Tetrahedron Letters No. 37, pp 3491 - 3494.
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0040-4039/78/0908-3491$02.00/0

TRIXAGOL, NATURAL γ-CYCLOGERANYL-GERANIOL FROM *BELLARDIA TRIXAGO* (L.) ALL.

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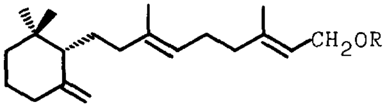
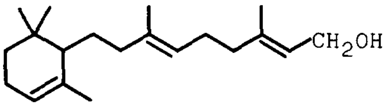
We have isolated a diterpene alcohol from the hemiparasite plant *Bellardia trixago* (L.) All. (= *Trixago apula* Steven or *Bartsia trixago* L., Fam. Scrophulariaceae, Subfam. Rhinanthoideae)[1], for which we have proposed the name trixagol. Chemical and spectroscopic properties are consistent with the proposed structure **1**: (2*E*,6*E*,1' *S*) 3,7-dimethyl-9(6,6-dimethyl-2-methylencyclohexyl) nona-2,6-dien-1-ol. This substance is the *exo* isomer of caulerpol, **2**, recently isolated from *Caulerpa brownii* (Algae)[2].



1 R=H

1a $R=CO(CH_2)_nCH_3$

1b $R=CO-CH_3$



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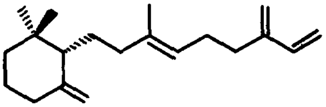

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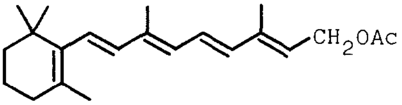
The air-dried and powdered leaves and capsules of *B. trixago*, were extracted with hot hexane. The deffated hexane extract was chromatographed on SiO_2 (dry column) and eluted with hexane/ether 1/1 to yield trixagol (main component) as well as fatty esters **1a**, the acetate **1b** and the alkene **3**.

Trixagol (oil, $[\alpha]_D=+8.0^{\circ}$, c, 0.76 $CHCl_3$) shows a molecular ion M^+ = 290 which is consistent with the formula $C_{20}H_{34}O$. Absorptions in the ir suggest the presence of hydroxyl groups (3320, 995 cm^{-1}) and unsaturations (3040, 1640, 890: $C{=}CH_2$; 1660, 840: $C{=}CH$). The ^1H nmr spectrum (CCl_4) shows signals at δ 5.28(t, *J*=7Hz, 1H, $C{=}CH{-}CH_2OH$), 5.00(bs,1H,$C{=}CH{-}CH_2-$), 4.68 and 4.48(2s, 2H, $C{=}CH_2$), 4.02(d,*J*=7Hz,2H, $={CH}{-}CH_2OH$), 1.63(s,3H, $C{=}C$-Me), 1.57(s,3H, $C{=}C$-Me), 0.90 and 0.82(2s,6H, *gem*-Me_2) and 2-3 ppm(s,1H, conc. dependent, -OH). Having in mind all the above data, and the isoprene rule, we proposed for trixagol the structure **1**.

The identity of the skeleton of trixagol with that of vitamin A, was **established** by catalytic hydrogenation.

Hydrogenation of vitamin A acetate[3], 4, on PtO_2/HOAc (24 hr, rt)[4], gives a mixture of (±)5a and (±)5b (4/1 w/w)[5]. Similar treatment of trixagol acetate led to (-)5a and (-)5b (2/1 w/w) which differ only from the former ones in the specific rotations: $[\alpha]_D$= -2.7º and -3.1º (c, ≃1% $CHCl_3$) respectively.



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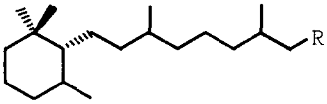
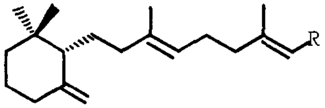


5a R= CH_2OAc

5b R= CH_3



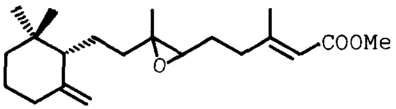
6a R= CHO

6b R= COOMe

The *trans* stereochemistry of 1 was suggested by comparation of nmr signals of the vinylic methyls with those of the closely related *trans-trans* farnesol[6] (absence of any methyl at 1.73 ppm).

To confirm the proposed *trans-trans* stereochemistry, the following transformations were carried out:

Oxidation of 1 with MnO_2/hexane (48 hr, rt) gives 6a ($[\alpha]_D$=+9.9º,c,1.1,$CHCl_3$; nmr(CCl_4):9.90(d, *J*=8Hz, CH—CHO), 5.77(d, *J*=8Hz, =CH—CHO), 2.16, 1.59, 0.90 and 0.82(4s, 4Me); ir, 2740, 1680 cm^{-1}, -CHO) which on treatment with MnO_2/NaCN/MeOH (44 hr, rt)[7] led to 6b ($[\alpha]_D$=+13.9º, c, 1.3 $CHCl_3$; nmr (CCl_4): 5.58(s, C═CH-), 5.02(bs, C═CH—CH_2-), 3.6(s, -COOMe), 2.16, 1.59, 0.90 and 0.82 ppm(4s, 4Me)). The observed deshielding for Me-3 in both 6a and 6b clearly suggests configuration *E* for the double bond C-2.



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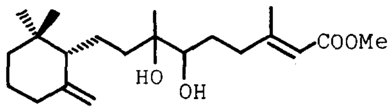

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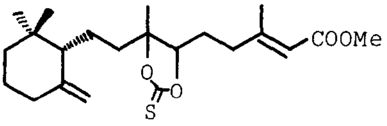
Epoxidation of 6b with *m*-CPBA/CH_2Cl_2(1.2 mol, 4 hr, rt) gives 7[8] which on hydrolysis (water/EtOH and 2 drops of 60% $HClO_4$) afforded 8. Treatment of diol

8 with N,N'-thiocarbonyldiimidazol in refluxing toluene (24 hr under N_2)[9], gives the thiocarbonate 9 whose nmr spectrum showed signals at 1.51(s, Me-7) and 4.32 (t, H-6). By comparation of these signals with those corresponding to trixagol, it can be concluded that diol 8 is the *erythro* isomer and 1 has configuration *E* at C-6.



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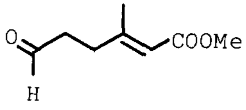

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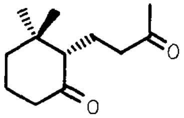

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The diol 8 was also useful to confirm the structure of 1. The oxidation of this diol with HIO_4/H_2O led to a mixture of cyclation products and fragment 10.

In order to stablish the configuration at C-1', trixagol was oxidized with $KMnO_4$/Acetone (mol $KMnO_4$/1 = 10; 4 hr, rt) and the diketone 11 was isolated ($[\alpha]_D$ = +5.5º, c, 1.5 $CHCl_3$; cd (hexane): $\Delta\varepsilon_{296}$ = + 1.57; nmr ($CDCl_3$): 2.08(s, $-CO-CH_3$), 1.08 and 0.78(2s, *gem*-Me_2)). The sign of the Cotton effect[10], allows us to asign the configuration *S*[11] for C-1'. This configuration is also in agreement with that deduced by comparation of specific rotations of diketone 11 from trixagol (+5.5º) and from other sources (+6.19º)[12].

The positive Cotton effect of 11 confirms also the revised *S* configuration alloted by Ohloff and Vial[12] for the chemically related (+) γ-ionone.

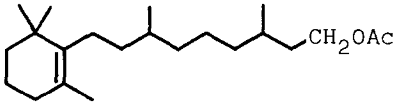
REFERENCES AND NOTES

1.- The plant was identified by Prof. B. Casaseca. Department of Botany. Universidad de Salamanca.

2.- A.J. Blackman and R.J. Wells. *Tetrahedron Letters*, **1976**, 2729.

3.- Purified from Arovit^{R} (Hoffmann-La Roche).

4.- Treatment of **4** with H_2-PtO_2/EtOAc, gives the Karrer's "perhydroretinol" acetate which shows positive tetranitromethane test (P. Karrer and R. Morf, *Helv. Chim. Acta*, **1933**, 16, 625). The product actually is octahydroretinol acetate (nmr, 1.57,s,C=C-Me; ms, M^+ = 336). Otherwise, hydrogenation of trixagol on PtO_2/EtOAc, led to a mixture of **5a**, **5b** and perhydrotrixagol in the ratio 1/6/1 (w)



5.- **5a**: nmr(CCl_4), 4.00(t, *J*=7Hz CH_2-CH_2OAc), 1.93(s, CH_3-COO), 0.80-0.93(5 Me).
ms, m/e(%):278(M^+-HOAc, 6), 193(8), 182(8), 167(14), 152(20), 137(22), 125(75), 123(100), 111(51), 96(31), 95(30), 81(25).
5b: nmr (CCl_4), 1.20(m, CH_2), 0.78-0.95(6 Me).
ms, m/e(%):280(M^+, 18), 276(13), 195(14), 181(18), 140(31), 125(100), 111(66), 97(19), 70(23).

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7.- E.J. Corey and W. Gilmann, *J. Amer. Chem. Soc*., **1968**, 90, 5616.

8.- Ir, ^{1}H nmr and ms data are in good accord with the assigned structures for compounds **6** through **10**.

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12.-G. Ohloff and C. Vial. *Helv. Chim. Acta*, **1977**, 60, 2767.

(Received in UK 26 June 1978; accepted for publication 14 July 1978)