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11,13-DEHYDROERIOLIN, SCHKUHRIOIDIN AND SCHKUHRIOLID, GERMACRANOLIDES FROM *SCHKUHRIA* SPECIES*

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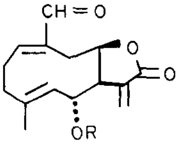
Key Word Index—*Schkuhria schkuhrioides*; *S. virgata*; Heliantheae; Compositae; germacranolides; sesquiterpene lactones.

Abstract—The isolation is reported of the new germacrolide, 11,13-dehydroeriolin, the new melampolide schkuhrioidin and schkuhriolide from *Schkuhria schkuhrioides*. 11,13-Dehydroeriolin is also a constituent of *S. virgata*. The structure and stereochemistry of the new compounds were established on chemical and spectroscopic grounds.

INTRODUCTION

The annual plants *Schkuhria schkuhrioides* (Link & Otto) Thellung and *S. pinnata* var. *virgata* (*S. virgata*) are abundant in central Mexico. They are members of the subtribe Bahiinae, now included in the tribe Heliantheae [1]. As sesquiterpene lactones are common constituents of the species belonging to this subtribe [2, 3], we expected to find them in the genus *Schkuhria*. The studies of several taxa confirmed our assumption, since they contain sesquiterpene lactones as well as other constituents [4–8]. The melampolide schkuhriolide (**5a**) was recently found as a constituent of *S. schkuhrioides* [9]. We independently examined the aerial part of the same species, and isolated, in addition to this compound, the germacrolide 11,13-dehydroeriolin (**1**) and the melampolide schkuhrioidin (**7a**). The germacrolide **1** was also found in *S. pinnata* collected in the valley of Mexico.



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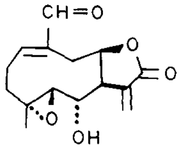

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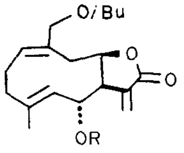

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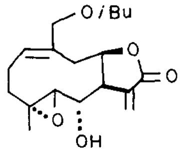
7b R = Ac



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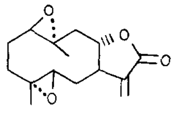

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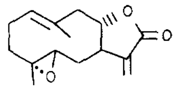

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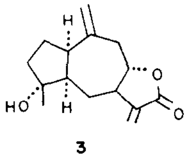

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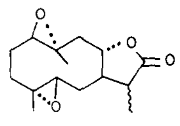

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RESULTS AND DISCUSSION

11,13-Dehydroeriolin (**1**), $C_{15}H_{20}O_4$, mp 173–174°, $[\alpha]_D$ $CHCl_3$ −36° contains an α,β-unsaturated γ-lactone as shown by its IR (1760, 1670 cm^{-1}) and UV spectra (UV λ_{max} 211 nm, ϵ 9000). The ^1H NMR spectral data are shown in Table 1. As the signals appeared better resolved in deuterobenzene (270 MHz), the decoupling was performed in this solvent. The doublets at δ 6.15 ($J = 3$ Hz) and δ 4.89 ($J = 3$ Hz) are H-13a and H-13b. Irradiation of either of these frequencies collapses the signals for H-7 at δ 1.92 to a broad triplet ($J \approx 9.5$ Hz). Conversely, irradiation of H-7 collapses H-13a and H-13b, the signal at δ3.43 to a doublet ($J = 10$ Hz) and affects the region δ 0.93. Hence H-6a and H-6b are located there. The lactone ring must be closed to C-8, since irradiation of the signal at δ 3.43 ($J = 10$, 7 Hz) collapses

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*Contribution No. 568.

Table 1. ^{1}H NMR spectral data of compounds **1** and **5–8** (100 MHz, $CDCl_3$)

	1	**1***	**5a**	**5b**	**6**	**7a**	**7b**	**8**
H-1	—	2.23 *br d* (10)	6.65 *m*	6.62 *m*	6.75 *m*	5.64 *m*	5.60 *m*	5.56 *m*
H-5	—	2.12 *dd* (11,9)	4.85 *br d* (10)	4.76 *br d* (10)	2.75 *d* (10)	4.95 *br d* (10)	4.83 *br d* (10)	—
H-6	—	0.93 *c*	3.99 *t* (10)	5.22 *t* (10)	3.27 *t* (10)	4.02 *t* (10)	5.26 *t* (10)	3.40 *t* (10)
H-7	2.98 *m*	1.92 *c*	2.54 *m*	—	—	2.84 *br dd* (10,5.5)	3.03 *br dd* (10,5.5)	
H-8	4.16 *ddd* (10,7.6,2.0)	3.43 (7)	5.46 *dt* (6,12,6)	5.54 *dt* (6,12,6)	5.53 *dt* (12,6,6)	4.72 *dt* (5.5,5.5,12)	4.72 *dt* (5.5,5.5,12)	4.58 *dt* (6,6,12)
H-9a	2.59 *dd* (2,16)	2.53 *d* (14)	—	—	—	—	—	—
H-9b	1.53 *dd* (10,16)	1.06 *dd* (14,10)	—	—	—	—	—	—
H-13a	6.31 *d* (3.4)	6.15 *d* (3.0)	6.22 *d* (1.5)	6.22 *d* (1.5)	6.27 *d* (1.5)	6.24 *d* (1.5)	6.24 *d* (1.5)	6.24 *d* (1.5)
H-13b	5.62 *d* (3.4)	4.89 *d* (3.0)	5.78 *d* (1.5)	5.76 *d* (1.5)	5.79 *d* (1.5)	5.82 *d* (1.5)	5.70 *d* (1.5)	5.83 *d* (1.5)
H-14	1.42 *s*†	0.93 *s*†	9.40 *d* (2)	9.42 *d* (2)	9.40 *d* (2)	4.53 (12)	4.52 (12)	4.5 (14)
H-15	1.26 *s*†	0.77 *s*†	1.81 *br s*	1.94 *br s*	1.51 *s*	1.78 *br s*	1.9 *br s*	1.45
-OH	—	—	3.34 *br s*	—	—	3.48 *br s*	—	—
Me-CO-	—	—	—	1.96*s*	—	—	2.0*s*	—
Me–C–Me		—	—	—	—	1.16 (7)	1.17 (7)	1.12 (7)

*270 MHz, pyridine.

†Interchangeable signals.

Coupling constants (Hz) in parentheses.

H-7 to a broad doublet ($J = 9.5$ Hz) and sharpens the signal at δ 2.53 (*br d*) and at δ 1.06 (*dd*). Hence, these signals correspond to H-9a and H-9b. This is confirmed by the inverse irradiation. The two remaining oxygen atoms are present in **1** as epoxides, according to the spectroscopic data and the molecular formula. The signals at δ 2.23 (*br d*, $J = 10$ Hz) and 2.12 (*dd*, $J = 11$ Hz) are the epoxide protons H-1 and H-5, according to the tri-substituted nature of this functionality. The singlets at δ 0.93 (3H) and 0.77 (3H) correspond to the methyl groups attached to tetrasubstituted carbon atoms bonded to epoxide oxygen. Due to superposition of signals, it was impossible to assign unambiguously the other protons.

The stereochemistry of the epoxy germacrolide should be as depicted in **1** based on the following facts: the epoxidation of the novel sesquiterpene lactone **2** (11,13-dehydroeriolin, 4,5-monoepoxide) [Dr. J. Calderón, I. Q. UNAM, personal communication] (full details will be reported elsewhere) afforded 11,13-dehydroeriolin (**1**). Substance **2** was converted upon cyclization to the guaianolide inuviscolide (**3**), thus establishing the lactone closure and the 4,5-epoxide stereochemistry. Assuming the peripheral 1,10-double bond epoxidation of the conformer of lower energy of **2** [10] the product obtained must have the stereochemistry depicted in **1**.

Hydrogenation of **1** afforded the dihydro derivative **4**, $C_{15}H_{22}O_4$, mp 240° whose physical constants and ^{1}H NMR spectrum are identical with those of eriolin (**4**) [11, 12].

The next compound, $C_{15}H_{18}O_4$, mp 160–163° $[\alpha]_D$ +170.8° is a melampolide with an aldehyde at C-10 as frequently found in this kind of compound [13]. The aldehydic proton resonates at δ 9.40, a chemical shift characteristic for an aldehyde attached to a *cis* double bond [14]. The physical constants and spectral data (IR, UV and ^{1}H NMR) of this melampolide are similar to that of schkuhriolide (**5a**) recently isolated from the same species [9]. Direct comparison established the identity of both substances. The acetyl and epoxide derivatives **5b** and **6** showed spectral data according with the proposed formulae.

Schkuhrioidin (**7a**), $C_{19}H_{25}O_5$, $[\alpha]_D^{20}$ +86.47° (MeOH) is an unstable oil whose NMR and IR data indicate that it differs from schkuhriolide only in a change of functionality at C-14. This is shown in the NMR spectrum of **7a** which does not show the low field singlet of the aldehydic proton, instead, it exhibits signals which correspond to an isobutyric ester attached to C-14. The C-14 methylene is shown as an AB system centred at δ 4.53 ($J = 12$ Hz). Consequently, with the lack of aldehydic function, there is an upfield shift of the signals of H-1 and H-8.

Nevertheless, the chemical shift of H-1 in **7a**, **7b** and **8** is still low (δ 5.60) due to the deshielding effect of the $-CH_2-OR$ present in the *cis* double bond [5, 6]. A similar chemical shift of H-1 is observed in the closely related melampolide dihydroacanthospermal A [17]. Hydrogens attached to equally substituted *trans* double bonds appear at higher field (near δ 5.00) [18, 19].

The mass spectrum of schkuhrioidin (**7a**) showed the molecular ion at m/z 344 and the parent peak at m/z 43 $[Me_2OH]^+$. The appearence of a peak at m/z 246 corresponding to $[M - C_3H_7CO]^+$ gives further support to the presence of an isobutyric ester.

Schkuhrioidin possesses a free hydroxyl group at C-6 as shown by the IR band at 3500 cm^{-1} and the ^{1}H NMR signals at δ 3.48 (*br*) which disappeared after equilibration with D_2O. The proton under the hydroxyl group at C-6 is shown as a triplet at δ 4.02 (J = 10 Hz). This signal moved downfield (δ 5.26) in the acetyl derivative **7b**. Epoxidation of **7a** afforded the epoxide **8**, whose H-6 signal moved upfield as expected.

Due to the close NMR similarities of schkuhriolide **5a** and schkuhrioidin **7a**, it is concluded that the lactone closure of the latter also belongs to the A-type [20] according to the observed coupling constant $J_{7-13} \leq 3$ Hz (A-type), corresponding to a *cis* C-8 lactone fusion. The α-configuration for the C-6 oxygenated function in **7a** is deduced from its large coupling constants with H-7 and H-5 both being 10 Hz. These large values can be explained assuming that H-7 is α-pseudo axial as in all sesquiterpene lactones of authenticated stereochemistry. H-6 should be β-oriented and 'anti' to H-7 and H-5. The downshift of H-7 on acetylation ($\Delta\delta = 0.19$) due to the β-acyl effect [21] provides further support to the 'syn' relationship between the C-6 hydroxyl and H-7.

The structure and stereochemistry of schkuhrioidin should therefore be represented by **7a**.

EXPERIMENTAL

Mps are uncorr.

Isolation of 11,13-*dehydroeriolin* (**1**), *schkuhrioidin A* (**5a**) *and schkuhrioidin B* (**7a**) *from* S. schkuhrioides (*voucher ARV* 040, *MEXU* 282537). *S. schkuhrioides* was collected near Lagos de Moreno, State of Jalisco, in Sept. 1978. Dried and ground plant material (2.7 kg of the aerial part) was extracted first with hexane and then with $CHCl_3$. The $CHCl_3$ extract was concd to give 107 g of an oily residue which was chromatographed over 3.2 kg Si gel (Merck, 70–230 mesh). 500 ml fractions were collected beginning with hexane–EtOAc (7:3). Fractions 96–126 containing a major spot were combined and kept for further purification (9g). Fractions 141 and 142, eluted with hexane–EtOAc (1:1), afforded 11,13-dehydroeriolin (390 mg), mp 172–173°, recrystallization from Me_2CO-Et_2O raised the mp to 173–174°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1760, 1670; UV $\lambda_{max}^{95\%EtOH}$ 211 nm (ϵ 3.95). Found: C, 68.30; H, 7.67; O, 24.00; $C_{15}H_{20}O_4$. Requires: C, 68.16; H, 7.63; O, 24.21%.

Fractions 181–193 (hexane–EtOAc, 2:3) afforded a solid substance which after crystallization from EtOAc–hexane left 4.3 g schkuhriolide (**5a**), mp 160–163°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3500, 1760, 1680, 1660; UV $\lambda_{max}^{95\%EtOH}$ 227 nm (ϵ 4.16). Found: C, 67.82; H, 6.92; O, 24.71%: $C_{15}H_{16}O_4$. Requires: C, 68.68; H, 6.92; O, 24.40. Fractions 96–126 (hexane–EtOAc 7:3) were combined affording 9.1 g of greenish-yellow oil with a major spot. This was rechromatographed affording schkuhrioidin B (**7a**) as a pale yellow oil (one spot in TLC). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3500, 1760 and 1660; UV $\lambda_{max}^{95\%EtOH}$: 210 nm (ϵ 4.03). The MS exhibited significant peaks at m/z 334 $[M]^+$ 246 $[M - C_3H_7COOH]^+$, 71 $[C_3H_7CO]^+$ and 43 [base peaks, $C_2H_3O]^+$.

11,13-*Dehydroeriolin* (**2**) *from* S. virgata. *S. virgata* was collected in the Valley of Mexico in Sept. 1975. Dried and ground plant material (2 kg) worked-up in the usual manner [3] afforded a gummy residue (19 g). This was chromatographed yielding 6.4 g of 11,13-dehydroeriolin, mp 172–173°, identical (direct comparison) with schkuhrioidin A obtained from *S. schkuhrioides*.

Eriolin (**4**). To a soln of 200 mg **1** in MeOH was added 20 mg PtO_2 in MeOH and the mixture hydrogenated until hydrogen uptake finished. After filtration, concn and addition of Et_2O crystallized the product (200 mg, mp 222–223°). Recrystallization from Me_2CO-Et_2O raised the mp to 240°. NMR: identical to that of eriolin [12]. Found: C, 67.64; H, 8.33; O, 24.03; $C_{15}H_{22}O_4$. Requires: C, 68.02; H, 8.21; O, 24.07%.

Schkuhrioidin A acetate (**5b**). Acetylation of 109 mg **5a** in 1 ml pyridine and 1 ml EtOAc followed by the usual work-up gave a solid substance which after recrystallization from EtOAc–hexane yielded 82 mg **5b**, mp 147–148°. $[\alpha]_D^{25} = +110.18°$ (MeOH) IR, $\nu_{max}^{CHCl_3}$ cm^{-1}: 1760, 1730, 1680 and 1630. Found: C, 67.12; H, 6.53; O, 26.34% $C_{17}H_{20}O_5$. Requires: C, 67.09; H, 6.62; O, 26.29%.

Schkuhriolide epoxide (**6**). To a soln of 114 mg **5a** in 20 ml $CHCl_3$ was added 50 mg *m*-chloroperbenzoic acid and refluxed for 30 min. The soln was washed with $NaHCO_3$ soln and H_2O, dried and evaporated. Purification of the crude product by prep. TLC yielded 60 mg **6**, mp 134–136° (crystallized from Me_2CO-hexane). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3500, 1775, 1725, 1688.

Schkuhrioidin acetate (**7b**). A soln of 105 mg **7a** in 1 ml pyridine and 1 ml EtOAc was left overnight at room temp. The acetate (**7b**) crystallized on addition of H_2O. It was filtered and crystallized from EtOAc–hexane affording 94 mg **6b**, mp 99–102°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1743m 1730, 1650. Found: C, 67.77; H, 7.44; O, 25.61% $C_{21}H_{26}O_6$. Requires: C, 67.00; H, 7.50; O, 25.50%.

Schkuhrioidin B epoxide (**8**). To a soln of 105 mg **7a** in 15 ml $CHCl_3$ was added 50 mg *m*-chloroperbenzoic acid and refluxed for 30 min. The soln was washed with H_2O and 10% $NaHCO_3$, dried with Na_2SO_4 and concd to give **8** as a yellow oil (59.8 mg). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3500, 1775, 1740 and 1660.

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REFERENCES

1. Stuessy, T. F., Heywood, V., Harborne, J. B. and B. L. (eds.) (1977) in *Chemistry and Biology of Compositae*. Academic Press, New York.
2. Romo de Vivar, A. and Ortega, A. (1969) *Can. J. Chem.* **47**, 2849.
3. Herz, W. and Bhat, V. (1972) *J. Org. Chem.* **37**, 906.
4. Pettei, M. J., Miura, I., Kubo, I. and Nakanishi, K. (1978) *Heterocycles* **11**, 471.

5. Herz, W. and Govindan, S. V. (1980) *Phytochemistry* **19**, 1234.
6. Bohlmann, F. and Zdero, C. (1977) *Phytochemistry* **16**, 780.
7. Bohlmann, F., Jakupovic, J., Robinson, H. and King, R. (1980) *Phytochemistry* **19**, 881.
8. Bohlmann, F. and Zdero, C. (1981) *Phytochemistry* **20**, 1431.
9. Samek, Z., Holub, M., Bloszyk, E. and Drozdz, B. (1979) *Z. Chem.* **19**, 449.
10. Tori, K., Horibe, I., Tamura, Y., Kuriyama, K., Tada, H. and Takeda, K. (1976) *Tetrahedron Letters* 387.
11. Torrance, S. J., Geissman, T. A. and Chedekel, M. R. (1969) *Phytochemistry* **8**, 2381.
12. Yoshioka, H., Mabry, T. J. and Timmerman, B. N. (1973) *Sesquiterpene Lactones. Chemistry, NMR and Plant Distribution* p. 187. University of Tokyo Press, Tokyo.
13. Herz, W. and Kalyanaraman, S. (1975) *J. Org. Chem.* **40**, 3486.
14. Herz, W. and Sharma, R. P. (1975) *J. Org. Chem.* **40**, 392.
15. Herz, W., Bhat, S. V. and Sundarsanam, V. (1972) *Phytochemistry* **11**, 1829.
16. Romo de Vivar, A., Guerrero, C., Díaz, E., Bratoeff, E. A. and Jiménez, L. (1976) *Phytochemistry* **15**, 525.
17. Saleh, A. A., Cordell, G. A. and Farnsworth, N. R. (1980) *J. Chem. Soc. Perkin Trans.* 1, 1090.
18. Barua, R. N., Sharma, R. P., Thyagarajan, G., Herz, W. and Govindan, S. V. (1980) *Phytochemistry* **19**, 323.
19. Fischer, N. H., Olivier, E. J. and Fischer, H. D. (1979) in *Progress in the Chemistry of Organic Natural Products* (Herz, W., ed.) Vol. 38. Springer, Wien.
20. Samek, Z. and Harmatha, J. (1978) *Collect. Czech. Chem. Commun.* **43**, 2779.
21. Samek, Z. and Budesinsky, M. (1979) *Collect. Czech. Chem. Commun.* **44**, 558.