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# ISOCROTOCAUDIN, A NEW NORCLERODANE-TYPE DITERPENE FROM *CROTON CAUDATUS*

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**Key Word Index**—*Croton caudatus*; Euphorbiaceae; structure-elucidation; furanoid norditerpene (norclerodane-type); isocrotocaudin.

**Abstract**—Isocrotocaudin, a new furanoid norditerpene (norclerodane type), has been isolated from the petrol extract of the stem-bark of *Croton caudatus* (Euphorbiaceae). From its spectral properties and chemical correlation with crotocaudin the structure and stereochemistry of isocrotocaudin have been established as *ent*-(8*S*,10*R*)-15, 16-epoxy-19-norcleroda-4, 11, 13 (16), 14-tetraene-18, 6*R*: 20, 12-diolactone.

## INTRODUCTION

Recently we have reported [1] the isolation and structure-elucidation of two furanoid norditerpenes, crotocaudin (1) and teucvidin (2) [2], from the petrol extract of the stem-bark of *Croton caudatus* (Euphorbiaceae). Further investigation of the petrol extract led to the isolation of another new furanoid norditerpene which was designated isocrotocaudin. This communication deals with the chemistry of isocrotocaudin.

## RESULTS AND DISCUSSION

The white, crystalline isocrotocaudin, $C_{19}H_{18}O_5$ ($M^+$ 326.116), mp 212°, $[\alpha]_D^{28}$ +152° ($CHCl_3$; *c* 0.11) was a mono-β-substituted furan derivative as evidenced from PMR spectrum, strong IR absorption at 875 $cm^{-1}$ and positive Ehrlich test [3]. The two α-protons on the furan ring resonated at δ 7.70 (*br.s*) and 7.48 (*ddd*, *J* = 1.5, 1, 0.5 Hz) while the β-proton of the furan ring was discernible at δ 6.56 (*dd*, *J* = 1.5, 1 Hz). The occurrence of a β,γ-unsaturated γ-lactone in isocrotocaudin was recognised by the characteristic IR absorption at 1795 $cm^{-1}$ while the presence of a second lactone ring was indicated by the diagnostic peak at 1750 $cm^{-1}$ in the IR spectrum. This is typical of an α,β-unsaturated γ-lactone which was consistent with the Baljet [4] and Kedde [5] colour reactions.

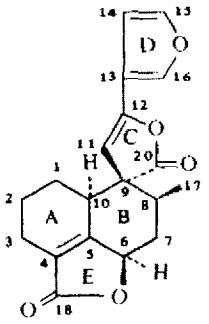
The electronic spectrum of isocrotocaudin in the UV region showed absorption maxima at 218 and 254 nm. The chromophore for the light absorption at 218 nm was the α,β-unsaturated γ-lactone whereas the absorption maxima at longer wavelength was assigned to a furan system with an extended conjugation.

The PMR spectrum showed the presence of a secondary methyl group (δ 0.99, 3H, *d*, *J* = 7 Hz) and an olefinic proton on a trisubstituted double bond (δ 5.33, 1H, *s*).

From these data and a comparison of the properties of crotocaudin (1) and isocrotocaudin it could be concluded that isocrotocaudin had the same planar structure as that of crotocaudin (1), but the chirality was different at C-6 and C-10. This was confirmed by a careful analysis of the corresponding PMR signals of the C-6 proton and the C-10 proton. In the PMR spectrum of isocrotocaudin the C-10 and C-6 protons were observed at δ 2.75 and δ 4.82 respectively while the corresponding signals in crotocaudin were discernible at δ 3.14 and δ 4.95 respectively. The chemical shifts of the C-10 proton in these two compounds differed by about 0.4 ppm. Obviously, the C-10 proton in crotocaudin (1) was deshielded by the C-20 carbonyl group, a situation that was possible because of the same steric disposition of the C-10 proton and the C-20 carbonyl group. It follows therefore that in isocrotocaudin the C-10 hydrogen and and the C-9 to C-20 bond must have the opposite steric disposition. By similar arguments the C-6 hydrogen and the C-9 to C-20 bond in isocrotocaudin must have opposite orientation, though the difference between the chemical shifts of the C-6 proton in the two compounds was not very large because of the rather long distance between the C-6 proton and the C-20 carbonyl group. The same stereochemistry of C-10 and C-6 hydrogens in isocrotocaudin was also supported from the fact that the Dreiding model of the compound could only be constructed with the same stereochemistry (both α or both β) of the C-10 and C-6 hydrogens, but not with the opposite stereochemistry (α, β or β, α) at these two centres.

To ascertain the absolute stereochemistry at the chiral centres of isocrotocaudin circular dichroism was utilised. The CD spectrum of both teucvin (3) [6] and the corresponding hexahydro derivative (4) displayed a (+) Cotton effect [2] with almost the same intensity at about the same wavelength. Therefore the observed Cotton effect was due to the α,β-unsaturated γ-lactone chromophore which is common in both teucvin (3) and hexahydroteucvin (4).

The CD spectrum of isocrotocaudin showed a (+) Cotton effect and the curve was identical to that of teucvin (3). It was also symmetrical to the CD curve of crotocaudin (1) which showed a (−) Cotton effect with similar intensity. This provided the same stereochemistry of the A, B and E ring system between teucvin (3) and



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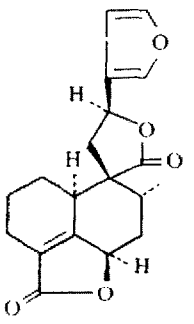

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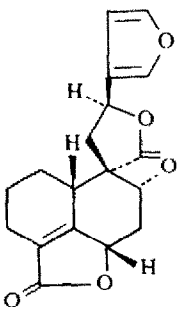

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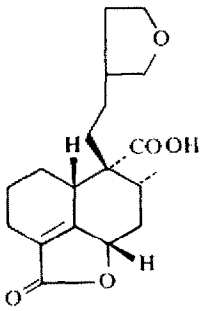

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isocrotocaudin and the opposite stereochemistry of the A, B and E ring system between crotocaudin (**1**) and isocrotocaudin, provided the conformation of these rings in these compounds does not differ. The conformations of both teucvin (**3**) and crotocaudin (**1**) have been established [1, 2] and the ring B exists in the chair form. From the molecular model studies of isocrotocaudin it was apparent that ring B cannot exist in the boat form, because the substituents at C-6 and C-7 and at C-9 and C-10 are totally eclipsed. Consequently ring B of isocrotocaudin has the chair conformation where this strain is lacking.

It may be concluded from the above discussions that both the C-10 hydrogen and the C-6 hydrogen in isocrotocaudin must have $\beta$-orientation, the absolute configuration at these centres being *R*. Since the C-10 hydrogen and the C-9 to C-20 bond are in the opposite direction, the C-9 to C-20 bond must have the $\alpha$-configuration. The methyl group in both crotocaudin (**1**) and isocrototocaudin obviously has the same stereochemistry which was confirmed by conversion of crotocaudin (**1**) to isocrotocaudin. This was achieved by treating crotocaudin (**1**) with $NaBH_4$ in a polar solvent like MeOH when a product, identical in all respects with natural isocrotocaudin, was obtained. The reaction obviously proceeded through the enolate anion (Scheme 1). Hence the methyl group at C-8 of isocrotocaudin has the $\beta$-orientation. Consequently the absolute structure of isocrotocaudin must be *ent*-(8*S*, 10*R*)-15, 16-epoxy-19-norcleroda-4, 11, 13 (16), 14-tetraene-18, 6*R*: 20, 12- diolactone (**5**). The MS fragmentation pattern was in accorded with this structure (**5**) and was similar to that of crotocaudin (**1**) [1].

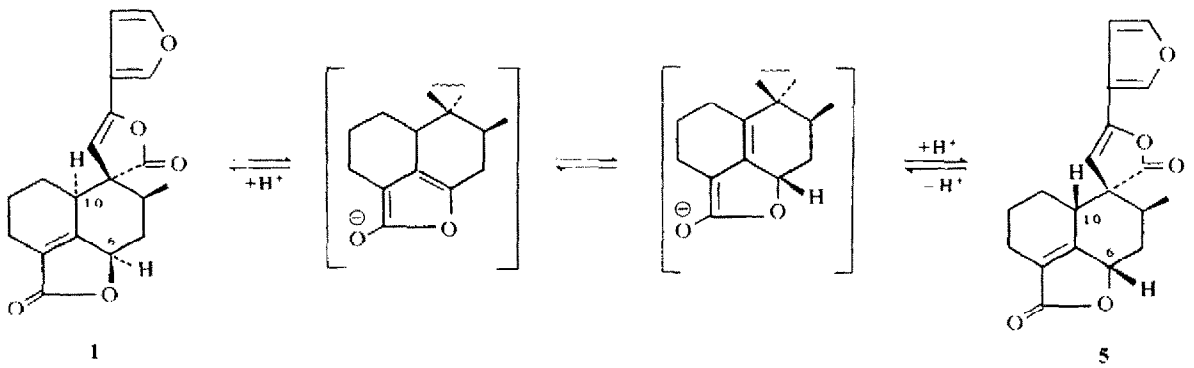
## EXPERIMENTAL

Mps. are uncorr. UV spectra were recorded in 95% EtOH (aldehyde-free) and IR spectra in $CHCl_3$. Specific rotations were measured in $CHCl_3$ in an automatic polarimeter. The 270 MHz PMR spectra was recorded in a Bruker WH 270 instrument in $CDCl_3$ soln with TMS as an internal standard. The CD spectrum was run in MeOH soln with a path-length of 0.05 cm in a Cary-61 instrument. All chromatographic separations were carried out with Si gel.

*Isolation of isocrotocaudin* (**5**). Dried and powdered stem-bark (2 kg) for *C. caudatus* Geisel was extracted in a Soxhlet with petrol for 70 hr. From the petrol extract taraxerone, taraxerol, sitosterol, taraxeryl acetate, crotocaudin (**1**) and teucvidin (**2**) were isolated by the procedure reported earlier [1]. The mother-liquour of the $CHCl_3$-eluate, after isolation of teucvidin (**2**), showed two spots on TLC, the major spot was isocrotocaudin (**5**) while the minor (very faint) spot was teucvidin (**2**). Isocrotocaudin (**5**) was isolated from this mother-liquour by PLC on Si gel developed with $C_6H_6$–EtOAc (4:1). Repeated crystallisation from petrol-$CHCl_3$ (2:1) mixture afforded pure isocrotocaudin (**5**) (30 mg) (found: C, 69.96; H, 5.50. $C_{19}H_{18}O_5$ requires: C, 69.93; H, 5.52%). UV $\lambda_{max}^{95\%\ EtOH}$ nm (log $\varepsilon$): 218 and 254 (4.26 and 4.00 respectively). IR $\nu_{max}^{CHCl_3}$ cm$^{-1}$: 1795, 1750, 1685, 1160, 1135, 1085, 1040, 1010, 975, 955, 875 and 785. PMR (270 MHz, $CDCl_3$): $\delta$ 7.70 (1H, *br. s*, 16-H), 7.48 (1H, *ddd*, $J$ = 1.5, 1, 0.5 Hz, 15-H), 6.56 (1H, *dd*, $J$ = 1.5, 1 Hz, 14-H), 5.33 (1H, *s*, 11-H), 4.82 (1H, *br. dd*, $J$ = 9, 7 Hz, 6-H), 2.75 (1H, *m*, 10-H) and 0.99 (3H, *d*, $J$ = 7 Hz, 17-$H_3$). MS: *m/e* (rel. int.): 326 [$M^+$] (23.3), 284 (11.7), 282 (20), 256 (30), 189 (51.7), 176 (56.7), 95 (100), 91 (20), 79 (18.3) and 77 (18.3); CD (MeOH; *C* 0.025): $[\theta]_{280}$ 0, $[\theta]_{258}$ + 6534, $[\theta]_{234}$ + 45606, $[\theta]_{220}$ 0. (Found: C, 69.96; H, 5.50. $C_{19}H_{18}O_5$ requires: C, 69.93; H, 5.52%)

*Ehrlich reaction.* TLC of isocrotocaudin (**5**) showed a rose-red red spot, $R_f$ = 0.47, $C_6H_6$–EtOAc (1:1) when a soln of *p*-dimethylaminobenzaldehyde in EtOH was sprayed on the plate followed by exposure to conc HCl vapour.

*Baljet reaction.* To isocrotocaudin (**5**) (1 mg) was added a



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mixture of equal vols of 1% picric acid soln in EtOH and 10% aq NaOH. The mixture became orange-red.

*Kedde reaction.* When a soln of 3,5-dinitrobenzoic acid (100 mg) in 0.5 M KOH in 50% MeOH (10 ml) was added dropwise to isocrotocaudin (**5**), it slowly became red-violet.

*Preparation of isocrotocaudin* (**5**) *from crotocaudin* (**1**). Isocrotocaudin was prepared from crotocaudin (**1**) by treatment with $NaBH_4$ in MeOH by the method described earlier [1]. It was found to be identical with natural isocrotocaudin (**5**) by direct comparison (mp, mmp and superimposable IR spectra). Found: C, 69.95; H, 5.51. $C_{19}H_{18}O_5$ requires: C, 69.93; H, 5.52%).

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