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SHORT COMMUNICATION

COUMARINS OF *ARTEMISIA DRACUNCULOIDES* AND 3′,6-DIMETHOXY-4′,5,7-TRIHYDROXYFLAVONE IN *A. ARCTICA*

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Abstract—Six coumarins were isolated from *Artemisia dracunculoides* Pursh. Two of these are new, 7,8-methylenedioxy-6-methoxycoumarin and the γ,γ-dimethylallyl ether of scopoletin. The four others were scopoletin, scoparone, daphnetin methylene ether and daphnetin 7-methyl ether. *Artemisia arctica* Less. ssp. *saxicola* (Rydb.) Hultén yielded 3′,6-dimethoxy-4′,5,7-trihydroxyflavone.

Investigation of a trial collection of *Artemisia dracunculoides* Pursh. from Arizona* afforded small amounts of a mixture of closely related sesquiterpene lactones one of which could be isolated in pure form and appeared to possess the gross structure of 8-hydroxyarbiglovin (I). U.v. and i.r. spectra were typical of those of similar cross-conjugated dienones isolated from other *Artemisia* species.† The NMR spectrum (see Experimental) was practically superimposable of that of arbiglovin,[8] but exhibited an additional low field signal associated with hydrogen on carbon carrying a hydroxyl group. The presence of a hydroxyl group was confirmed by the i.r. spectrum and the formation of an acetate.

In an effort to secure larger quantities of this new substance for chemical studies, we extracted a large-scale collection of *A. dracunculoides* from a different location in Arizona. Instead of a sesquiterpene lactone, however, we isolated six coumarins which were identified

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* The taxonomic status of *A. dracunculoides* Pursh., which belongs to subgenus (section) *Dracunculus*, is somewhat uncertain. In the most comprehensive treatment[1] of the genus *Artemisia*, *A. dracunculus* Pursh. is considered merely a variety of *A. dracunculus* L., subspecies *glauca* Pall. whose distribution includes the Western prairies, the Far West and Siberia. Other subspecies of *A. dracunculus* are listed as ssp. *typica* (Eastern U.S. and Old World) and ssp. *dracunculina* Watson (from Kansas, Texas and Chihuahua to New Mexico and Arizona). According to the more recent Kearney and Peebles,[2] much of Arizona material of *A. dracunculoides* Pursh, the only species listed for that state, approaches var. *dracunculina* (Wats.) Blake said to be synonymous with *A. glauca* Pall. var. *dracunculina* Fern.

† Matricarin and artilesin from *A. tilesii* Ledeb.,[3] desacetylmatricarin from *A. tilesii* Ledeb.,[3] *A. austriaca* Jacq.,[4] *A. juncea Kar.* & Kir.,[5] and *A. leucodes* Schrenk.,[6] desacetoxymatricarin (leucodin) from *A. leucodes*[6] and *A. tridentata* Nutt. ssp. *tridentata*,[7] arbiglovin from *A. bigelovii* Gray.[8]

[1] H. M. Hall and F. E. Clements, *The Phylotenetic Method in Texonomy*, Carnegie Institution of Washington, Publication No. 326 (1923).

[2] T. H. Kearney and R. H. Peebles, *Arizona Flora* (2nd ed.), University of California Press, Berkeley (1946).

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[6] K. S. Rybalko and P. S. Massagetov, *Med. Prom. SSR*, **15**, 25 (1961); M. Holub and V. Herout, *Coll. Czechoslov. Chem. Commun.* **27**, 2980 (1962).

[7] T. A. Geissman, T. Stewart and M. A. Irwin, *Phytochem.* **6**, 1901 (1907).

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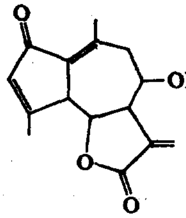
as the methylene ether (II) of daphnetin, 7,8-methylenedioxycoumarin (III), the 7-γ,γ-dimethylallyl ether (IV) of scopoletin, scoparone (V), the 7-methyl ether (VI) of daphnetin and scopoletin (VII). The observed difference in crystalline constituents isolated from the two separate collections can probably be ascribed to the variability referred to in Ref. 2.

Compounds III and IV are new. The former was identified by conversion to fraxetin (VIII) through hydrolytic cleavage of the methylenedioxy group. The latter was identified by spectroscopic methods and hydrogenation–hydrogenolysis to IX which was in turn prepared by hydrogenation of VII. Substance VI, although previously known, has apparently not been found as such in a natural source. Substance V and herniarin (7-methoxycoumarin) have been isolated previously[9] from *A. dracunculus* L., presumably the Old World subspecies.

We also record the results of a phytochemical investigation of *A. arctica* Less. ssp. *saxicola* (Rydb.) Hultén.* The only substance which could be isolated in crystalline form was identified as 3',6-dimethoxy-4',5,7-trihydroxyflavone (X).[10, 11]



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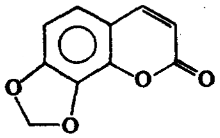

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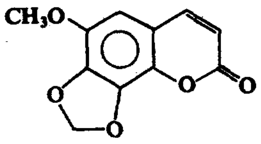

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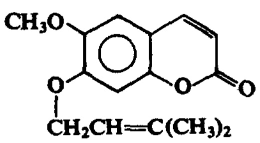

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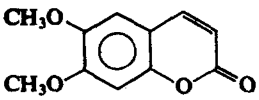

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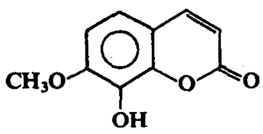

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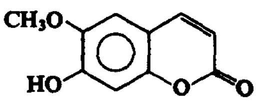

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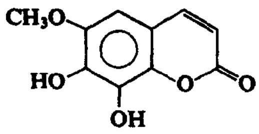

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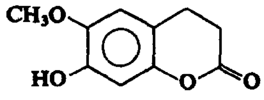

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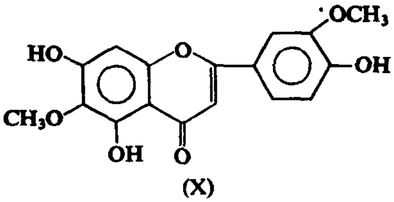

(X)

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EXPERIMENTAL

M.p.s were determined in capillaries and are uncorrected. NMR spectra were determined in acetone-d_6, unless mentioned otherwise, using a Varian A-60 spectrometer with tetramethylsilane as internal standard; i.r. spectra in $CHCl_3$ using Perkin Model 137 or 257 spectrophotometers; u.v. spectra in 95% ethanol using a Cary Model 14 recording spectrophotometer. Petroleum ether had b.p. 30–60°, silicic acid was Mallinckrodt 100 mesh. Analyses were by Dr. F. Pascher, Bonn, Germany.

Extraction of Artemisia dracunculoides *Pursh*

(*A*) Above ground parts, wt. 1 kg, collected by R. J. Barr at Forestdale, Navajo County, Arizona, on 23 July, 1962 (Barr voucher 62-425, on deposit in the Florida State University Herbarium), was extracted in the usual fashion.[12] The crude gum, wt. 14 g, was chromatographed over silicic acid, 200-ml eluates being collected. Fractions 1–9 (benzene) and 10–21 (benzene-$CHCl_3$, 3:1) eluted oils or nothing. Fractions 22–36 (benzene–$CHCl_3$, 1:1) and 37–51 (benzene–$CHCl_3$, 1:3) eluted gummy mixtures (TLC). Fractions 52–71 ($CHCl_3$) eluted a crystalline mixture of two closely related sesquiterpene lactones which was rechromatographed over silicic acid. The $CHCl_3$ eluate was recrystallized from acetone–hexane and afforded 0·2 g of a new sesquiterpene lactone which had m.p. 206–212°, λ_{max} 205 (strong end absorption) and 255 nm (ϵ 14,000), i.r. bands at 3600 and 3500 (non-bonded and bonded —OH), 1765 (γ-lactone), 1685 (cyclopentenone), 1645 (sh, double bond) and 1630 cm^{-1} (strong, cisoid double bond), NMR signals at 6·12d and 5·50d (3, exocyclic methylene), 6·02q (1·5, H-2), 3·9–3·1 (overlapping multiplets, H-5, H-6, H-7 and H-8), 2·5 (multiplet H-9a partially obscurred by vinyl methyl signal), 2·42 (C-10 methyl), 2·17d (1·5, C-4 methyl) and 1·3m (H-9b). (Found: C, 69·66; H, 5·78; O, 24·26. Calc. for $C_{15}H_{16}O_4$: C, 69·22; H, 6·20; O, 24·59.) The other component of the sesquiterpene lactone mixture could not be obtained in pure form.

Acetylation with Ac_2O–pyridine afforded a monoacetate which had m.p. 198° (previous sintering at 192°) and i.r. bands at 1765 (γ-lactone), 1745 (acetate), 1690 (cyclopentenone), 1640 (sh, double bond) and 1630 cm^{-1} (strong, cisoid double bond). (Found: C, 68·14; H, 6·10; O, 26·06. Calc. for $C_{17}H_{18}O_5$: C, 67·54; H, 6·00; O, 26·46.) The NMR spectrum (acetone-d_6-DMSO-d_6, very dilute) exhibited distinguishable signals at 6·18q (1·5, H-2), 6·05d and 5·67d (3, exocyclic methylene), 3·9dd (10, 2·5, H-6?) partially superimposed on other multiplets, 2·40 (C-10 methyl), 2·10 (acetate superimposed on C-4 methyl) and 1·4dd (14, 12, H-9b).

(*B*) Above ground parts of *A. dracunculoides*, wt. 14·5 kg, collected by R. J. Barr on 27 August, 1967 along the road from Rustler Park to Fly Peak in the Chiricahua Mountains, Cochise County, Arizona (Barr voucher 67-293), was extracted in the usual manner. The crude gum, wt. 98 g, was chromatographed over 1·0 kg of silicic acid. The following 800-ml fractions were collected; fraction 1–8 (benzene), 9–28 (benzene–$CHCl_3$, 2:1), 29–58 (benzene–$CHCl_3$, 1:2), 59–78 ($CHCl_3$), 78–87 ($CHCl_3$–ether, 9:1), 88–97 ($CHCl_3$–ether, 9:2), 98–107 ($CHCl_3$–methanol, 9:1) and 108–118 ($CHCl_3$–MeOH, 3:1).

Fraction 4 gave crude II which was purified by repeated recrystallization from ethanol, wt. 0·050 g. Fractions 9–28 (20·5 g) gave a mixture of III and IV which was separated by fractional crystallization from benzene–$CHCl_3$. III, being less soluble, crystallized out (wt. 3·5 g) and was purified further by repeated recrystallization. The mother liquors (wt. 17·0 g) were chromatographed over 200 g of silica gel. The earlier fractions (benzene–$CHCl_3$, 2:1) eluted pure IV (wt. 5·2 g) which was recrystallized from EtOAc–petroleum ether. Fractions 33–37 gave 4·2 g of V which was recrystallized from petroleum ether–EtOAc. Fractions 40–42 gave 2·2 g of VI which was recrystallized from $CHCl_3$. Fractions 49–52 gave 3·2 g of VII which was recrystallized from EtOAc. The later fractions eluted gums.

Daphnetin methylene ether (*II*). Substance II had m.p. 187–189° (lit.[13] 188°), i.r. bands at 1735, 1640, 1580, 1465 and 825 cm^{-1}, u.v. absorption at 318, 262 and 254 nm (ϵ 11,200, 8400 and 7300), NMR signals at 7·93d and 6·25d (AB system, $J = 9·5$ Hz, H-3 and H-4), 7·25d and 6·90d (AB system, $J = 8·5$ Hz, H-5 and H-6) and 6·23s (two protons of methylenedioxy group).

7,8-Methylenedioxy-6-methoxy coumarin (*III*). Compound III had m.p. 219–221°, M.W. 220 by mass spectrometry, i.r. bands at 1736, 1628, 1595, 1460 and 655 cm^{-1}, u.v. absorption λ_{max} 330, 259 and 213 nm (14,600, 8400 and 52,000), NMR signals (DMSO-d_6) at 7·85d and 6·24d (AB system, $J = 9·5$ Hz, H-3 and H-4), 6·95s (H-5), 6·19s (2 protons of methylenedioxy group) and 3·83s (3 protons, methoxyl). Found: C, 59·95; H, 3·57; O, 36·45. Calc. for $C_{11}H_8O_5$: C, 60·00; H, 3·66; O, 36·33.)

A mixture of 175 mg of III, 215 mg of resorcinol and 2 ml of conc. H_2SO_4 was heated on a water bath for 1 hr, poured into 100 ml of water and extracted with ether. The ether extracts were washed with satd. NaCl, dried and evaporated *in vacuo*. The residue was repeatedly recrystallized from benzene–acetone to give pure VII which had m.p. 224–226° (lit.[14] 227–228°), blue-green color with $FeCl_3$, M.W. 208 (by mass spectrometry), i.r. bands at 3510, 1720, 1610, 1584, 1460 and 840 cm^{-1}, NMR signals at 7·87d and 6·20d (AB system, $J = 9·5$

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[14] V. K. Ahluwalia, V. N. Gupta, C. L. Rustagi and T. R. Seshadri, *J. Sci. Ind. Research* **17B**, 345 (1960).

Hz, H-3 and H-4), 6·82s (H-5) and 3·91s (methoxyl). The diacetate was prepared by the Ac_2O–pyridine method and had m.p. 193–194° (lit.[14] 193–194°).

Scopoletin γ,γ-dimethylallyl ether (IV). This substance had m.p. 81–83°, M.W. 260 (by mass spectrometry), i.r. bands at 1720, 1615, 1564, 1465 and 860 cm^{-1}, u.v. absorption λ_{max} at 345, 295, 259, 253 and 229 nm (ϵ 12,500, 6600, 6200, 7000 and 18,000), NMR signals ($CDCl_3$) at 7·50d and 6·13d (AB system, J = 9·5 Hz, H-3 and H-4), 5·40t (J = 6·5 Hz, vinyl proton in ether chain) 4·57d (2 protons, J = 6·5 Hz, —OCH_2—CH=), 6·77s and 6·70s (H-8 and H-5), 3·83s (methoxyl) and 1·75s (two vinyl methyls). (Found: C, 69·65; H, 6·18; O, 24·18. Calc. for $C_{15}H_{16}O_4$: C, 69·22; H, 6·20; O, 24·59.)

A solution of 105 mg of IV in 20 ml HOAc was hydrogenated overnight in the presence of 50 mg of 10% Pd-C. The solution was filtered and evaporated at reduced pressure. The product IX was recrystallized from EtOAc–petroleum ether, yield 55 mg, m.p. 158–160°, i.r. bands at 3560, 1750, 1620 and 868 cm^{-1}, NMR signals at 6·90s and 6·75s (H-8 and H-5), 3·87s (methoxyl) and 2·84c (4 protons, —CH_2—CH_2—). The same substance was prepared in 90% yield by hydrogenation of 20 mg of VII, m.p. 158–160°, mixed m.p. undepressed, i.r. spectra superimposable.

Scoparone (V). Compound V had m.p. 144–146° (lit.[9] 145–146°), M.W. 206 (by mass spectrometry), mass spectrum identical with that reported in the literature,[15] i.r. bands at 1730, 1630, 1575, 1478 and 872 cm^{-1}, u.v. absorption λ_{max} 343, 295, 258, 250 and 230 nm (ϵ 12,100, 5700, 5300, 6200 and 19,000), NMR signals at 7·90d and 6·25d (AB system, J = 9·5 Hz, H-3 and H-4), 7·20s and 6·98s (H-8 and H-5), 3·97s and 3·88s (two methoxyls). (Found: C, 64·38; H, 4·72; O, 30·90. Calc for $C_{11}H_{10}O_4$: C, 64·07; H, 4·87; O, 31·04.)

Demethylation of V with anhydrous $AlCl_3$ gave esculetin, m.p. 268–270° (lit.[16] 268–270°).

Daphnetin 7-methyl ether (VI). This compound had m.p. 169–171° (lit.[20] 172–173°) M.W. 192 (by mass spectrometry), green color with $FeCl_3$, i.r. bands at 3502, 1730, 1610, 1580, 1462 and 845 cm^{-1}, u.v. absorption λ_{max} 325, 257 and 210 nm (ϵ 13,600, 4500 and 31,500), NMR signals at 7·87d and 6·20d (AB system, J = 9·5 Hz, H-3 and H-4), 7·18d and 6·87d (AB system, J = 8·5 Hz, H-5 and H-6) and 3·94s (methoxyl). (Found: C, 62·43; H, 4·15; O, 33·14. Calc. for $C_{10}H_8O_4$: C, 62·50; H, 4·20; O, 33·30.)

The acetate, prepared with Ac_2O-pyridine, melted at 131–133° after recrystallization from methanol. The methyl ether, prepared with Me_2SO_4–K_2CO_3, was recrystallized from EtOAc and had m.p. 117–119° (lit.[17] 119–120°).

Scopoletin (VII). Compound VII had m.p. 205–209° (lit.[18] 204°), M.W. 192 (by mass spectrometry), green color with $FeCl_3$, i.r. bands at 3505, 1720, 1615, 1578, 1465 and 870 cm^{-1}, u.v. absorption λ_{max} 346, 296, 261, 253 and 228 nm (ϵ 15,800, 6750, 6400, 7000 and 18,000), NMR signals at 7·89d and 6·22d (AB system, J = 9·5 Hz, H-3 and H-4), 7·23s and 6·85s (H-8 and H-5) and 3·92s (methoxyl). (Found: C, 62·91; H, 4·04; O, 33·90. Calc. for $C_{10}H_8O_4$: C, 62·50; H, 4·20; O, 33·30.)

The acetate was recrystallized from methanol and melted at 180–182° (lit.[18] 177°). The methyl ether was recrystallized from EtOAc–petroleum ether and had m.p. 144–146°, mixed m.p. with V undepressed, i.r. spectra superimposable.

Extraction of Artemisia arctica *Less. ssp.* saxicola (*Rydb.*) *Hultén*

Above ground parts, wt. 620 g, collected by Dr. B. H. Braun with permission of the National Park Service near the ski lift, Hidden Valley, Rocky Mountain National Park, Colorado, on 2 August, 1962, was extracted in the usual fashion. The crude gum, wt. 20 g, was chromatographed over 250 g of 1962, silicic acid (200-ml fractions). Fractions 1–3 (benzene–$CHCl_3$, 3:1), 4–13 (benzene–$CHCl_3$, 1:1), 14–23 (1:2), and 24–29 (1:4) eluted nothing or gummy mixtures. $CHCl_3$ eluted a small amount of yellow solid which was recrystallized from EtOAc and then melted at 226–230° (Kofler), yield 15 mg. The NMR spectrum (DMSO-d_6) indicated the presence of two methoxyl groups (signals at 4·0 and 3·98 ppm) and free positions at C-3, C-8, C-2′, C-5′ and C-6′ (H-3 and H-8 at 6·66 and 6·60 ppm, H-2′ at 7·57d-2, *m*-coupling-H-5′ at 6·98d-10- and H-6′ at 7·55dd-10,2). The substance was identified as 3′,6-dimethoxy-4′,5,7-trihydroxyflavone by comparison with material isolated earlier[10] and an authentic sample kindly supplied by Professor W. B. Whalley.[11]

Acknowledgement—This work was supported in part by a grant (RG-05814) from the United States Public Health Service.

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