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THE CONSTITUTION OF ISO-TRICHOTHECOLONE AND OF ALLODIHYDRO-TRICHOTHECOLONE

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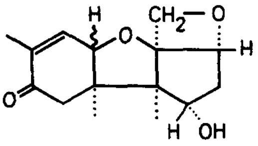
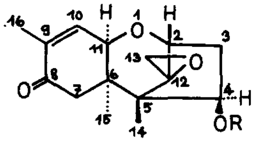
TRICHOTHECOLONE, $C_{15}H_{20}O_4$, is a ketonic alcohol which is formed upon hydrolysis of trichothecin [1], an antifungal metabolite produced by *Trichothecium roseum* Link. The original structure I proposed by Freeman et al.[2] and Fishman et al.[3] for trichothecolone has been revised recently by Godtfredsen and Vangedal [4]. They proved structure II by interrelating trichothecolone with roridin C[5] (trichodermol[4]) the structure of which was elucidated by X-ray analysis [6]. Whereas the majority of the reactions of trichothecolone described by the British authors [1,2,3] can be interpreted readily in terms of the new formula II, unequivocal structures can not be assigned to iso-trichothecolone and to allodihydro-trichothecolone and their transformation products on the basis of the data available in the literature. We therefore have reinvestigated these compounds which were of interest to us in connection with our studies on the various re-



I trichothecolone
old structure

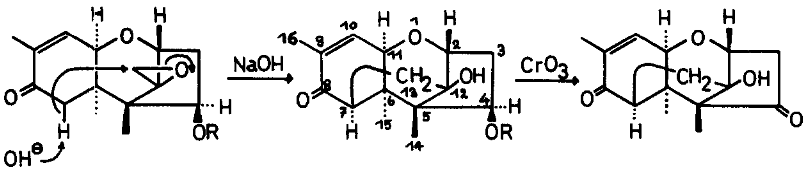


II R=H : trichothecolone
III R= CH_3-CH=CH-CO— : trichothecin

arrangements of the closely related verrucarol[5] and diacetoxyscirpenol[7] derivatives.

Iso-trichothecolone is formed by treating trichothecin or trichothecolone with hot alkali[2,3], whereas in the presence of zinc and alkali trichothecolone is reduced to allodihydro-trichothecolone [2,3]. Since neither verrucarol[6] nor diacetoxyscirpenol[7] showed the same type of transformations, the keto group at C-8 must be responsible for the base catalysed reactions of trichothecolone.

Iso-trichothecolone ($C_{15}H_{20}O_4$) still contains the original chromophoric system and the secondary hydroxyl group, but instead of the terminal oxiran ring (cf.[2,3]), a tertiary hydroxyl group. It forms a monoacetate, dihydro derivatives and a diketone[2,3]. Treatment of dihydro-trichothecolone with hot alkali gives dihydro-iso-trichothecolone. This observation indicates that the olefinic double-bond of trichothecolone (II) is not involved in this reaction. We propose structure IV for iso-trichothecolone, since the IR and n.m.r.spectra of all compounds agree well with this structure. The assignments of the



II R = H

III R = CH_3-CH=CH-CO-

IV R = H : iso-trichothecolone

V R = Ac

VI iso-trichothecodione

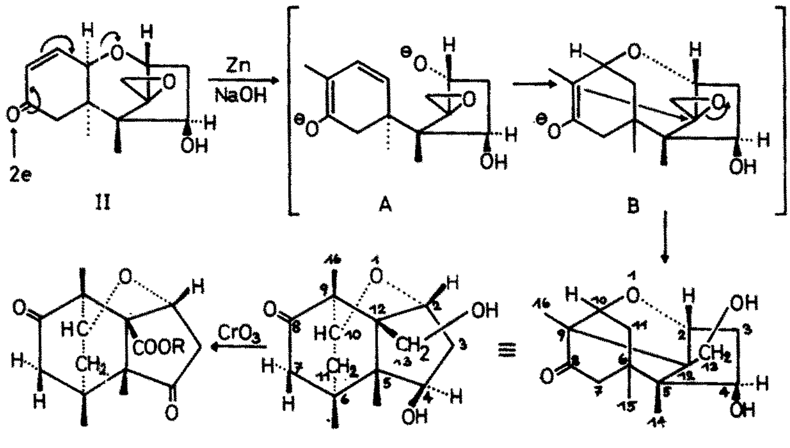
principal signals of the n.m.r. spectra are listed in the TABLE which also contains the corresponding data of trichothecolone for comparison. The detailed analysis of the high resolution spectrum of iso-trichothecodione VI combined with double resonance experiments (see Fig. 1)was especially conclusive. The following coupling systems were recognized by spin-spin decoupling experiments: the two protons at C-10 and C-11 as an AX-system, the three protons at C-2 and C-3 as an ABX-system and the 7α-proton with the two protons at C-13 also as an ABX-system. The high value of the spin-spin coupling constant (J = 13 cps) of the 7α-proton and the trans-proton of the C-13-bridge is remarkable. The 2β and 3α-proton do not show any coupling because of a torsion angle of ca. 90° [8]. Besides the normal coupling transmitted by three σ-bonds, long-range allylic coupling (transmitted by the π-electrons)[9] of $J \simeq 1.5$ cps is observed between the vinylic proton at C-10 and the 16-methyl group. Further long-range coupling ($J \simeq 1.5$ cps) involving 4σ-bonds is exhibited by the 7α- and 11α-proton, which possess the demanded W-conformation [9,10]. Corresponding protons of some derivatives of verrucarol [11] and of diacetoxyscirpenol [7] show similar long-range coupling. The formation of iso-trichothecolone (IV) from trichothecolone (II) can be interpreted as an attack of the base at the activated 7β-hydrogen atom with subsequent stabilization of the negative charge at C-7 by an internal S_N-2 reaction at carbon atom No 13 with cleavage of the oxiran ring.

All the described reactions [2,3] of iso-trichothecolone can be well understood on the basis of structure IV except the formation of the diketo acid $C_{15}H_{20}O_5$ (m.p. 104-109°) which was obtained from iso-trichothecodione VI by a mysterious sequence of reactions [3]. Since we were not able to reproduce the preparation of this acid, its structure could not be elucidated.

A spatial formula of IV is shown further below.

Allodihydro-trichothecolone ($C_{15}H_{22}O_4$) contains a tertiary hydroxy-methyl group, three angular methyl groups attached to saturated carbon atoms, a secondary hydroxyl group in a five-membered ring and a saturated keto group in a six-membered ring [2,3]. The olefinic double of trichothecolone (II) has been reduced. Structure VII is assigned to allodihydrotrichothecolone on the basis of the above information and the interpretation of the n.m.r. spectra of the diacetate VIII (Fig. 2) and of the diketo ester X (Fig. 3).

The hitherto unknown diketo ester X (m.p. 174-175°, $C_{16}H_{20}O_5$, Calc.: C 65,74 H 6,90 %, Found C 65,99 H 6,95 %, IR.-spectrum (CH_2Cl_2): bands at 2950, 1730-1735, 1382, 1308, 1193, 1125, 1078, 1033, 1011, 995, 935, 924 cm^{-1}) was obtained by CrO_3-oxidation of VII and subsequent treatment of the diketo acid IX with diazomethane. In the less complex n.m.r. spectrum of the diketo ester X the 16-methyl group appears as a singlett at $\delta = 1.10$. The protons of the methylene group at C-7 give rise to an AB-



IX R H
X $R=CH_3$

VII R=H : allodihydro-trichothecolone
VIII R=Ac

system, the three protons at C-2 and C-3 to an ABX-system and finally the three protons at C-10 and C-11 to an A_2X-system. Interestingly the protons at C-11 show the same chemical shift. They appear as a double doublet since one of them undergoes a long-range coupling (J = 2cps) with the 7β-proton. On irradiation of the 11-protons, the two triplets of the 7β-proton collaps and a doublet results (J = 19 cps), coupling with the 7α-proton. The two protons involved in the long-range coupling show the planar W-structure [9,10]. The n.m.r. spectrum of the diacetate VIII is more complex. It was interesting to note that the 2- and 3α- resp. 10- and one of the 11-protons did not couple with each other because of a torsion angle of ca. 90°. Therefore the fine structure of their signals is relatively simple. The 7β-proton and 11-proton mentioned above show again long-range coupling of ca. 3 cps but no coupling occurs between the 7α- and the other 11-proton. The two protons of the C-13-methylene group appear as an AB-system of $J \simeq 12$ cps (compare verrucarol [6]). Since the 16-methyl group gives rise to a singlet, allodihydro-trichothecolone (VII) must contain an additional bond originating at C-9 and since the terminal epoxy group has been transformed to a tertiary hydroxymethyl (C-13) group, the other terminal of this bond would be C-12.

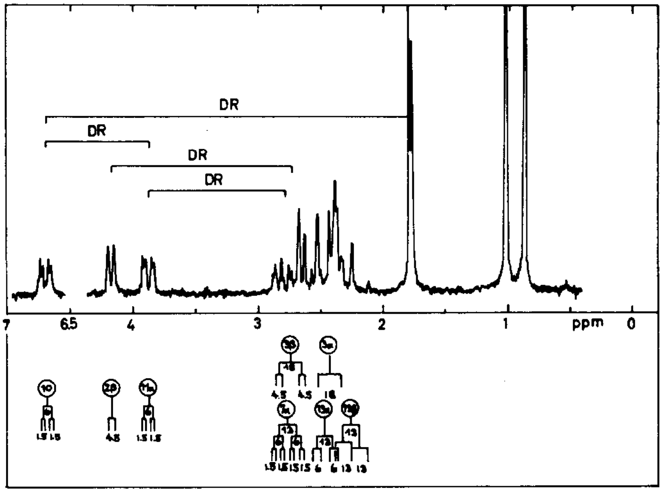


Fig. 1 100 MHz-n.m.r. spectrum of iso-trichothecodione (VI) in $CDCl_3$. * +

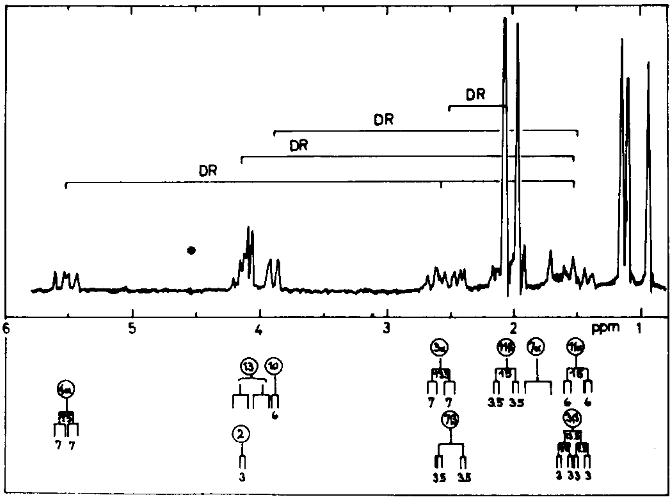


Fig. 2 100 MHz-n.m.r. spectrum of di-O-acetyl-allodihydro-thrichothecolone (VIII) in $CDCl_3$. * +

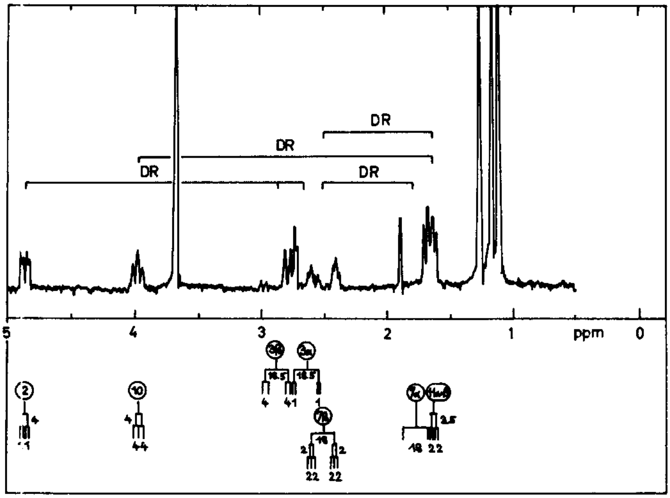


Fig. 3 100 MHz-n.m.r. spectrum of the diketo methyl ester X in $CDCl_3$. * +

The first step in the formation of VII from II is the reductive cleavage of the α,β-unsaturated-γ-alkoxy system (cf.[12]) leading to the intermediate A. By addition of a proton, A is transformed to the anion B in which ring closure takes place at C-10. The negative charge of C is stabilized by an intramolecular S_N2-reaction at C-12 with the concurrent opening of the epoxy group which is protonated. Essentially the same mechanism has been proposed by Jones et al.[3]. The alternative structure VIIa was ruled out because it would require long-range coupling between a 7-proton and a 10-proton (5 σ -bonds!) and because it would represent a very strained system. The proposed structure VII was also favoured on mechanistic grounds. It is a bicyclo-octane-[2.2.2.]system with two fused five-membered rings, as depicted by the following spatial formula:

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*) We are indebted to Dres. A. Melera and U. Scheidegger, Varian A.G., Zürich, for the measurement of the spectrum and the double resonance experiments.

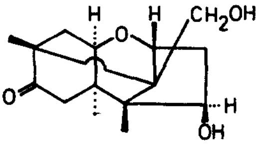
+) The spin-spin couplings, which were determined by double resonance experiments, are indicated by arrows (DR). The splitting patterns are shown below the spectra, the numbers indicating the assignment of the protons, resp. the coupling constants.

TABLE: Assignment of the protons in the n.m.r.spectra (selection of data) *)

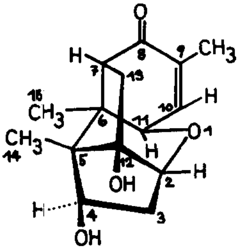
	MHz	C-2	C-4	C-10	C-11	C-13	C-14	C-15	C-16	Diverse
II +)	60	3.93 d (5)	4.3 m	6.45 dd (1.5;6)	3.85 m	3.13+2.84 AB (4)	0.80 s	1.0 d (1)	1.83 d (1)	
IV	60	3.98 d (4.5)	4.1 m	6.78 dd (1.5;6.5)	3.71 dd (ca.1;6.5)	ca. 2-3	0.91 s	1.05 s	1.83 d (1.5)	
V	60	3.99 d (4.5)	5.28 dd (5;7.5)	6.81 dd (1.5;6.5)	3.84 dd (ca.1;6.5)	ca.2-3	0.96 s	0.96 s	1.84 d (1.5)	1 Ac: 2.09 s
VI	100	4.15 d (4.5)	---	6.69 dd (1.5;6)	3.86 dd (1.5;6)	ca.2.3 m	0.87 s	1.02 s	1.78 d (1.5)	
VIII	100	4.14 d (3)	5.52 dd (7;9.5)	3.89 d (6)	ca. 2	4.13 + 4.03 AB (12)	1.16 s;	1.12 s;	0.95 s	2 Ac: 2.07s 1.97s
X	100	4.85 dd (ca.1;4)	---	3.96 t (3.5)	1.64 dd (2;3.5)	---	1.27 s;	1.17 s;	1.10 s	OCH_3: 3.68s

*) Measured by a Varian Spectrometer A-60 (60 MHz) in the laboratory for physical chemistry of Sandoz A.G., Basel (Dres. K. Frei and P. Niklaus) or by a Varian Spectrometer HR-100 (100 MHz) of Varian A.G., Zürich (Dr. A. Melera and Dr. U. Scheidegger). Chemical shifts in ∂ -values with $Si(CH_4)_4$ (TMS) as internal standard (∂ = 0). Solutions in $CDCl_3$ were used: s = singlet; d = doublet; dd = double doublet; t = triplet; m = multiplet, AB = AB-coupling system. The numbers in brackets are the spin-spin-coupling constants J in c.p.s. Ac = CH_3CO- .

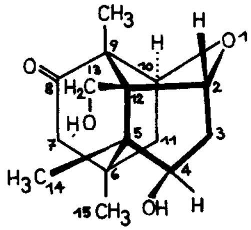
+) The assignments of the protons at C-2 and C-11 in trichothecolone (II) are based on double resonance experiments. In an earlier paper ^{5} we have given the reverse interpretation.



VII a



IV Iso-trichothecolone



VII Allodihydro-trichothecolone

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REFERENCES

1. G.G. Freeman and R.I. Morrison, Nature 162, 30 (1948); Biochem. J. 44, 1 (1949).
2. G.G. Freeman, J.E. Gill and W.S. Waring, J.Chem.Soc. 1959, 1105
3. J. Fishman, E.R.H. Jones, G. Lowe and M.C. Whiting, J.Chem.Soc. 1960, 3948.
4. W.O. Godtfredsen and S. Vangedal, Proc.Chem.Soc. 1964, 188.
5. J. Gutzwiller, R. Mauli, H.P. Sigg and Ch. Tamm, Helv.Chim.Acta 47, 2234 (1964).
6. S. Abrahamsson and B. Nilsson, Proc.Chem.Soc. 1964, 188.
7. H.P.Sigg, R.Mauli, E.Flury and D.Hauser, Helv.Chim.Acta, 48,962 (1965).
8. M. Karplus, J.Chem.Phys. 30, 11 (1959).
9. S.Sternhell, Rev. Pure and Appl. Chemistry (Australia) 14, 15 (1964).
10. A.Rassat, C.W.Jefford, J.M.Lehn and B.Waegell, Tetrahedron Letters 1964, 233.
11. W.Zürcher, J.Gutzwiller and Ch.Tamm, Helv.Chim.Acta 48, 840 (1965).
12. R.B. Woodward, F. Bader, H. Bickel, A.Frey and R. Kierstead, Tetrahedron Letters 1958, 1.