenzofuran-2-yl)-butyro-1, 4-lactone 2, 3-*bis* (acylhydrazones) (12)

R	R_2	Yield	Solv.	M.P. (°C)	Molecular Formula	Anal. % Calc./Found C	H	N	S
5-CH_3	H_2N-C$_6$H$_4$-	40	E-W	98	$C_{28}H_{24}N_6O_5$	64.1	4.6	16.0	–
						64.0	4.7	16.1	
5-CH_3	N-C$_5$H$_4$-	35	E-W	102	$C_{26}H_{20}N_6O_5$	62.9	4.0	16.9	–
						62.8	4.2	16.7	
5-CH_3	SO_2NH_2-C$_6$H$_4$-NH	40	E-W	238	$C_{28}H_{26}N_8O_9S_2$	49.3	3.8	16.4	9.4
						49.3	3.6	16.3	9.5
7-CH_3	H_2N-C$_6$H$_4$-	40	E-W	209	$C_{28}H_{24}N_6O_5$	64.1	4.6	16.0	
						64.0	4.7	16.1	

Table 4. 4-(3, 5- or 3, 7-Dimethylbenzofuran-2yl)Butyro-1, 4-lactone 2, 3-bis(arylhydrazones) (13)

R	R_1	Yield	Solv.	M.P. °C	Molecular formula	Anal. % Calc./Found C	H	N	S
5-CH_3	H	55	E-W	102	$C_{26}H_{22}N_4O_3$	71.2	5.0	12.8	–
						71.1	5.1	12.9	
5-CH_3	NO_2	50	E-W	95	$C_{26}H_{20}N_6O_7$	69.1	3.8	15.9	–
						59.0	4.0	16.0	
5-CH_3	SO_2NH_2	50	E-W	99	$C_{26}H_{24}N_6O_7S_2$	52.4	4.0	14.1	10.7
						52.4	3.9	14.3	
5-CH_3	SO_2NH	45	E-W	104	$C_{34}H_{28}N_{10}O_7S_2$	54.3	3.7	18.6	8.5
						54.5	3.8	18.7	8.5
5-CH_3	2, 4(NO_2)$_2$	50	E-W	158	$C_{26}H_{18}N_8O_{11}$	50.5	2.9	18.1	–
						50.6	2.7	18.0	
7-CH_3	NO_2	45	E	239	$C_{26}H_{20}N_6O_7$	59.1	3.8	15.9	–
						59.1	4.0	15.8	
7-CH_3	2, 4(NO_2)$_2$	50	E	254	$C_{26}H_{18}N_8O_{11}$	50.5	2.9	18.1	–
						50.4	3.0	18.0	

solution of 4 (0.5 g) in 40 % acetic acid (50 ml) was boiled under reflux for 1 hr. An excess of the desired arylhydrazine (3 g) was cooled and the product that separated out after 24 hr was filtered off, washed with ethanol and light petroleum (b.p. 40-60°) mixture in yellow needles recrystallized from ethanol to give orange needles (Table 5).

2-Carboxamido-3-(3, 5- or 3, 7-dimethylbenzofuran-2-yl), methylquino-xalines (11). A solution of the imino-lactone 4 (0.2 g) in 40 % acetic acid (30 ml) was refluxed

Table 5. [1-Aryl-4-(arylhydrazono)-2-pyrazolin-5-one-2-yl] -(3, 5- or 3, 7- dimethylbenzofuran-2-yl)methanes. (10)

R	R_2	Yield	Solv.	M.P. °C	Molecular formula	Anal. % Calc./Found C	H	N	Cl
5-CH_3		35	E	148	$C_{26}H_{22}N_4O_2$	73.9	5.2	13.3	–
						74.0	5.3	13.3	
5-CH_3	Cl 	40	E-W	153	$C_{26}H_{20}N_4O_2Cl_2$	63.7	4.1	11.4	14.3
						63.6	4.3	11.5	14.5
7-CH_3		40	E	152	$C_{26}H_{22}N_4O_2$	73.9	5.2	13.3	–
						74.0	5.1	13.4	
7-CH_3	Cl 	35	E	183	$C_{26}H_{20}N_4O_2Cl_2$	63.7	4.1	11.4	14.3
						63.7	4.2	11.4	14.2

Table 6. 2-Carboxamido-3-(3, 5- or 3, 7-dimethylbenzofuran-2-yl) methylquinoxalines (11)

R	Yield	Solv.	M.P. °C	Molecular Formula	Anal. % Calc./Found C	H	N
5-CH_3	45	B-P	97	$C_{20}H_{17}N_3O$	72.5	5.1	16.7
					72.4	5.2	16.9
7-CH_3	45	B-P	97	$C_{20}H_{17}N_3O$	72.5	5.1	16.7
					72.5	5.0	16.6

B=benzene; P=light petroleum (40-60°)

Table 7. 1-Hydroxy-1-(3, 5- or 3, 7-dimethylfuran-2-yl)-2-(2-quinoxalinones-3-yl) ethanes (14)

R	Solv.	Yield	M.P. °C	Molecular Formula	Anal. % Calc./Found C	H	N
5-CH_3	E-W	30	92	$C_{20}H_{16}N_2O_4$	69.0	4.6	8.1
					69.1	4.4	8.0
7-CH_3	E-W	30	163	$C_{20}H_{16}O_4$	69.0	4.6	8.1
					69.0	4.8	8.2

E=ethanol; W=water.

for 1 hr. An excess of *o*-phenylenediamine (0.6 g) was added and boiling was continued for another 90 min. The mixture concentrated and the deposited mass was separated out, and purified by crystallization from benzene-light petroleum (b.p. 40-60°) mixture in yellow needles (Table 6).

1-Hydroxyl-1-(3, 5- or 3, 7-dimethylbenzofuran-2-yl)-2-(2-quinoxalinone-3-yl) ethanes (14). A solution of compound 7 (1 m mole) in ethanol (20 ml) was refluxed with *o*-phenylenediamine (1 m mole) for 2 hr. on a steam-bath. On concentration and cooling, the solid separated out was filtered and recrystallized from dilute ethanol in needles (Table 7). IR: 1660-1670 cm^{-1} (CO and OCN), 3350 cm^{-1} (OH).

1-Hydroxy-2-(p-chloro-benzoylhydrazono)-1-(3,7-dimethylbenzofuran-2-yl)-2-(2-quinoxalinone-3-yl) ethane (15). A solution of compound 7 (1 m mole) in ethanol (15 ml) was treated with a solution of *o*-phenylenediamine (1 m mole) and *p*-chlorobenzoylhydrazine in ethanol (20 ml) and the mixture was boiled on a hot-water bath for 4 hr. Upon concentration, cooling, the hydrazone that separated out was filtered off, washed with alcohol and dried (yield, 60 %). Recrystallization was effected from ethanol to give brown needles, m.p. 148°. IR. 3350 (OH) and 1665 cm^{-1} (OCN).

Anal.Calc. for $C_{27}H_{21}N_4Cl$: C, 64.7 ; H, 4.2 ; N, 11.2; Cl, 7.1. Found: C, 64.6 ; H, 4.4 ; N, 11.2 ; Cl, 7.0.

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