Phytochemistry, 1973, Vol. 12, pp. 875 to 878. Pergamon Press. Printed in England.

NOVANIN: A GERMACRANOLIDE FROM *ARTEMISIA NOVA**

M. A. Irwin and T. A. Geissman†

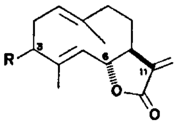
Department of Chemistry, University of California, Los Angeles, CA 90024, U.S.A.

(*Received* 10 *October* 1972. *Accepted* 21 *October* 1972)

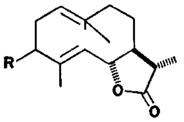
Key Word Index—*Artemisia nova*; Compositae; sesquiterpene lactone; germacranolide; stereochemistry; conformation.

Abstract—A new germacranolide, novanin (I), has been isolated from *Artemisia nova* and its structure determined. The compound is also present in small amount in *A. tripartita* Rydb. ssp. *rupicola* Beetle.

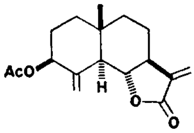
Earlier studies of various species of *Artemisia* belonging to the section *Seriphidium* Bess.[1] (*Tridentatae* Rydb.[2]) in this laboratory included *A. nova* Nels., from which the isolation of cumambrin-*A* and -*B* and 8-deoxycumambrin-*B* have been reported.[3] Later examination of a large collection of the plant[4] has disclosed the presence, along with the cumambrins,[5] of a compound (0·06%) called novanin (I). Novanin could not be obtained in crystalline form, and was very unstable in keeping, a property common to many germacranolides. It was converted by reduction with sodium borohydride into 11,13-dihydronovanin (II), a stable crystalline compound, and by acid-catalyzed cyclization into crystalline derivatives, the properties of which form the basis for most of the results to be described.



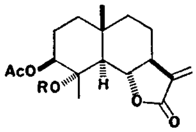
(I) R = β-OAc novanin
(III) R = H costunolide



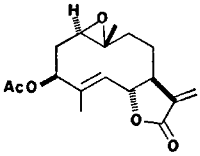
(II) R = β-OAc
(IV) R = α-OAc



(V)



(VI) R = H
(VII) R = Ac



(X)

Dihydronovanin (II), m.p. 135–136°, showed IR absorption characteristics of an α-methylene-γ-lactone (1765, 1660 cm^{-1}) and an acetate (1735 cm^{-1}). Although there is no absorption maximum near 200 nm in the UV, the intensity of absorption in the 220 nm region is characteristic of the transannular interaction observed in germacranolides possessing double bonds located as in I.[6] Prominent MS ions of m/e 292 (M^+), M−42 and M−60, in combination with the elemental analysis, establish its composition and the presence of the acetoxyl group.

---

* Contribution No. 2952 from the Department of Chemistry, U.C.L.A.

† From the Ph.D. thesis of M. A. Irwin, U.C.L.A., January 1971.

[1] Ward, G. H. (1953) *Contr. Dudley Herb.* **4**, 155.

[2] Beetle, A. A. (1960) *Univ. Wyom. Agric. Exptl. Sta. Bull.* No. 368.

[3] Irwin, M. A. and Geissman, T. A. (1969) *Phytochem.* **8**, 305.

[4] We are indebted to Professor R. O. Asplund, University of Wyoming, for collection and authentication of the plant material used in this work.

[5] Stigmasterol and sitosterol were also isolated.

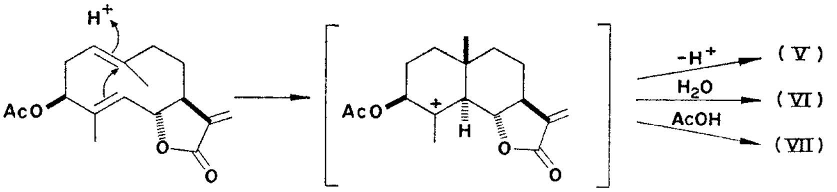
[6] Šorm, F. (1961) *Chemistry of Natural Products, I.U.P.A.C. International Symposium of* 1960, *Australia*, Butterworths, London.

The NMR spectrum of novanin (I) conforms in nearly every detail, except for features associated with the C-3 acetoxyl group, with that of costunolide (III), and can be regarded as evidence for their common structure, stereochemistry and conformation. The structure of costunolide (III) has been established by the results of a number of investigations.[7]

The NMR spectrum of dihydronovanin ($CDCl_3$) shows the following signals. The C-4 and C-10 methyl groups, coupled with H-5 and H-1, respectively, appear as doublets (1·3 Hz) at δ 1·68 and 1·45 respectively. The relative positions of the C-4 and C-10 methyl signals of costunolide-like germacranolides have been assigned, and the unusually high field of the vinylic C-10 methyl group has been attributed to transannular shielding by the 4,5-double bond.[8] The C-11 methyl group, coupled (7 Hz) with H-11, gave a doublet at δ 1·24, and the acetyl methyl group a sharp singlet at δ 2·08. Analysis of the 4-proton complex in the δ 4·3–5·3 region was facilitated by comparison of the 60 and 100 MHz spectra. The C-6 proton, coupled with H-5 (10 Hz) and H-7 (7 Hz), gave a quartet at δ 4·54. The C-5 proton, coupled (10 Hz) with H-6, gave a doublet, broadened by allylic coupling, at δ 4·75. The C-3 proton, coupled (10 and 7 Hz), with the protons at C-2, gave a quartet at δ 5·13. The vinylic H-1, coupled with the C-2 protons, the C-10 methyl group and the C-9 protons, gave a broad signal at δ 4·9.

Dihydronovanin (II) is the C-3 epimer of dihydrotamaulipin-*B* acetate (IV).[9] The principal features of the NMR spectra of these compounds are in excellent agreement, differing chiefly in the signal for the C-3 proton, which in dihydrotamaulipin-*B* acetate is a triplet (3 and 3 Hz) at δ 5·3.

Treatment of novanin with strong acid in dioxan and in acetic acid furnished the eudesmanolides V, VI and VII and a fourth eudesmanolide whose structure is still not established. Analogous cyclizations of costunolide and other germacranolides are well established.[10] The generation of V, VI and VII is readily rationalized by the following common course:



The structures V, VI and VII assigned to these compounds are fully in accord with their spectral properties. The negative Cotton effect displayed by VI shows that the C-6/C-7 lactone is *trans*-fused.[11] Information to substantiate the stereochemical assignments is found in the NMR spectra. The large couplings (10–11 Hz) in the signals of H-5, H-6 and

---

[7] Rao, A. S., Kelkar, G. R. and Bhattacharyya, S. C. (1960) *Tetrahedron* **9**, 275; Herout, V., Suchý, M. and Šorm, F. (1961) *Colln. Czech. Chem. Commun.* **26**, 2612; Corey, E. J. and Hortman, A. G. (1965) *J. Am. Chem. Soc.* **87**, 5736.

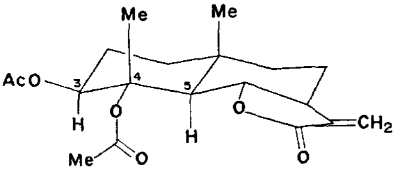
[8] Sathe, R. N., Kulkarni, G. H. and Kelkar, G. R. (1968) *Chem. & Ind.* 448; Bates, R. B. and Gale, D. M. (1960) *J. Am. Chem. Soc.* **82**, 5749.

[9] Fischer, N. H. and Mabry, T. J. (1967) *Chem. Commun.* 1235; Mabry, T. J., Yoshioka, H., Renold, W., Fischer, N. H. and Higo, A. (1970) *Phytochem.* **9**, 823. The NMR spectrum of dihydrotamaulipin-*B* acetate was kindly provided by Dr. H. Yoshioka and Professor T. J. Mabry, University of Texas.

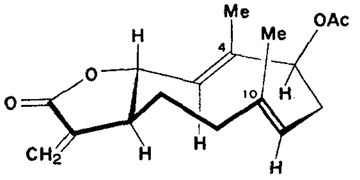
[10] Geissman, T. A. (1972) *Biosynthesis of Sesquiterpene Lactones of Compositae, Proc. XI Annual Symposium Phytochem. Soc. N. Amer., Monterrey, Mexico, October*, 1971, Academic Press, New York.

[11] Stöcklin, W., Waddell, T. G. and Geissman, T. A. (1970) *Tetrahedron* **26**, 2397.

H-7 reveal their all-*trans*-axial arrangement, and the width of the H-3 signal (18–20 Hz) is that expected for the disposition of this proton in a *trans*-diaxial, *cis*-axial-equatorial relationship to the protons at C-2. The stereochemistry at C-3 and C-4 may be inferred from the fact that the C-3 and C-5 protons of VII (located at δ 5·90 and 3·44, respectively) are deshielded relative to those of VI (located at δ 4·78 and 1·88, respectively). In both compounds H-3 is a complex multiplet of overall width 18 Hz and H-5 a doublet (11 Hz). The desheilding is the result of the proximity of the carbonyl group to H-3 and H-5, which is caused by rotational restriction of the C-4 acetoxyl group to the sterically favorable conformation between C-3 and C-5. The above information leads to the conclusion that the configuration and conformation of the cyclo-product VII can be expressed as VIII.



(VIII)



(IX)

Studies of costunolide (III) by X-ray crystallography[12] and of dihydrotamaulipin-*A* acetate (2-α-acetoxydihydrocostunolide) by nuclear Overhouser effects[13] have revealed that the C-4 and C-10 methyl groups are β-oriented. Similar results have been obtained from the studies of conformations of other germacrane-derived sesquiterpenes.[14] The conformation of novanin can therefore be expressed as IX.

Treatment of novanin (I) with *m*-chloroperbenzoic acid provided the oxide X. Its NMR spectrum still shows the signal for the C-6 proton (at δ 4·20) coupled (10 Hz) with a vinyl proton (H-5 at δ 5·5), and thus establishes the 1,10-position for the oxide ring. The stereochemistry of the epoxide, as shown in X, is that expected from novanin of conformation IX and follows from the stereochemistry of the product formed by acid-catalyzed cyclization of the analogous dihydrocostunolide 1,10-oxide.[15]

The diazomethane C-11/C-13 adduct (pyrazoline) of novanin and the 11,13-dihydroderivative of compound V were prepared during the course of this investigation. We were informed by Professor A. Yoshikoshi, Tohoku University, that dihydronovanin has been prepared from α-santonin.[16] Dihydronovanin, the synthesis of which establishes structure II, is identical with our material.

EXPERIMENTAL

Spectra were measured on: NMR, ($CDCl_3$), Varian A-60D and HA-100; MS (70 eV, direct insertion), AEI-MS9; IR ($CHCl_3$), Perkin-Elmer 237. The $CHCl_3$ extractive of 5 kg of dried, ground *A. nova* was extracted with hot H_2O and with hot 35% EtOH, and the aqueous part was clarified and extracted with $CHCl_3$. The tarry residue (a) and the final $CHCl_3$ extract (b) were passed over columns of silica gel with mixtures of CH_2Cl_2–$CHCl_3$–Me_2CO as eluants. A total of 40 g of cumambrin-*B* (20 g from a, 20 g from b)

---

[12] Šorm, F., Suchý, M., Holub, M., Línek, A., Hadinec, I. and Novak, C. (1970) *Tetrahedron Letters* 1893.

[13] Bhacca, N. and Fischer, N. H. (1969) *Chem. Commun.* 68.

[14] McClure, R. J., Sim, G. A., Coggon, P. and McPhail, A. T. (1970) *Chem. Commun.* 128; Allen, F. H. and Rogers, D. (1967) *Chem. Commun.* 588; Hikino, H., Kono, C. and Takemoto, T. (1969) *Chem. Commun.* 662.

[15] Suchý, M., Herout, V. and Šorm, F. (1966) *Colln. Czech. Chem. Commun.* **31,** 2899.

[16] Watanabe, M. and Yoshikoshi, A. (1972) *Chem. Commun.* 698.

and a total of 14 g of cumambrin-*A* were isolated in the initial separations, and extensive rechromatography of less polar eluates gave stigmasterol, sitosterol, a compound of still undermined structure (0·5 g) and 3 g of novanin (I) as a homogeneous (on TLC), oily material. It was characterized only by NMR; the relevant details have been described above. The pure compound was quite unstable on keeping, polymerizing to a $CHCl_3$-insoluble gel, but could by preserved in $CHCl_3$ without rapid deterioration. Novanin was detected by TLC in smaller amount in *A. tripartita* Rydb. ssp. *rupicola* Beetle.

Dihydronovanin (II). To a solution of 100 mg novanin in 10 ml of MeOH was added 100 mg of $NaBH_4$. After 5 min the solution was acidified and extracted with $CHCl_3$. Removal of the solvent left dihydronovanin, which crystallized from Et_2O–EtOAc as platelets, m.p. 135–136°. Its IR spectrum had peaks at 1765, 1735 and 1660 cm^{-1}. It showed intense end absorption (no maximum) with $[\epsilon]$ 2000 (230 nm), 5000 (220) and 8200 (210). The NMR spectrum has been described in the Discussion. The MS showed ion peaks at *m/e* (rel. int.) 292 (3·4, M^+), 250 (21), 232 (13), 217 (3), and others including 43 (100) (*Anal.* Calc. for $C_{17}H_{24}O_4$: C, 69·83; H, 8·27. Found: C, 69·71; H, 8·23%).

Transannular cyclization of novanin, compounds V, VI and VII. A solution of 200 mg novanin in 15 ml HOAc containing 1 drop of conc. H_2SO_4 was allowed to stand for 20 hr, then poured into H_2O and extracted with $CHCl_3$. Chromatography of the $CHCl_3$-extractable material (silica gel) separated V, VI and VII. In another experiment, a solution of 300 mg novanin in 5 ml of dry dioxan containing a few mg of *p*-toluenesulfonic acid was allowed to stand overnight and worked up in the same way. Chromatography separated unchanged novanin, V and a third compound of still undetermined structure (m.p. 155–157°).

Cyclonovanin-A (*V*). Crystallized from Et_2O–light petrol., as needles, the compound had m.p. 143–144°. Its IR spectrum showed absorption at 1765, 1730 and 1655 cm^{-1}. The MS showed peaks at *m/e* (rel. int.) 290 (0·3, M^+), 272 (0·7), 257 (0·5), 248 (10), 233 (6), 230 (22), 215 (12), and others including 43 (100). The NMR spectrum showed the C-10 methyl group as a singlet at δ 0·88, the C-11 methylene protons as doublets (3 Hz) at δ 5·40 and 6·08, the acetoxy (methyl) group at δ 2·12, and the protons of the C-4 methylene group as one-proton signals at δ 4·95 and 5·14. The signals (with coupling constants) for the protons at C-3, C-5, C-6 and C-7 were found at δ 5·1 (*b m*), 2·25 (11 Hz), 3·99 (11 and 11 Hz) and 2·55 (*b m*), respectively.

Dihydrocyclonovanin-A. Hydrogenation (Pd–C) of the mother liquor from which V had crystallized afforded 11,13-dihydro-V as colorless needles from EtO_2–light petrol., m.p. 167–169°. The NMR spectrum still showed the signals (δ 4·93 and 5·12) of the C-4 methylene group (as in V), and now showed a 3-proton doublet (7 Hz) at δ 1·22 for the newly formed C-11 methyl group. The remainder of the spectrum was similar to that of V and requires no special comment.

Cyclonovanin-B (VI). Crystallized from Et_2O–light petrol., VI formed colorless granules, m.p. 168–172°. Its circular dichroism curve showed a maximum $[\theta]_{257}$ −2390°. The NMR spectrum showed all the features seen in that of V, with the notable exception of the signal for the C-4 substituent. In the spectrum of VI there is seen a 3-proton singlet at δ 1·36 for the C-4 methyl group, and a broad 1-proton signal at δ 2·92 for the C-4 hydroxyl group.

Cyclonovanin-C (VII). Crystallized from Et_2O–light petrol., VII formed granules with m.p. 185–186°. Its NMR spectrum showed the C-4 methyl group as a singlet at δ 1·39, and two acetyl methyl signals (δ 2·10 and 2·22) for the acetoxyl groups at C-3 and C-4. The other features of the spectrum were similar to those of V and VI. The MS of VII did not show the molecular ion (350), but showed fragment ions of *m/e* (rel. int.) 290 (1·9) and 230 (35) for the loss of 1 and 2 molecules of HOAc.

Novanin oxide (X). A solution of novanin in $CHCl_3$ was treated with *m*-chlorobenzoic acid and after a few min was washed with aq. sodium sulfite and sodium carbonate. Concentration of the $CHCl_3$ solution gave crystalline X, which was recrystallized from Et_2O–EtOAc–light petrol. as needles, decomposing at 140–160°. Its NMR spectrum showed H-6 as nearly a triplet (10 and 9 Hz) at δ 4·20 coupled with the vinyl proton at C-5, which appeared at δ 5·5. That H-6 was coupled with the C-5 vinyl proton, whose signal was obscured, was clear from the relative magnitudes of the peaks within the H-6 signal. Other features of the spectrum are in accord with the requirements of the structure X.

Diazomethane adduct of novanin. A solution of novanin in Et_2O was treated with an Et_2O solution of CH_2N_2, concentrated, and the product isolated by chromatography over silica gel. Recrystallized from Et_2O the compound formed colorless needles, m.p. 180–181° (foaming). Its NMR spectrum was in accord with the assigned structure; in particular, the doublets at about δ 5·5 and 6·3 (exocyclic methylene group at C-11) were absent.

Acknowledgements—This study was supported by a research grant GM-14240 from the U.S. Public Health Service. Dr. G. Chmurny assisted in the NMR measurements, and analyses are by Miss Heather King, U.C.L.A.