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THYMOL DERIVATIVES FROM *SCHIZOGYNE GLABERRIMA*

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Key Word Index—*Schizogyne glaberrima*; Compositae; monoterpenes; thymol derivatives.

Abstract—An investigation of *Schizogyne glaberrima* afforded in addition to known compounds 3-(acetoxy-methyl)-6-methyl-5-methoxy-benzofuran, 10-acetoxy-8,9-epoxy-6-methoxy-thymol isobutyrate, 10-acetoxy-8-hydroxy-9-isobutyryloxy-6-methoxy-thymol, 8-hydroxy-9,10-isobutyryloxy-thymol and 8,10-dihydroxy-9-isobutyryloxy-thymol, five new thymol derivatives, 8-ethoxy-9-isobutyryloxy-thymol, 10-acetoxy-8,9-dehydro-6-methoxy-thymol isobutyrate, 6-acetoxy-8,9-dehydro-9-carbomethoxy-10-hydroxy-thymol and 8,9-dihydroxy-10-isobutyryloxy-6-methoxy-thymol.

INTRODUCTION

This study is a continuation of our work on the constituents of the genus *Schizogyne* [1], which has been shown to produce thymol derivatives. We have previously isolated five such compounds: 3-(acetoxy-methyl)-6-methyl-5-methoxy-benzofuran, 10-acetoxy-8,9-epoxy-6-methoxy-thymol isobutyrate, 10-acetoxy-8-hydroxy-9-isobutyryloxy-6-methoxy-thymol, 8-hydroxy-9,10-isobutyryloxy-thymol and 8,10-dihydroxy-9-isobutyryloxy-thymol. In the present paper, we describe the isolation of five new thymol derivatives obtained in small quantities.

RESULTS AND DISCUSSION

The aerial parts of *Schizogyne glaberrima* DC [2] afforded a complex mixture of ten thymol derivatives which were separated by repeated TLC. Their structures were deduced by spectroscopic methods and a few chemical transformations.

8-Ethoxy-9-isobutyryloxy-thymol (**1**) was obtained as an oil. The mass spectrum indicated a molecular ion at m/z 280 in agreement with the molecular formula $C_{16}H_{24}O_4$. The ^{1}H NMR spectrum was in agreement and was typical of a 1,3,4-trisubstituted aromatic ring (Table 1). The IR spectrum showed the presence of a hydroxyl (3300 cm^{-1}), ester (1730 cm^{-1}) and an aromatic ring (1610, 1460 cm^{-1}). This substance may have been formed during the extraction process.

Acetylation of **1** with acetic anhydride in pyridine at room temperature afforded the monoacetate oil (**1a**) whose structure was in accordance with its ^{1}H NMR spectrum (Table 1). The IR spectrum indicated the presence of an ester (1750–1725 cm^{-1}). Its ^{13}C NMR spectrum (Table 2) was in agreement with the proposed structure.

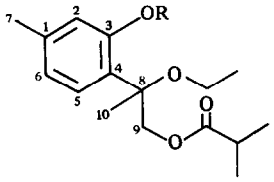
Table 1. ^{1}H NMR spectral data for compounds **1**, **1a**, **3**, **4**, **6** and **10**

	1	**1a**	**3**	**4**	**6**	**10**
H-2	6.7 *br s*	6.86 *br s*	6.75 *s*	6.69 *s*	6.7 *s*	6.6 *s*
H-5	6.92 (9)*	7.34 (9)	6.83 *s*	6.51 *s*	6.86 *s*	6.98 *s*
H-6	6.64 *br s*	7.03 (9)				
H-7	2.27 *s*	2.33 *s*	2.2 *s*	2.16 *s*	2.30 *s*	2.15 *s*
H-9	4.4–4.2	4.4 *s*	5.39 *br s*	6.36 *s*	5.0 *br s*	4.55
	dd (10)		5.22 *br s*			4.40 *dd* (10)
H-10	1.65 *s*	1.6 *s*	4.8 *br s*	5.05 *s*	7.3 *s*	3.84 *s*
MeOAr			3.83 *s*		3.80 *s*	3.75 *s*
Ac		2.28 *s*	2.1 *s*	2.03 *s*	2.15 *s*	
$C(Me)_2$	1.08 (7)	1.08 (7)	1.27 (7)		1.02 (7)	1.13 (7)
	2.56 *m*	2.5 *m*	2.76 *m*		2.56 *m*	2.56 *m*
$OC\underline{H_2}Me$	3.45 *c*	3.25 *c*				
$OCH_2\underline{Me}$	1.06 *t*	1.06 *t*				
COOMe				3.77 *s*		3.77 *s*

*Figures in parentheses are coupling constants in Hz.

Table 2. ^{13}C NMR spectral data for compound **1**, **1a**, **3**, **4**, **6** and **10**

	1	1a	3	4	6	10
C-1	139.6	138.9	122	135.3	126.7	129.7
C-2	117.4	124.7	124.4	118.7	124.5	120.0
C-3	155.8	148.5	140.4	151.4	141.3	149.6
C-4	126.5	129.9	127.4	120.9	127.5	120.4
C-5	127.0	128.5	110.7	121.8	111.3	108.7
C-6	120.3	126.4	146.0	146.7	155.2	150.9
C-7	20.9	20.8	16.0	16.0	16.0	15.8
C-8	77.6	77.2	146.0	128.8	130.8	78.6
C-9	66.8	68.5	116.7	111.6	59.6	65.6
C-10	20.9	22.0	66.1	62.6	136.7	67.2
OMe					55.6	56.1
OAc		21.4	20.9	20.6	20.7	
				170.8	167.0	
OCOR	176.3	176.5				178.7
C(Me)$_2$	33.9	34.0	34.0		33.9	34.0
C(Me)$_2$	18.7	18.9	18.9		18.8	18.8
OCH$_2$Me	15.3	15.4				
OCH$_2$Me	59.7	58.2				
COOMe				55.9		56.1
				163.8		



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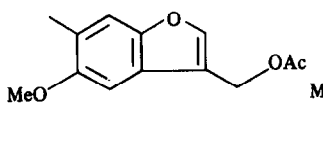
1a R = Ac



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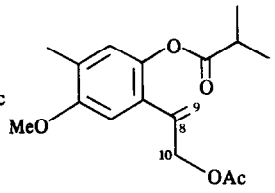

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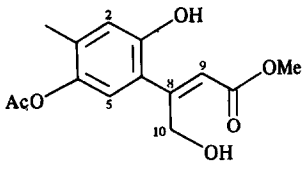

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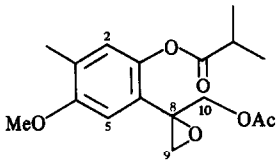

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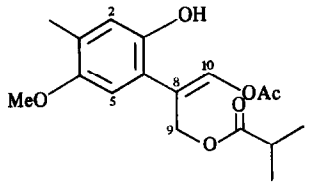

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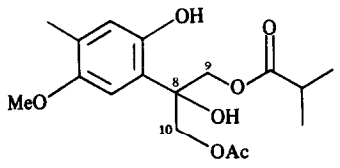

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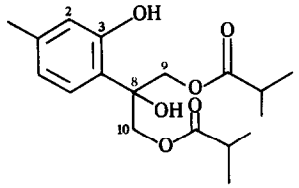

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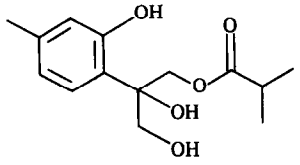

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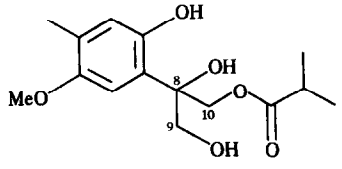

10

10-Acetoxy-8,9-dehydro-6-methoxy-thymol isobutyrate (**3**) was isolated as an oil. The mass spectrum clearly indicated the molecular formula $C_{17}H_{22}O_5$. Its IR spectrum showed absorptions at 1740 cm^{-1} (ester) and 1665 and 1500 cm^{-1} (aromatic ring). The ^1H NMR was characteristic of a 1,2,4,5-tetrasubstituted aromatic ring (Table 1). Its structure was confirmed by the ^{13}C NMR spectrum (Table 2).

6-Acetoxy-8,9-dehydro-9-carbomethoxy-10-hydroxy-thymol (**4**) had the molecular formula $C_{14}H_{16}O_6$. The IR spectrum indicated the presence of a hydroxyl (3300 cm^{-1}), an ester (1730 cm^{-1}) and an aromatic ring (1500, 1460 cm^{-1}). The ^1H NMR spectrum was characteristic of a 1,2,4,5-tetrasubstituted aromatic ring (Table 1). The structure was confirmed by its ^{13}C NMR spectrum (Table 2).

10-Acetoxy-8,10-dehydro-9-isobutyryloxy-6-methoxy-thymol (**6**) was obtained as an oil. The molecular ion at *m/z* 322 was in agreement with the formula $C_{17}H_{22}O_6$. Strong unconjugated carbonyl absorptions (1750 cm^{-1}, br) were assigned to the acetate and isobutyrate moieties. The acetate assignment was supported by the broad absorption at 1210 cm^{-1}. The structure is supported by its ^1H NMR spectrum (Table 1).

Acetylation of **6** with acetic anhydride in pyridine at room temperature afforded a monoacetate with a molecular ion at *m/z* 364. The structure of **6** is consistent with the ^{13}C NMR spectrum (Table 2). However, the stereochemistry of the 8(10)-double bond could not be assigned with certainty. Inspection of the ^1H NMR spectrum suggested a *Z*-configuration because the signal at δ7.3 is modified in the acetate.

8,9-Dihydroxy-10-isobutyryloxy-6-methoxy-thymol (**10**) was isolated as an oil, with a molecular ion at *m/z* 298 in agreement with the molecular formula $C_{15}H_{22}O_6$. Its IR spectrum showed absorptions characteristic of hydroxyls (3375 cm^{-1}), an ester (1725 cm^{-1}) and aromatic ring (1500, 1465 cm^{-1}). The ^1H NMR spectrum showed characteristic signals of a 1,2,4,5-tetra-substituted aromatic ring (Table 1). The structure of the product was confirmed by its ^{13}C NMR spectrum (Table 2).

3-(Acetoxy-methyl)-6-methyl-5-methoxy-benzofuran (**2**), 10-acetoxy-8,9-epoxy-6-methoxy-thymol isobutyrate (**5**), 10-acetoxy-8-hydroxy-9-isobutyryloxy-6-methoxy-thymol (**7**), 8-hydroxy-9,10-isobutyryloxy-thymol (**8**) and 8,10-dihydroxy-9-isobutyryloxy-thymol (**9**) were also isolated and have been described in a preliminary communication [1]. Compound **5** was first isolated from *Ageratina glabrata* by Bohlmann *et al.* [3] and **9** from *Brasilia sickii* [4].

EXPERIMENTAL

^1H NMR spectra were recorded at 60 and 90 MHz and ^{13}C NMR at 25 MHz in $CDCl_3$ with TMS as internal standard. Analytical TLC was performed on silica gel and CC was on silica gel. The plant material was extracted with EtOH.

Schizogyne glaberrima DC, collected in Maspalomas (Gran Canaria), was identified by Dr. David Bramwell from Botanical Garden of Las Palmas, where a specimen is deposited (Herbarium no 552/86-2-17). The aerial parts (1 kg) afforded 50 mg **1**, 30 mg **2**, 25 mg **3**, 20 mg **4**, 200 mg **5**, 30 mg **6**, 210 mg **7**, 100 mg **8**, 25 mg **9** and 20 mg **10**.

8-Ethoxy-9-isobutyryloxy-thymol (**1**). Oil (C_6H_6). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3300 (OH), 1730 (ester), 1610–1460 (aromatic). MS *m/z* (rel. int.): 280 (1.6) $[M]^+$ ($C_{16}H_{24}O_4$), 192 (1.4), 179 (57.6). 165 (12.7), 147 (37.3), 71 (49.4).

Acetylation of compound **1**. Compound **1** (30 mg) was dissolved in Ac_2O and pyridine. The soln was left for 12 hr, then concd *in vacuo* to give the monoacetate which was purified by silica gel CC: oil; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1750–1725 (ester), 1610–1460 (aromatic).

10-Acetoxy-8,9-dehydro-6-methoxy-thymol isobutyrate (**3**). Oil (yellow gum). IR $\nu_{max}^{CHCl_3}$: 1740 (ester), 1615, 1500 and 1460 (aromatic ring). MS *m/z* (rel. int.): 306 (71.35) $[M]^+$ $C_{17}H_{22}O_5$, 264 (2.7) $[M - C_2H_2O]^+$, 236 (63.8) $[M - O{=}C{=}C(Me)_2]^+$, 194 (62.5) $[M - O{=}C{=}C(Me)_2 - C_2H_2O]^+$, 176 (100), 71 (44.5).

6-Acetoxy-8,9-dehydro-9-carbomethoxy-10-hydroxy-thymol (**4**). Oil; IR $\nu_{max}^{CHCl_3}$: 3300 (OH), 1739 (ester), 1500 and 1460 (aromatic ring). MS *m/z* (rel. int.): 280 (0.8) $[M]^+$ ($C_{14}H_{16}O_6$), 221 (0.8) $[M - CO_2Me]^+$, 195 (26.57), 192 (10.7), 175 (100), 77 (9.26), 71 (1.49).

10-Acetoxy-8,10-dehydro-9-isobutyryloxy-6-methoxy-thymol (**6**). Oil; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400 (OH), 1750 (ester), 1460, 1400 (aromatic ring) and 1210 (OAc). MS *m/z* (rel. int.): 322 (3.5) $[M]^+$ ($C_{17}H_{22}O_6$), 262 (18.7) $[M - 60]^+$, 209 (0.7), 192 (100).

The acetate of **6** was prepared by acetylation (20 mg) with Ac_2O-pyridine to provide a monoacetate: MS *m/z* (rel. int.): 364 (8.8), 322 (1.9), 192 (46.0), 162 (25.1), 71 (17.3), 43 (100)

8,9-Dihydroxy-10-isobutyryloxy-6-methoxy-thymol (**10**). Oil; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3375 (OH), 1725 (ester), 1500 and 1465 (aromatic ring). MS *m/z* (rel. int.): 298 (6.28) $[M]^+$ ($C_{15}H_{22}O_6$), 280 (1.3) $[M - H_2O]^+$, 267 (3.5) $[M - CH_2OH]^+$, 197 (13.8) $[M - CH_2OH{-}C{=}C{=}C(Me)_2]^+$, 192 (22), 164 (12.87), 91 (31.92), 71 (57.44), 43 (100).

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