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New Tetracyclic Spiro-1,2,4-trioxolanes (Ozonides). Synthesis and Mass Spectrometric Study

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Abstract—New tetracyclic dispiro-1,2,4-trioxolanes (ozonides) were synthesized by reactions of 5–7-membered alicyclic 1,5-diketones with 30% hydrogen peroxide in diethyl ether or ethanol in the presence of boron trifluoride–diethyl ether complex or a strong mineral acid (HCl, H_2SO_4, $HClO_4$). Mass spectrometric study of the title compounds under atmospheric pressure chemical ionization revealed specificity of fragment ion decomposition with respect to the ring size, which makes it possible to identify such compounds by their mass spectra.

Keywords: alicyclic 1,5-diketones, hydrogen peroxide, spiro-1,2,4-trioxolanes, tetracyclic ozonides, mass spectrometry, atmospheric pressure chemical ionization, quasi-molecular ions.

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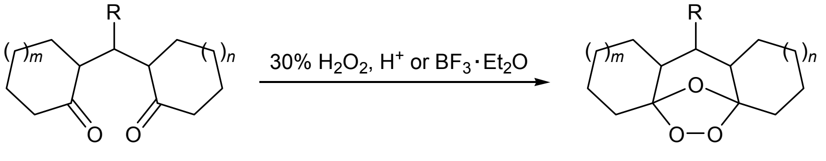
We previously found [1] that alicyclic 1,5-diketones **1**–**5** are oxidized with 30% hydrogen peroxide in diethyl ether or ethanol in the presence of boron trifluoride–diethyl ether complex or a strong mineral acid (HCl, H_2SO_4, $HClO_4$) to give novel compounds, tetracyclic dispiro-1,2,4-trioxolanes (ozonides) **6**–**10** in good yields (70–90%; Scheme 1). The classical method for the synthesis of ozonides by ozonation of olefins dates back to the past century. The preparation of ozonides from 1,5-diketones and hydrogen peroxide is quite unusual since the products are obtained without using ozone.

Up to now, only one compound of this type has been reported, namely ozonide **6** which was synthesized from diketone **1** by the action of peroxyformic acid or hydrogen peroxide in methanol in the presence of V_2O_5 [2]. Terent'ev et al. [3, 4] recently reported the synthesis of a series of bicyclic ozonides by reaction of aliphatic 1,5-diketones with hydrogen peroxide in acetonitrile in the presence of $BF_3 \cdot OEt_2$; the same compounds were obtained previously [5] from β,δ-triketones in 15–25% yield as mixtures with bridged tetraoxanes and monoperoxides. The first ozonide of this series was synthesized from heptane-2,6-dione [6]. Tricyclic ozonides can be synthesized according to Griesbaum [7, 8] by ozonation of a mixture of ketone oxime *O*-alkyl ether and monocarbonyl compound in pentane at –78°C.

Scheme 1.



1–5 **6–10**

1, **6**, $m = n = 0$, R = H; **2**, **7**, $m = n = 1$, R = H; **3**, **8**: $m = 1$, $n = 0$, R = H; **4**, **9**, $m = 1$, $n = 2$, R = H; **5**, **10**, $m = n = 1$, R = Me.

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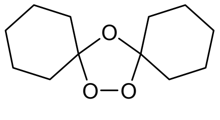
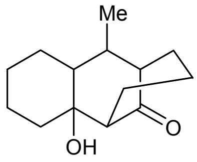
† Deceased.

Over the past two decades, tricyclic ozonides like **A** have attracted increased interest due to their pronounced antimalarial activity [9–11]. Therefore, they are considered to be synthetic analogs of the natural peroxide artemisinin which is the main drug for the treatment of malaria [12–22]. Tetracyclic ozonides **6–10** synthesized by us possess the same pharmacophoric fragment as in structure **A**.



A



5a

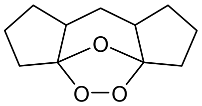
1,5-Diketones **1–4** exist in the stable diketone form, whereas compound **5** has cyclic structure **5a** which undergoes thermal ring opening at 180–186°C. Compounds **6–10** are highly resistant to heat; they do not decompose on melting (110–130°C), burn with a flash in an open flame, and give a positive test for peroxides with a solution of potassium iodide.

The structure of ozonides **6–10** was confirmed by IR, NMR, and mass spectra. The IR spectra of **6–10** (KBr) showed no carbonyl stretching bands typical of initial diketones, but contained bands in the region 900–970 cm^{-1} due to peroxide O–O bond. Their ^{13}C NMR spectra (DEPT-135) displayed signals typical of quaternary carbon atoms linked to two oxygen atoms (spiro carbon atoms) at δ_C 122, 108–110, and 112 ppm for cyclopentane, cyclohexane, and cycloheptane derivatives. The number and position of signals from quaternary, tertiary, secondary, and primary carbon atoms were consistent with the proposed structures. The number of signals in the spectra of **6**, **7**, and **10** was twice as low as the number of carbons in their molecules due to their symmetric structure corresponding to *meso* form. The ^1H NMR spectra of **6–10** were low informative; all proton signals appeared as a multiplet in the region δ 1.07–1.9 ppm [9–11].

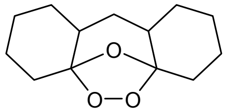
The mass spectra of **6–10** showed some specific features related to the size of the carbocycles and substituent nature. Taking into account that these compounds were not described previously, their mass spectra were analyzed in more detail with a view to further identification of related structures with different sizes of the rings.

Mass spectrometric study showed that compounds **6–10** under atmospheric pressure chemical ionization (APCI) give rise to quasi-molecular ions $[M + H]^+$ which undergo fragmentation via successive elimination of three water molecules. The MS^2 fragmentation pattern of the quasi-molecular ions of **6–10** differs from that observed for ozonides derived from linear olefins [23, 24]. The MS^2 spectra of compounds **6** and **7** containing two five- or six-membered alicyclic fragments displayed signals arising from elimination of similar neutral species from the $[M + H]^+$ ions (Table 1).

However, the spectra of **6** and **7** showed some differences which may be related to specific fragmentations of the five- and six-membered carbocycles. Thus, the $[M + H]^+$ ion of **6** loses C_2H_6O and $C_3H_6O_2$ species, while elimination of $2H_2O + C_3H_6$, $C_6H_{10}O$, and $2H_2O + C_5H_6$ is observed from the quasi-molecular ion of **7**. The C_2H_6O species is likely to consist of water and ethylene molecules, and elimination of ethylene is possible only in combination with water molecule. Presumably, joint elimination of C_2H_6O and CO molecule is responsible for the loss of the $C_3H_6O_2$ species. This becomes possible when elimination of one water molecule due to cleavage of the oxygen–oxygen bond in the peroxide fragment is followed by carbonylation of the carbon atom at the remaining oxygen atom in the resulting ion. Elimination of propylene in combination with two water molecules, as well as of cyclopentadiene, also together with two water molecules, may be noted as specific for the decomposition of six-membered alicyclic fragments of



6



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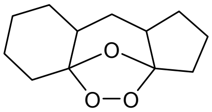

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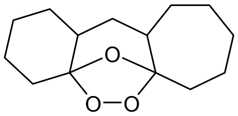

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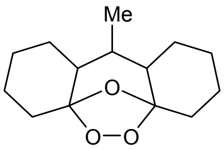

10

Table 1. Mass spectra (APCI) of compounds **6**–**10**

Comp. no.	APCI, m/z (I, %)	Monoisotopic molecular weight		Formula	MS^2		
		found	calculated		fragment ion $[M + H - X]^+$		X
					m/z (I, %)	composition	
6	$[M + H]^+$, 197.1191 (100);	196.1118	196.1099	$C_{11}H_{16}O_3$	179.1093 (100)	$[C_{11}H_{15}O_2]^+$	H_2O
	$[M + H - H_2O]^+$, 179.1096 (42);				161.0963 (30)	$[C_{11}H_{13}O]^+$	$2H_2O$
	$[M + H - 2H_2O]^+$, 161.0983 (11.5);				143.0906 (8)	$[C_{11}H_{11}]^+$	$3H_2O$
	$[M + H - 3H_2O]^+$, 143.0904 (1.8)				**151.0791 (41)**	**$[C_9H_{11}O_2]^+$**	**C_2H_6O**
					133.0630 (83)	$[C_9H_9O]^+$	$2H_2O + C_2H_4$
					123.0773 (15)	**$[C_8H_{11}O]^+$**	**$C_3H_6O_2$**
					105.0404 (2.8)	$[C_7H_4O]^+$	$2H_2O + C_4H_8$
7	$[M + H]^+$, 225.1455 (100);	224.1382	224.1412	$C_{13}H_{20}O_3$	207.1357 (100)	$[C_{13}H_{19}O_2]^+$	H_2O
	$[M + H - H_2O]^+$, 207.1355 (72);				189.1232 (67)	$[C_{13}H_{17}O]^+$	$2H_2O$
	$[M + H - 2H_2O]^+$, 189.1229 (19);				171.1183 (6.5)	$[C_{13}H_{15}]^+$	$3H_2O$
	$[M + H - 3H_2O]^+$, 171.1172 (3.5)				161.0931 (7)	$[C_{11}H_{13}O]^+$	$2H_2O + C_2H_4$
					147.0774 (2.5)	**$[C_{10}H_{11}O]^+$**	**$2H_2O + C_3H_6$**
					133.0648 (0.3)	$[C_9H_9O]^+$	$2H_2O + C_4H_8$
					127.0751 (0.1)	**$[C_7H_{11}O_2]^+$**	**$C_6H_{10}O$**
					123.0774 (2.7)	**$[C_8H_{11}O]^+$**	**$2H_2O + C_5H_6$**
8	$[M + H]^+$, 211.1352 (100);	210.1279	210.1256	$C_{12}H_{18}O_3$	193.1287 (100)	$[C_{12}H_{17}O_2]^+$	H_2O
	$[M + H - H_2O]^+$, 193.1287 (35);				175.1168 (44)	$[C_{12}H_{15}O]^+$	$2H_2O$
	$[M + H - 2H_2O]^+$, 175.1165 (10);				157.1063 (1.5)	$[C_{12}H_{13}]^+$	$3H_2O$
	$[M + H - 3H_2O]^+$, 157.1067 (1.3)				165.0951 (1)	$[C_{10}H_{13}O_2]^+$	C_2H_6O
					147.0771 (16)	$[C_{10}H_{11}O]^+$	$2H_2O + C_2H_4$
					137.0972 (0.1)	$[C_9H_{13}O]^+$	$C_3H_6O_2$
					133.0681 (0.3)	$[C_9H_9O]^+$	$2H_2O + C_3H_6$
					119.0545 (1)	$[C_8H_7O]^+$	$2H_2O + C_4H_8$
					113.0685 (3)	$[C_6H_9O_2]^+$	$C_6H_{10}O$
					109.0661 (0.5)	$[C_7H_9O]^+$	$2H_2O + C_5H_6$
9	$[M + H]^+$, 239.1612 (74);	238.1549	238.1569	$C_{14}H_{22}O_3$	221.1464 (100)	$[C_{14}H_{21}O_2]^+$	H_2O
	$[M + H - H_2O]^+$, 221.1462 (100);				203.1385 (45)	$[C_{14}H_{19}O]^+$	$2H_2O$
	$[M + H - 2H_2O]^+$, 203.1368 (10.5);				185.1273 (15)	$[C_{14}H_{17}]^+$	$3H_2O$
	$[M + H - 3H_2O]^+$, 185.1277 (2.5)				175.1041 (8)	$[C_{12}H_{15}O]^+$	$2H_2O + C_2H_4$
					161.0932 (0.5)	$[C_{11}H_{13}O]^+$	$2H_2O + C_3H_6$
					147.0776 (0.1)	$[C_{10}H_{11}O]^+$	$2H_2O + C_4H_8$
					143.0841 (1)	**$[C_{11}H_{11}]^+$**	**$3H_2O + C_3H_6$**
					137.0933 (31)	$[C_9H_{13}O]^+$	$2H_2O + C_5H_6$
					123.0771 (2)	**$[C_8H_{11}O]^+$**	**$2H_2O+C_6H_8$**
					119.1085 (3.5)	**$[C_6H_{14}O_2]^+$**	**C_8H_8O**
10	$[M + H]^+$, 239.1643 (45);	238.1570	238.1569	$C_{14}H_{22}O_3$	221.1566 (100)	$[C_{14}H_{21}O_2]^+$	H_2O
	$[M + H - H_2O]^+$, 221.1535 (100);				203.1450 (82)	$[C_{14}H_{19}O]^+$	$2H_2O$
	$[M + H - 2H_2O]^+$, 203.1410 (9);				185.1322 (10.5)	$[C_{14}H_{17}]^+$	$3H_2O$
	$[M + H - 3H_2O]^+$, 185.1280 (1.2)				175.1114 (7)	$[C_{12}H_{15}O]^+$	$2H_2O + C_2H_4$
					161.1001 (6.5)	$[C_{11}H_{13}O]^+$	$2H_2O + C_3H_6$
					159.1205 (0.5)	**$[C_{12}H_{15}]^+$**	**$3H_2O + C_2H_2$**
					137.0998 (9)	$[C_9H_{13}O]^+$	$2H_2O + C_5H_6$

Table 2. Fragmentation of quasi-molecular ions $[M + H]^+$ of 1,2,4-trioxolanes **6**–**10**

Comp. no.	Product ion composition												
	$C_6H_{14}O_2$	$C_6H_9O_2$	$C_7H_{11}O_2$	C_7H_4O	C_7H_9O	C_8H_7O	$C_8H_{11}O$	C_9H_9O	$C_9H_{11}O_2$	$C_9H_{13}O$	$C_{10}H_{13}O_2$	$C_{10}H_{11}O$	$C_{12}H_{15}$
	Relative intensity, % lost neutral fragments												
6				2.8[a] $2H_2O + C_4H_8$			15[b] $C_3H_6O_2$	83[a] $2H_2O + C_2H_4$	41[b] C_2H_6O				
7			0.1[c] $C_6H_{10}O$				2.7[c] $2H_2O + C_5H_6$	0.3[a] $2H_2O + C_4H_8$				2.5[c] $2H_2O + C_3H_6$	
8		3[c] $C_6H_{10}O$			0.5[c] $2H_2O + C_5H_6$	1[a] $2H_2O + C_4H_8$		0.3[c] $2H_2O + C_3H_6$		0.1[b] $C_3H_6O_2$	1[b] C_2H_6O	16* $2H_2O + C_2H_4$	
9	3.5[d] C_8H_8O									31[c] $2H_2O + C_5H_6$		0.1[a] $2H_2O + C_4H_8$	
10										9[c] $2H_2O + C_5H_6$			0.5[e] $3H_2O + C_2H_2$

[a] Nonspecific ions.
[b] Ions specific for five-membered alicyclic structures.
[c] Ions specific for six-membered alicyclic structures.
[d] Ions specific for seven-membered alicyclic structures.
[e] Ion specific only for compound **10**.

compound **7**. Furthermore, the MS^2 spectrum of **7** showed elimination of $C_6H_{10}O$ species which can be interpreted as joint expulsion of water and cyclohexadiene.

The tandem mass spectrum of the $[M + H]^+$ ion of **8** contained signals both common and specific for compounds **6** and **7**. The MS^2 fragmentation pattern of the quasi-molecular ion of **9** was characterized by formation of all ions typical of decomposition of the six-membered ring and ions specific for this compound, namely those resulting from simultaneous loss of two water molecules and cyclohexadiene and of three water molecules in combination with propylene. In addition, a ion peak corresponding to elimination of a C_8H_8O species was observed, which is likely to indicate the presence of a seven-membered ring in the parent ion.

Unlike compounds **6**–**9**, the MS^2 fragmentation of the $[M + H]^+$ ion of **10** involved joint elimination of three water molecules and acetylene. Presumably, this is determined by the presence of a methyl group in the bridging fragment connecting the cyclohexane rings. Elimination of acetylene molecule provides the possibility of directly linking the rings to each other, and the loss of three water molecule leads to the formation of a stable conjugated bicyclic structure.

Comparison of the compositions of ions formed by the MS^2 fragmentation of the $[M + H]^+$ ion of **6**–**10** (Table 2) showed preferential formation (apart from the dehydration processes) of $[C_8H_{11}O]^+$ ions from **6**, **7**, and **9**, $[C_9H_9O]^+$ ions from **6**, **7**, and **8**, and $[C_9H_{13}O]^+$ species from **8**, **9**, and **10**. Thus, we can exclude ions resulting from simultaneous loss of two water molecules and ethylene, which are highly abundant in the spectra of all compounds but are not structure-specific, as well as ions resulting from loss of two water molecules and butene.

It is seen that the presence in the mass spectra of intense ion peaks due to elimination of one water molecule and ethylene both jointly with CO molecule and without it indicates that the quasi-molecular ion contains a five-membered carbocycle. Analogous compounds with a cyclohexane fragment are characterized by preferential elimination of two water molecules and propylene, as well as of two water molecules and cyclopentadiene, from the $[M + H]^+$ ion. Compound **8** containing five- and six-membered alicyclic fragments shows reduced intensities of ring size-specific ion peaks (see above). Simultaneously, increased intensity is observed for ion peaks corresponding to joint elimination of water molecule and cyclohexadiene that are typical of fragmentation of the quasi-molecular ion of **7** with two cyclohexane rings. In the MS^2 spectra of **9** and **10**, relatively abundant ions are those arising from decomposition of the six-membered ring. However, the quasi-molecular ion of **9** loses a neutral C_8H_8O species which, as noted above, is specific for seven-membered alicyclic fragment. On the other hand, fragmentation of the $[M + H]^+$ ion of **10** involves elimination of acetylene molecule together with three water molecules, indicating the presence of a methyl group in the bridging moiety.

Thus, peculiar features of fragmentation of the quasi-molecular ions of compounds **6**–**10** (Table 2) provide the possibility of identifying ozonides containing five-, six-, and seven-membered rings.

EXPERIMENTAL

The IR spectra were recorded in KBr on a Bruker Vertex-70 spectrometer. The ^1H and ^{13}C NMR spectra were measured on a Bruker Avance II 400 spectrometer (400 and 125 MHz, respectively) at 30°C using $CDCl_3$ as solvent and tetramethylsilane as internal standard. Signals in the ^{13}C NMR spectra were assigned using DEPT-135 pulse sequence. The mass spectra were obtained on a Shimadzu LCMS-IT-TOF instrument (atmospheric pressure chemical ionization; simultaneous positive and negative ion detection; ion source temperature 300°C; nebulizer gas nitrogen, flow rate 2 L/min; drying gas pressure 20 kPa; source voltage +4.5 kV for positive ions and –3.8 kV for negative ions; a.m.u. range 100–1500). The melting points were measured in sealed capillaries with a Buchi Melting Point V-540 apparatus. The progress of reactions was monitored by TLC on Silufol plates (eluent hexane–ethyl acetate, 5 : 1), following the disappearance of the initial diketone.

General procedure for the synthesis of ozonides 6–8 and 10. A solution of 0.001 mol of diketone **1**, **2**, **3**, or **5** in 2 mL of diethyl ether was cooled in an ice bath, 0.18 mL (0.015 mol) of 30% aqueous hydrogen peroxide was added with stirring, and a solution of 0.15 mL (0.001 mol) of boron trifluoride–diethyl ether complex in 2 mL of diethyl ether was added dropwise, maintaining the temperature at 0°C. The mixture was left to stand for 12 h at 20°C and neutralized with a saturated solution of sodium carbonate, and the organic layer was separated, washed with water (3 × 3 mL), dried over $MgSO_4$, and evaporated at 20°C.

2,3,14-Trioxatetracyclo[8.3.0.1^{1,4}.0^{4,8}]tetradecane (6). Yield 86%, white powder, mp 122–124°C (from

EtOH). IR spectrum, ν, cm^{-1}: 2939, 2860, 1149, 1137, 1072, 922. ^{1}H NMR spectrum: δ 1.18–2.11 ppm, m. ^{13}C NMR spectrum, δ_C, ppm: 122.42 (OCO), 42.36 (CH); 32.05, 31.13, 22.40 (CH_2). Mass spectrum: *m*/*z* 197.1191 [*M* + H]$^+$. $C_{11}H_{16}O_3$. Calculated: *M* 196.1099.

2,3,16-Trioxatetracyclo[9.4.0.$1^{1,4}$.$0^{4,9}$]hexadecane (7). Yield 92%, white plates, mp 118.5–120°C (from EtOH); published data [2]: mp 119–120°C (from MeOH). IR spectrum, ν, cm^{-1}: 2938, 2857, 1269, 1157, 1138, 1066, 972, 923. ^{1}H NMR spectrum: δ 1.18–1.91 ppm, m. ^{13}C NMR spectrum, δ_C, ppm: 108.5 (OCO), 41.21 (CH); 32.56, 31.59, 30.75, 25.11, 23.96 (CH_2). Mass spectrum: *m*/*z* 225.1455 [*M* + H]$^+$. $C_{13}H_{20}O_3$. Calculated: *M* 224.1412

2,3,15-Trioxatetracyclo[9.3.0.$1^{1,4}$.$0^{4,9}$]pentadecane (8). Yield 81%, oil. IR spectrum, ν, cm^{-1}: 2940, 2867, 1446, 1349, 1099, 1045, 928. ^{1}H NMR spectrum: δ 1.18–2.1 ppm, m. ^{13}C NMR spectrum, δ_C, ppm: 123.62, 111.21 (OCO); 47.79, 43.57 (CH); 34.52, 34.15, 33.43, 32.52, 30.44, 25.58, 23.66, 22.58 (CH_2). Mass spectrum: *m*/*z* 211.1352 [*M* + H]$^+$. $C_{12}H_{18}O_3$. Calculated: *M* 210.1256.

2,3,17-Trioxatetracyclo[10.4.0.$1^{1,4}$.$0^{4,10}$]heptadecane (9). Diketone **4**, 100 mg (0.45 mmol), was dissolved in 2 mL of ethanol, 0.2 mL (1.64 mmol) of 30% aqueous hydrogen peroxide and a drop of 33% H_2SO_4 (0.4 mmol) were added, and the mixture was left to stand for 12 h at room temperature. The product was isolated according to the general procedure (see above). Yield 60 mg (56%), needles, mp 60–61°C (from EtOH). IR spectrum, ν, cm^{-1}: 2938, 2858, 1157, 1138, 1066, 967, 923. ^{1}H NMR spectrum: δ 1.18–1.91 ppm, m. ^{13}C NMR spectrum, δ_C, ppm: 112.8, 109.6 (OCO); 44.89, 41.50 (CH); 35.99, 33.11, 32.34, 30.36, 30.15, 30.15, 29.06, 25.10, 23.89, 22.53 (CH_2). Mass spectrum: *m*/*z* 239.1612 [*M* + H]$^+$. $C_{14}H_{22}O_3$. Calculated: *M* 238.1569

10-Methyl-2,3,16-trioxatetracyclo[9.4.0.$1^{1,4}$.$0^{4,9}$]-hexadecane (10). Ketol **5a**, 200 mg (0.9 mmol), was melted at 180–186°C on a metal bath and was kept for 30 min at that temperature. Diketone **5** thus obtained was dissolved in 2 mL of diethyl ether, and the undissolved material (ketol **5a**, 44 mg) was filtered off. The filtrate was placed in an ice bath, 0.18 mL (15 mmol) of 30% aqueous hydrogen peroxide was added, and a solution of 0.15 mL (1 mmol) of boron trifluoride–diethyl ether complex in 2 mL of diethyl ether was added dropwise, maintaining the temperature at 0°C. The mixture was stirred for 12 h at 20°C and was then treated according to the general procedure. Yield 168 mg (70%), white powder, mp 121–123.5°C (from EtOH). IR spectrum, ν, cm^{-1}: 2956, 2935, 2863, 1205, 1190, 1126, 1062, 977, 923. ^{1}H NMR spectrum, δ, ppm: 0.90–0.91 d (3H, CH_3), 1.07–1.90 m (19H). ^{13}C NMR spectrum, δ_C, ppm: 108.24 (OCO); 41.21, 35.51 (CH); 32.92, 28.17, 25.29, 23.86 (CH_2); 15.98 (CH_3). Mass spectrum: *m*/*z* 239.1643 [*M* + H]$^+$. $C_{14}H_{22}O_3$. Calculated: *M* 238.1569.

CONFLICT OF INTERESTS

The authors declare the absence of conflict of interests.

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