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4-(3-METHYLBENZOFURAN-2-Y1)-2-HYDROXYTETRONIMIDE AND ITS DERIVATIVES: ARYL ANALOGUES OF IMINO-L-ASCORBIC ACID

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The synthesis of 4-(3-methylbenzofuran-2-y1)-2-hydroxytetronimide (I), its monoacyl derivatives (III), and hydrazone (VI) is described. The oxidation of the tetronimide (I) with nitrous acid yielded 2,3-dioxo-4-(3-methylbenzofuran-2-y1)butyro-1,4-lactone (VII). Reaction of the lactone (VII) with acylhydrazines afforded bis acylhydrazones (VIII). In the case of arylhydrazines, it gave the corresponding bis-aryl-hydrazones (IX) which were cyclized to 1-aryl-4-aryl-hydrazono-3-[hydroxy (3-methylbenzofuran-2-yl)methyl] pyrazole-5-ones (X). Furthermore, the reaction of compound (VII) with *o*-phenylenediamine gave a quinoxaline derivative (XI).

INTRODUCTION

Ascorbic acid is one of the naturally occurring compounds containing the tetronic acid nucleus which possesses interesting biological activities [1-3]. It was reported that many derivatives of the tetronic acid showed effective anti-neoplastic [4], anti-bacterial [5], hypnotic [6] and analgesic [7] activities.

In continuation of our previous work [8-13] on the synthesis of L-ascorbic acid analogues and their ring transformation into nitrogen heterocycles, we now report the synthesis of a methylbenzofuranyl analogue. It gives the characteristic colour reactions for the tetronimide nucleus and possesses strong reducing properties [14,15]. The tetronimide (I) was prepared according to the procedure described in our previous paper [13]. The reaction is carried out between 2-formyl-3-methylbenzofuran [16], glyoxal sodium bisulphite and potassium cyanide in 2N sodium carbonate solution under a nitrogen atmosphere followed by acidification with glacial acetic acid to pH 6. The formation of (I) can be explained by a mechanism similar to that postulated for the triazolyl analogue [11]. The IR spectrum of (I) revealed hydroxyl, NH, carbonyl, and C=C–C=N absorptions and this may be ascribed to the tautomerization of the enediol (I) to the hydroxycarbonyl compound (II).

Acylation of tetronimide (I) yielded 2-acyloxy-4-(3-methylbenzofuran-2-yl)tetronimide (III), which may result from (I) or its tautomers.

Compounds (I) reacted readily with an excess of phenylhydrazine in aqueous acetic acid to give an orange product, 3-(3-methylbenzofuran-2-yl methyl)-1-phenyl-4-phenylhydrazono-2-pyrazolin-5-one (VI) that differed from the red bishydrazone (IX) and was a deoxygenated product of the absorption of lactum (CON) at 1665 cm^{-1}, NH at 3380 cm^{-1} but another carbonyl group and a 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 acylation of (VI) under conditions similar to that of (I) and consequently it was formulated as (VI). Moreover, its elemental analysis agreed with that calculated for $C_{25}H_{20}N_4O_2$, containing one oxygen atom less than (X). Comparison of this reaction with the reaction sequence (VII – IX – X) indicated that for the formation of (VI), hydrolysis accompanied by the deoxygenation of the tetronimide (I) occurred primarily affording a deoxygenated intermediate of possible structure IV (not isolated). This was followed by the reaction of IV with phenylhydrazine to give the corresponding bisphenylhydrazone that underwent cyclization to (VI) by nucleophilic attack of the nitrogen pair of electrons of the hydrazone (V) on the carbonyl group followed by the loss of ammonia. These results are in accord with those for the phenyl analogue, which indicated that no deoxygenation had occurred during the opening of the lactone ring in the bis-arylhydrazones (IV). The structure of compound (VI) was further confirmed by measuring its p.m.r. spectrum.

Treatment of (I) with nitrous acid resulted in the hydrolysis of the imino group and the oxidation of enediol group to give 2,3-dioxo-4-(3-methylbenzofuran-2-yl)butyro-1,4-lactone (VII), aryl analogue of dehydro-L-ascorbic acid. Its IR spectra showed two carbonyl absorptions at 1715, 1705 and the lactone carbonyl band at 1775 cm^{-1}.

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Lactone (VII) reacted readily with acylhydrazines to give the bisacylhydrazones (VIII), whereas the reaction with arylhydrazines gave the corresponding bisarylhydrazones (IX) that were red in colour similar to the bisarylhydrazones of dehydro-L-ascorbic acid. Furthermore, the red bis-2,4-dinitrophenylhydrazone was prepared. The IR spectra of (IX) revealed the lactone carbonyl group at 1720 cm^{-1} and the absence of the absorptions on the basis of the two carbonyl frequencies appearing in the IR spectrum of (VII) at 1715 and 1705 cm^{-1}. The shift of the lactone carbonyl band in the bishydrazones (IX) to a lower frequency is due to its hydrogen bonding with the imino proton of the hydrazone part. This action is similar to the bis arylhydrazones of dehydro-L-ascorbic acid and its analogue [17,18].

Opening of the lactone ring of (IX) with alkali, followed by acidification, afforded the carboxylate intermediate. The ring closure by the nucleophilic attack of the imino group of the hydrazone part to the carboxylate carbonyl group gave the rearrangement products (X). The orange colour of the resulting 2-pyrazolinones (X) was characteristic of such compounds, and their IR spectrum revealed a lactum (CON) absorption at 1660 cm^{-1} instead of the lactone band at 1710 cm^{-1}, appearing in the spectrum of their precursors.

Another heterocyclic compound resulting from the 5-furanone nucleus was achieved via reaction with *o*-phenylenediamine. Thus the reaction of (VII) with an equimolar portions of *o*-phenylenediamine gave a quinoxaline derivative (XI).

EXPERIMENTAL PROCEDURE

Melting points were taken in open glass capillaries and are uncorrected. IR spectra were measured on a Unicam SP 1025 spectrophotometer (ν_{max} in cm^{-1}) using potassium bromide pellets and PMR spectra in $CDCl_3$ on a Varian HA 100 instrument using TMS as internal standard (chemical shift in δ ppm), whereas microanalyses were performed in the Chemistry Department, Faculty of Science, Cairo University, Cairo, Egypt.

4-(3-Methylbenzofuran-2-yl)-2-hydroxytetronimide (I). To a well stirred cold solution of potassium cyanide (26 m mole) in 35 ml of 2N sodium carbonate solution, powdered glyoxal sodium bisulphite (15 m mole) was added in one portion under nitrogen atomosphere. The resulting solution was treated in one portion with a dioxane solution (15 ml) of 2-formyl-3-methylbenzofuran[16] (1 m mole). A yellow precipitate was observed after 15 min., and stirring was continued for another 40 min. The nitrogen was disconnected and the mixture was acidified with glacial acetic acid and stirred for another 3 hr. The tetronimide was filtered off, washed successively with water, dried and recrystallized from methanol to give needles, m.p. 140° (yield 85%).
IR: 3400 (OH), 1710 (CO), 2940 (NH), 1630 (–C=C–C=N), 1210 (–C–O–C) and 1550 cm^{-1} (NH, C–N coupling), PMR: 1.92 (s, 3H, CH_3), 9.3 (s, 1 H, NH), 5.4-7.0 (m, 6 H, OH and aromatic rings protons), 4.64 (s, 1 H, NH), 5.4-7.0 (m, 6 H, OH and aromatic rings protons), 4.64 (s, 1 H, CH of furanone nucleus). (Found: C, 63.8; H, 4.5; N, 4.5. $C_{13}H_{11}NO_4$ requires C, 63.7; H, 4.5; N, 5.7%).

2-Acetyloxy-4-(3-methylbenzofuran-2-yl)tetronimide (III). It was prepared by heating a mixture of the tetronimide (I; 2 m mole) and acetic anhydride (3 ml) on a steam bath for 10 min. and then keeping the reaction mixture at room-temperature for 2 hr. The mixture was then poured into ice-cold saturated sodium hydrogen carbonate solution (100 ml) and the separated solid was filtered off, washed with water, dried and purified by recrystallization from benzene to give colourless needles, m.p. 203° (yielded 65%).
IR: 3300 (NH), 1740 (OAc), 1710 (CO) and 1640 cm^{-1} (C=N). (Found: C, 63.0; H, 4.9; N, 5.1; $C_{15}H_{13}NO_5$ requires; C, 62.7; H, 4.5; N, 4.9%).

2-Aroyloxy-4-(3-methylbenzofuran-2-yl)tetronimides (III). A solution of (I; 2 m mole) in pyridine (6 ml) was warmed with (2 m mole) of anisoyl or benzoyl chloride for 12 min. and then standing at room temperature for 5 hr. The reaction mixture was poured into an ice-cooled (10%) sulphuric acid solution (25 ml) and the solid mass deposited was mixed well with saturated sodium hydrogen carbonate solution (30 ml), filtered off, washed with water then recrystallized from benzene to give needles. Yield, 30-45%. The derivatives, (R_2 = COC_6H_5), m.p. 186° and (R_2 = p–$CH_3OC_6H_4CO$), m.p. 162°, were prepared and satisfactory analyses (C, H, N) were obtained for (III).

3-(3-Methylbenzofuran-2-yl-methyl-)-1-phenyl-4-phenyl-hydrazono-2-pyrazolin-5-one (VI). A solution of (I; 0.5 g) in 40% acetic acid 60 ml) was refluxed for 1 hr. Phenylhydrazine (3 ml) was added to the resulting solution and boiling was continued for another 1½ hr. On cooling the titled derivative separated out, it was filtered off, washed with a little of alcohol and recrystallized from ethanol to give orange needles, m.p. 187° (yield, 70%).
IR: 1665 (CON) 3140 (NH); PMR: 2.34 (s, 3 H, CH_3), 4.1 (s, 2 H, CH_2), 10.91 (NH), 7.0-8.1 (m, 14 H, aromatic protons). (Found: C, 73.6; H, 4.6; N, 14.1. $C_{25}H_{20}N_4O_2$ requires C, 73.5; H, 4.9; N, 13.7%).

2,3-Dioxo-4-(3-methylbenzofuran-2-yl)butyro-1,4-lactone (VII). A suspension of (I; 3 m mole) in acetone (5 ml)

Table 1. 2(3-Dioxo-4-methylbenzofuran-2-yl)butyro-1,4-lactone 2,3-bis-acylhydrazones (VIII).

R_1	Solv.	m.p. (°C)	Molecular formula	Analysis % Calcd. C	H	N	Found C	H	N	νKBr max (cm^{-1})
-C6H4-N	E-W	169	$C_{25}H_{18}N_6O_5$	62.2	3.7	17.4	62.3	4.0	17.2	1690
-C6H4-Cl	E-W	149	$C_{27}H_{18}Cl_2N_4O_5$	59.1	3.3	10.2	59.0	3.5	10.2	1680
-C6H4-Br	E	262	$C_{27}H_{18}Br_2N_4O_5$	50.8	2.8	8.8	50.6	3.1	9.1	1680
-C6H4-NH_2	E	166	$C_{27}H_{22}N_5O_5$	63.5	4.3	16.5	63.3	4.5	16.6	1660
-NH-C6H4-SO_2NH_2	E	229	$C_{27}H_{24}N_8O_9S_2$	50.9	3.8	17.6	50.6	4.0	17.5	1695

Table 2. 2,3-Dioxo-4-(3-methylbenzofuran-2-yl)butyro-1,4-lactone 2,3-bis arylhydrazones (IX).

R_1	Solv.	m.p. (°C)	Molecular formula	Analysis % Calcd. C	H	N	S	Found C	H	N	S	νKBR max (cm^{-1})
H	E-W	103	$C_{25}H_{20}N_4O_3$	70.8	4.7	13.2		70.6	5.1	13.1		1715
SO_2NH_2	E	195	$C_{25}H_{22}N_6O_7S_2$	54.6	4.0	15.3	5.8	54.6	4.3	15.3	5.9	1720
NO_2	E	192	$C_{25}H_{18}N_6O_7$	58.4	3.8	16.3		58.5	3.8	16.5		1715
$2,4(NO_2)_2$	E	192	$C_{25}H_{16}N_8O_{11}$	49.7	2.7	18.5		49.5	3.0	18.6		1720

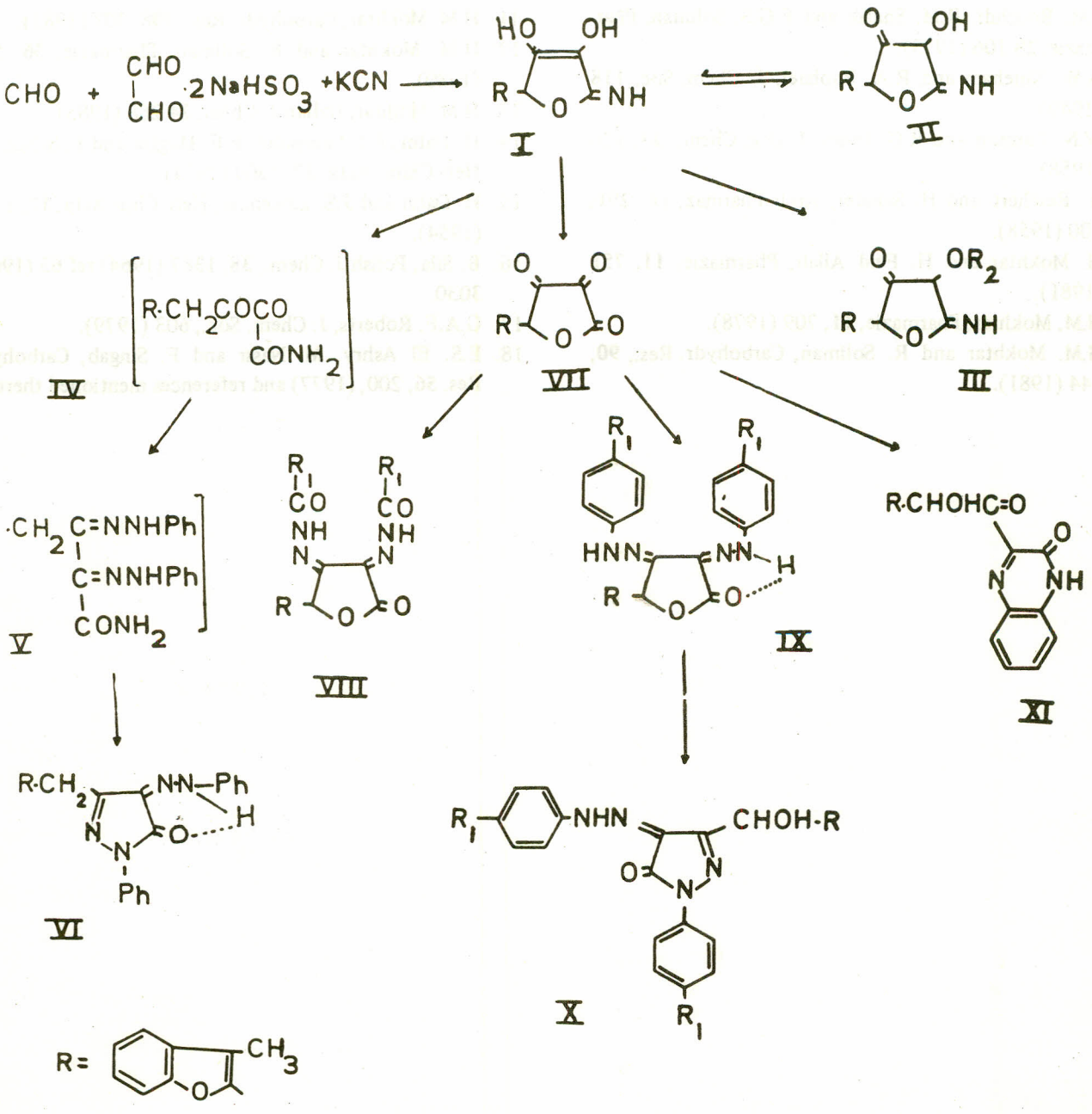
E = ethanol, W = water

and 2N sulphuric acid (8 ml) was cooled to 10° and, than treated dropwise with 10% sodium nitrite solution 5 ml. The mixture was warmed to expel the nitrogen and allowed to cool. The separated solid was filtered off, washed with water, dried and recrystallized from dilute ethanol to give needles, m.p. 180°, (yield, 35%).
IR: 1715, 1705 (CO) and 1775 cm^{-1} (COO). (Found: C, 64.3; H, 3.4; $C_{13}H_8O_5$ requires: C, 63.9; H, 3.3%).

2,3-Dioxo-4-(3-methylbenzofuran-2-yl)butyro-1,4-lactone 2,3-bis acylhydrazones (VIII). These compounds were prepared by heating a solution of (VII; 1 m mole) in 20 ml dilute ethanol (1 ; 1) containing two drops of glacial acetic acid, with an alcoholic solution of the desired acylhydrazine (2 m mole) for 3 hr. Concentration, cooling, dilution with water afforded the bis-acylhydrazones that were recrystallized from the appropriate solvent to give reddish-brown needles (Table 1).

2,3-Dioxo-4-(3-methylbenzofuran-2-yl)butyro-1,4-lactone 2,3-bisarylhydrazones (IX). A solution of (VII; 1 m mole) in 20 ml dilute ethanol (1 : 1) and two drops of glacial acetic acid was boiled with 2 m moles of the appropriate arylhydrazines on a steam bath for 3 hr. The bis-arylhydrazones that separated out were filtered off, washed with water and recrystallized from the appropriate solvent to give reddish-brown needles (see Table 2).

3-(3-Methylbenzofuran-2-yl hydroxymethyl)-1-aryl-4-aryl-hydrazono-2-pyrazolin-5-one (X). These compounds were obtained by heating the bis-arylhydrazones (IX; 0.5 g) with 2N sodium hydroxide solution (25 ml) for 30 min. on a water bath. Cooling and subsequent acidification with



glacial acetic acid furnished solid products which were recrystallized from dilute ethanol to give brown needles, yield 35%.

IR: 3400 (OH) and 1660 cm^{-1} (CON). The prepared compounds were (R_1 = H), m.p. 131° and(R_1 = SO_2NH_2), m.p. 171°. Satisfactory analyses (C, H, N) were obtained for compounds (X).

Quinoxaline derivative (XI). A mixture of (VII; 1 m mole) and *o*-phenylenediamine (1 m mole) in ethanol 25 ml was refluxed for 2 hr. Upon cooling the quinoxiline derivative separated out and recrystallized from benzenemethanol mixture to give yellow needles, m.p. 232°, yield 80%.

IR: 1690 cm^{-1} (CON), 3350 cm^{-1} (OH). (Found: C, 72.0; H, 4.0; N, 8.9; $C_{19}H_{12}N_2O_3$ requires C, 72.1; H, 3.8; N, 8.9%).

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