123. ^{13}C-NMR.-Spectroscopy of the Trichothecane Derivatives Verrucarol, Verrucarins A and B and Roridins A, D and H

Verrucarins and Roridins, 33rd Communication [1]

by **Werner Breitenstein** and **Christoph Tamm**

Institut für Organische Chemie der Universität, 4056 Basel, Schweiz

(19. III. 75)

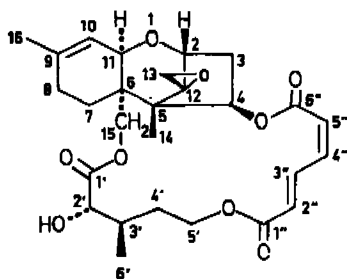
Summary. Partial decoupling experiments permitted assignment of carbon magnetic resonance spectra of verrucarins A (**1**) and B (**4**), of roridin A (**2**), D (**5**), and H (**6**), and of verrucarol (**9**). In this connection new verrucarol derivatives were prepared and are described.

1. Introduction. – ^{13}C-labelled precursors have proved to be very useful tools for the study of biosynthetic pathways of secondary metabolites [2]. They are complementary to methods using labelling by deuterium, ^{15}N and radioactive isotopes. The position of incorporated ^{13}C-label can be determined directly by ^{13}C-NMR. spectroscopy instead of difficult and time-consuming degradations. However, this determination requires correct interpretation of the ^{13}C-NMR. spectrum of the compound under investigation. In this paper we report the assignment of the ^{13}C-NMR. spectra of verrucarin A (**1**) and roridin A (**2**), the major secondary metabolites of various *Myrothecium* species [3], and of the minor metabolites verrucarin B (**4**), roridin D (**5**), and roridin H (**6**) [3]. These substances are esters of the sesquiterpene alcohol verrucarol (**9**). Consequently, the ^{13}C-NMR. spectrum of this trichothecane derivative has also been carefully analyzed. For this purpose a series of new transformation products were synthesized. A subsequent paper will deal with the incorporation of ^{13}C-labelled precursors into these antibiotics, and the corroboration of these results with those obtained by the utilization of ^{14}C- and ^{3}H-labelled substances [4].

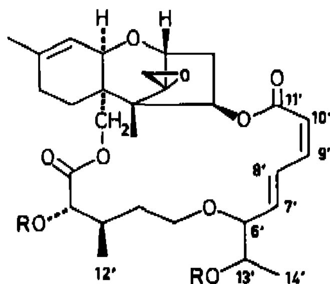
2. Isolations and Synthesis. – Verrucarins A (**1**) and B (**4**) and roridins A (**2**), D (**5**) and H (**6**) were isolated from the crude extract[1]) of cultures of the strain S 118 of *Myrothecium verrucaria* (ALBERTINI & SCHWEINITZ) DITMAR EX FRIES, as previously described [5]. Di-O-acetyl roridin A (**3**) was prepared by known methods [6]. Verrucarol (**9**) was obtained by hydrolysis of verrucarin A (**1**) with methanolic K_2CO_3 [7]. Oxidation of **9** with CrO_3/H_2SO_4 in acetone gave the known keto-aldehyde **10** [8]. Treatment of verrucarol (**9**) with an excess of acetic anhydride in pyridine yielded the di-O-acetyl derivative **7**; reaction with one equivalent of acetyl chloride in pyridine gave primarily 4-O-acetyl-verrucarol (**11**). The latter was transformed to the aldehyde **12** by oxidaton with CrO_3/H_2SO_4 in acetone. Hydrolytic removal of the acetyl group with K_2CO_3 in aqueous methanol led to the hydroxy aldehyde **13**. The chemical shifts of the protons in the ^{1}H-NMR. spectra (see Table 1) of compounds **11**, **12** and **13** as well as of the

---

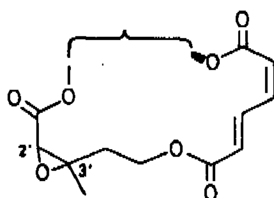
[1]) A 500 liter fermentation was carried out in the microbiological laboratories of *Sandoz AG.*, Basel, by Dr. *E. Härri* and *J. Bianchi*. We are very grateful to them for their kind support.



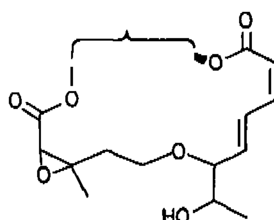
1 Verrucarin A



2 R = H : Roridin A
3 R = Ac

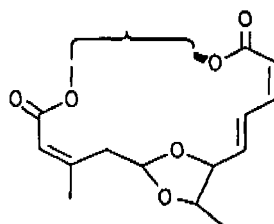


4 Verrucarin B



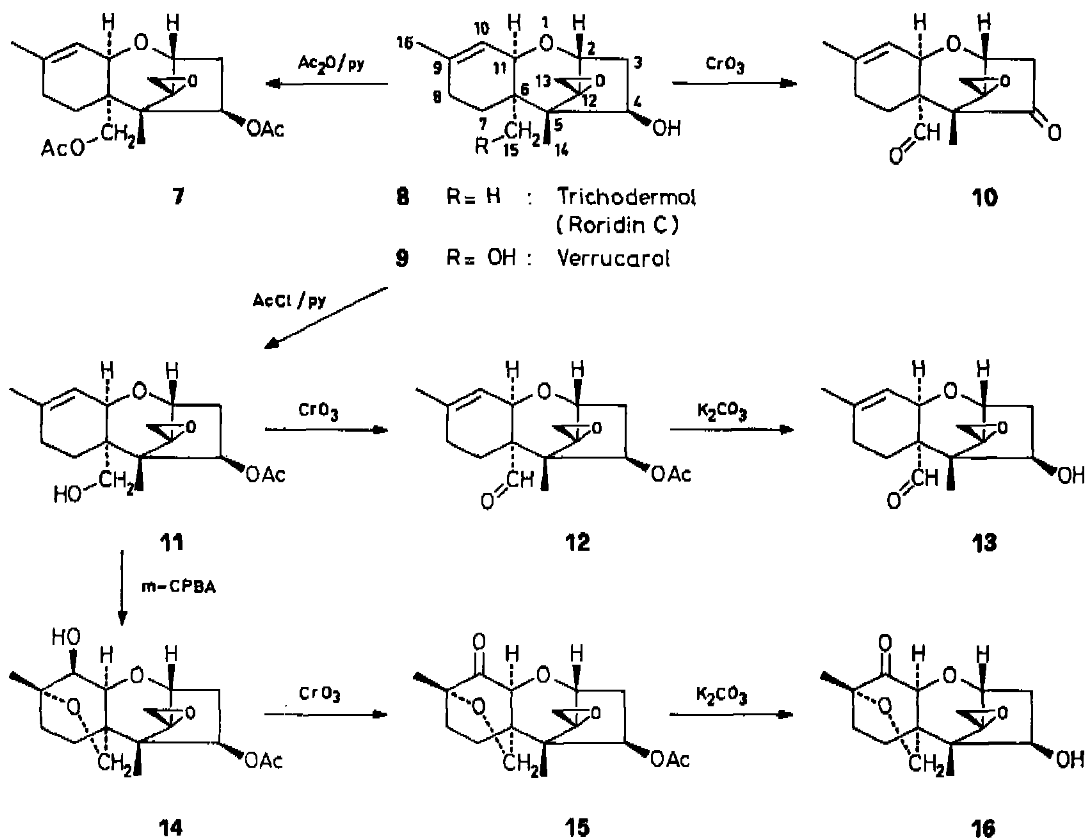
5 Roridin D

Ac = CH_3CO



6 Roridin H

products **14**, **15** and **16** described below, are compatible with their structure and stereochemistry. Treatment of 4-O-acetyl-verrucarol (**11**) with *m*-chloroperbenzoic acid in chloroform led to the hydroxy-ether **14**. This substance is formed by nucleophilic attack of the free 15-hydroxy group at the intermediary 9,10β-epoxide analogous to a transformation described earlier [9]. Inspection of molecular models demonstrates that the formation of such an ether bridge is possible without a significant change of the configuration of the trichothecane skeleton. This point is important with regard to the assignment of the ^{13}C-NMR. spectra. In the IR. spectrum of compound **14** a new absorption band at 3550 cm^{-1} is found in place of the hydroxyl absorption of the neopentyl system of **11** at 3620 cm^{-1}. In addition, the ^{1}H-NMR. spectrum of the hydroxy-ether **14** does not show any protons in α-position to an oxirane ring other than those of the C(13)-methylene group. Oxidation of the hydroxy-ether **14** with CrO_3/H_2SO_4 in acetone and subsequent hydrolysis of the resulting keto-ether **15** with K_2CO_3 in aqueous methanol yielded the hydroxy-keto-ether **16**.



m-CPBA = m-chloroperbenzoic acid
Ac = CH_3CO
py = pyridine

3. Assignments of ^{13}C-NMR. Signals of Verrucarol. – The assignments of ^{13}C-NMR. signals as summarized in Table 2 are based essentially on the comparison of the partially decoupled *Fourier* Transform (FT)-spectra with the spectra obtained by proton noise decoupling. Further information was gained by selective proton decoupling and by measurement of spectra of the derivatives of verrucarol described in the preceeding section.

Signals in the area of the sp^2-hybridized carbon atoms, the singlet at 140.4 ppm and the doublet at 118.7 ppm are directly assigned to C(9) and C(10) respectively. The only singlet in the region of carbon atoms which are attached directly to oxygen at 65.6 ppm, corresponds to C(12). The triplet at 47.4 ppm was recognized as C(13) by selective proton decoupling. As demonstrated by the irradiation of the three protons of the 14-methyl group, C(14) is responsible for the resonance at 6.8 ppm. Hence the second quartet at 22.9 ppm can be assigned to the allylic 16-methyl group.

Table 1. *Assignment of the H-Atoms in the* ¹*H-NMR. Spectra*[2])

Compound	C(2)	C(4)	C(10)[a])	C(11)[b])	C(13)[d])	C(14)	C(15)[c])	C(16)[a])	Ac)
4-O-Acetyl-verrucarol (**11**)	*ca.* 3.8	6.03 $d \times d$ (4; 8)	5.50 *d* (5)	*ca.* 3.8	2.98 *AB* (4)	0.83 *s*	*ca.* 3.7	1.73 *s*	2.10 *s*
Aldehyde **12**	3.84 *d* (5)	5.50 $d \times d$ (4; 8)	5.50	4.38 *d* (5)	2.98 *AB* (4)	0.88 *s*	9.66 *s*	1.67 *s*	2.05 *s*
Hydroxy-aldehyde **13**	3.86 *d* (5)	4.37 $d \times d$ (3.5; 8)	5.53 *d* (5)	4.29 *d* (5)	2.98 *AB* (4)	0.98 *s*	9.64 *s*	1.68 *s*	
Hydroxy-ether **14**	*ca.* 3.8	5.52 $d \times d$ (4; 8)	3.94 *d* (5)	*ca.* 3.8	2.93 *AB* (4)	0.62 *s*	3.82	1.17 *s*	2.06 *s*
Hydroxy-keto-ether **16**	4.00	4.42 $d \times d$ (3.5; 8)	–	4.20 *d* (2)	2.93 *AB* (4)	0.78 *s*	4.01	1.22 *s*	

a) These signals often show fine structure.
b) Because of long range coupling ($J \simeq 2$ Hz) no sharp signals are observed [9].
c) Sometimes *AB* system.
d) Distance between doublets $\simeq$ 0.3 ppm.

Table 2. *Assignment of the C-Atoms in the* ¹³*C-NMR. Spectra of Verrucarol and of its Derivatives*[3])

	Di-O-acetyl-verrucarol (**7**)	Verrucarol (**9**)	Keto-aldehyde **10**	Hydroxy-aldehyde **13**	Hydroxy-keto-ether **16**
C(2)	78.4 *d*	78.5 *d*	75.8 *d*	78.7 *d*	79.3 *d*[b])
C(3)	36.0 *t*	39.5 *t*	41.6 *t*	39.7 *t*	39.3 *t*
C(4)	74.7 *d*	74.0 *d*	212.7 *s*	73.4 *d*	72.8 *d*[b])
C(5)	48.2 *s*	48.7 *s*	53.4 *s*[a])	48.8 *s*	46.1 *s*[a])
C(6)	42.7 *s*	43.7 *s*	54.7 *s*[a])	54.0 *s*	44.7 *s*[a])
C(7)	20.7 *t*	20.9 *t*	18.6 *t*	20.5 *t*	21.2 *t*
C(8)	27.4 *t*	28.0 *t*	27.2 *t*	27.8 *t*	31.5 *t*
C(9)	139.6 *s*	140.4 *s*	142.2 *s*	140.3 *s*	76.4 *s*
C(10)	118.2 *d*	118.7 *d*	117.7 *d*	118.8 *d*	208.5 *s*
C(11)	66.2 *d*	66.4 *d*	65.4 *d*	65.3 *d*	75.1 *d*[b])
C(12)	64.7 *s*	65.6 *s*	64.1 *s*	64.8 *s*	64.8 *s*
C(13)	47.1 *t*	47.4 *t*	49.3 *t*	46.9 *t*	46.5 *t*
C(14)	5.8 *q*	6.8 *q*	5.5 *q*	6.5 *q*	6.3 *q*
C(15)	63.0 *t*	62.1 *t*	199.4 *d*	202.3 *d*	66.2 *t*
C(16)	22.4 *q*	22.9 *q*	23.1 *q*	23.1 *q*	17.9 *q*
CH_3(Ac)	20.2 *q*				
C=O(Ac)	169.6 *s*				
C=O(Ac)	169.8 *s*				

a) b) These assignments could be reversed.

2) Measured by a *Varian* A-60, *Varian*-HA-100D and a *Bruker*-WH-90-Spectrometer in $CDCl_3$ solution. δ-values in ppm relative to TMS. The spin-spin coupling constants J (Hz) are noted in brackets.

3) Determined on a *Bruker* WH-90 FT spectrometer operating at 22.63 MHz; $CDCl_3$ solution (0.2–0.8 M); deuterium lock; δ_C in ppm from TMS.

Acetylation of verrucarol (**9**) causes a downfield shift of the triplet at 62.1 ppm and of the doublet at 74.0 ppm. Thus these signals are derived from C(15) and C(4) respectively. The characteristic change of the position of the triplet at 39.5 ppm which is induced by esterification leads to the conclusion that it is the signal of C(3). These three assignments are confirmed by the spectrum of the keto-aldehyde **10**.

The singlet at 43.7 ppm of verrucarol (**9**) undergoes a downfield shift of ca. 10 ppm after the selective oxidation of the 15-hydroxy group which leads to compound **13**. Hence this signal is assigned to C(6). Consequently C(5) is responsible for the singlet at 48.7 ppm. The pronounced upfield shift of the doublet at 78.5 ppm which is observed by the transformation of verrucarol (**9**) into the keto-aldehyde **10** leads to the conclusion that C(2) is responsible for this signal. On the basis of these arguments the remaining doublet at 66.4 ppm is to be assigned to C(11). These assignments of C(2) and C(11) are confirmed by the observation that the resonance at 66.4 ppm of verrucarol (**9**) appears in the keto-ether **16** at a considerable lower field[4]). The distinction of C(7) and C(8) is based on the fact that transformation of verrucarol (**9**) to the keto-ether **16** shifts only one of these two triplets. Therefore C(8) must be responsible for the signal at 28.0 ppm and C(7) for the triplet resonance at 20.9 ppm.

4. Assignments of the ^{13}C-NMR. Signals of Verrucarin A and Verrucarin B. – The comparison of the proton noise decoupled ^{13}C-FT-NMR. spectra of verrucarin A (**1**) (Fig. 1) and verrucarin B (**4**) allows unambiguous assignment for C(1′), since the two muconic carbonyl resonances are not shifted. The distinction between C(1″) and C(6″) is not as easy. The resonances of C(3″) and C(4″) are localized by selective

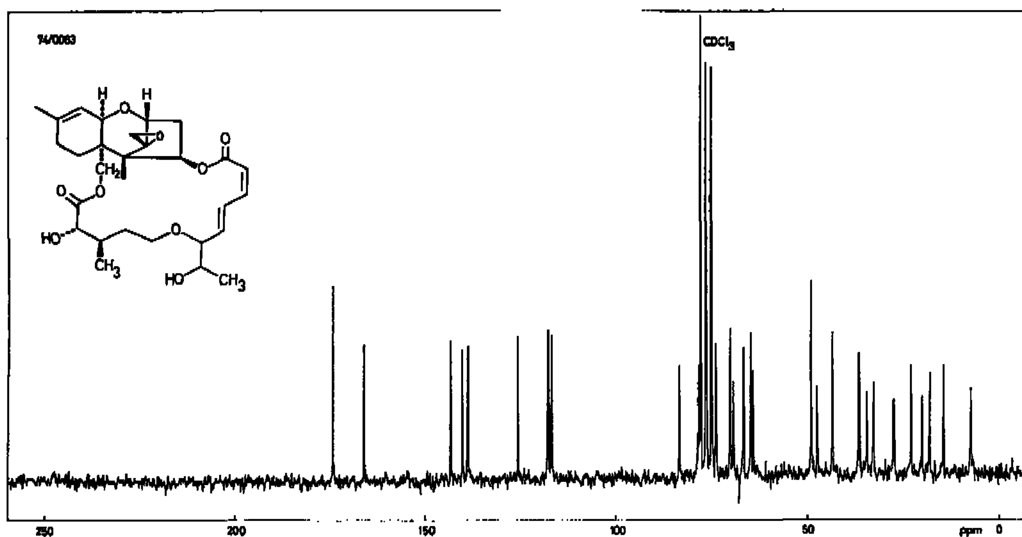


Fig. 1. *Proton noise decoupled ^{13}C-FT-spectrum of verrucarin A* (**1**) in $CDCl_3$ (550 mg in 2.5 ml); spectral width 5000 Hz; tipping angle 20°; pulse interval 6 s; 8400 pulses; 8k/4k data points

4) *Hanson et al.* [10] have proposed the opposite assignment of C(2) and C(11) in the case of trichodermol (**8**). We believe that our conclusions for verrucarol (**9**) are also valid for trichodermol (**8**) and possibly also for other trichothecanes.

proton decoupling. However, this method fails for the assignments of the doublets derived from C(2″) and C(5″). A comparison with analogous data of maleic acid, fumaric acid and other similar α,β-unsaturated systems [11] indicates that C(5″) is responsible for the doublet which appears at higher field. The signals of C(2′) to C(6′) are readily assigned for verrucarin A (**1**) as well as for verrucarin B (**4**) on the basis of the splitting patterns and the chemical shifts.

5. Assignments of the ^{13}C-NMR. Signals of Roridins A, D and H. – The localization of the carbonyl carbon atoms is deduced from the comparison of the spectra of roridin A (fig. 2), D and H. Selective proton decoupling allows the assignment of the signals of C(7′) to C(10′) (see Table 3) [5]). The triplet which is present in all these metabolites in the region of the non-hetero bonded carbon atoms is undoubtedly due to C(4′). The doublet resonance in the spectrum of roridin A (**2**) at 36.7 ppm has to be assigned to C(3′) because it is present neither in roridin D (**5**) nor in roridin H (**6**). The unambiguous distinction of the two quartets between 14 and 19 ppm was not possible. In the case of roridin A (**2**) the assignment relies mainly on comparison with the corresponding signals of roridin D (**5**). Acetylation of roridin A (**2**) yields the di-O-acetyl derivative **3**, and shifts only the doublet at 83.7 ppm of the three doublets between 70 and 84 ppm to higher field. Hence C(6′) is responsible for this signal. From the comparison with the spectrum of roridin D (**5**) it is concluded that the doublets at 70.4 and 70.5 ppm respectively, originate from C(13′). In analogy to verrucarin B (**4**) the doublet resonance of roridin D (**5**) at 57.9 ppm is assigned to C(2′). The assignment of all remaining signals of roridin A (**2**), roridin D (**5**) and roridin H (**6**) is deduced from the splitting patterns and the chemical shifts.

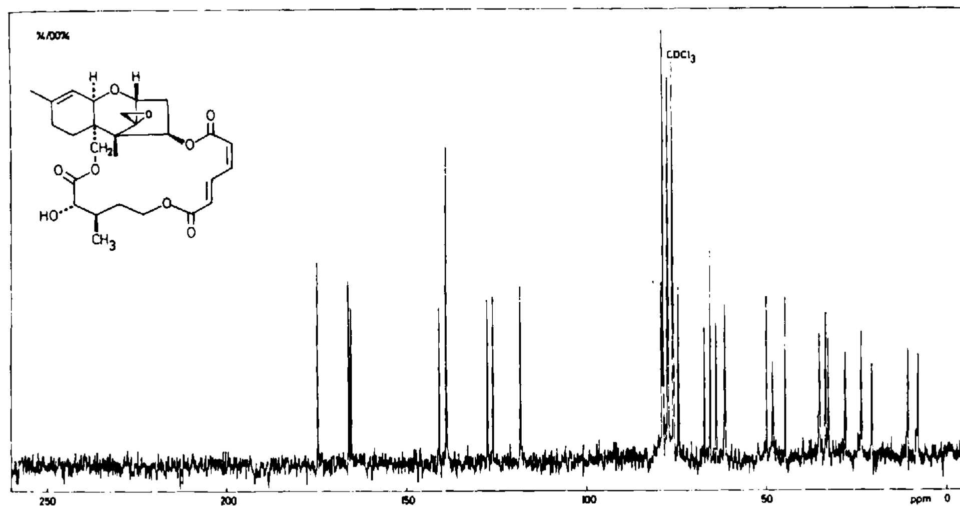


Fig. 2. *Proton noise decoupled ^{13}C-FT-spectrum of roridin A* (**2**) in $CDCl_3$ (500 mg in 2.7 ml); spectral width 5000 Hz; tipping angle 25°; pulse interval 6 s; 12600 pulses; 8k/4k data points

[5]) Similar α,β,γ,δ-unsaturated systems were recently assigned in the ^{13}C-NMR. spectra of the ansamycin antibiotics rifamycin [12], streptovaricin [13] and geldanamycin [14].

Table 3. *Assignments of the C-Atoms in the* ^{13}*C-NMR. Spectra of Verrucarin A and B, Roridin A, D and H*[3])

	Verr. A (**1**)	Verr. B (**4**)		Ror. A (**2**)	Acetyl-ror. A (**3**)	Ror. D (**5**)	Ror. H (**6**)
C(2)	78.6 *d*	78.7 *d*		78.8 *d*	78.8 *d* [b])	78.8 *d*	79.0 *d*
C(3)	34.6 *t*	34.8 *t*		34.6 *t*	34.6 *t*	34.9 *t*	34.8 *t*
C(4)	75.3 *d*	75.4 *d*		74.2 *d*	74.3 *d*	74.3 *d*	74.0 *d*
C(5)	49.2 *s*	49.0 *s*		49.1 *s*	49.1 *s*	49.0 *s*	48.9 *s*
C(6)	43.9 *s*	43.6 *s*		43.6 *s*	43.7 *s*	43.1 *s*	43.2 *s*
C(7)	19.7 *t*	19.8 *t*		20.0 *t*	20.7 *t*	20.4 *t*	20.5 *t*
C(8)	27.2 *t*	27.4 *t*		27.5 *t*	27.2 *t*	27.4 *t*	27.6 *t*
C(9)	140.7 *s*	140.4 *s*		140.4 *s*	140.7 *s*	140.1 *s*	139.9 *s*
C(10)	117.7 *d*	118.0 *d*		118.2 *d*	117.9 *d* [c])	118.4 *d* [c])	118.6 *d* [c])
C(11)	66.6 *d*	66.9 *d*		66.9 *d*	67.0 *d*	66.9 *d*	67.6 *d*
C(12)	64.9 *s*	64.9 *s*		64.9 *s*	64.9 *s*	65.1 *s*	65.3 *s*
C(13)	47.4 *t*	47.5 *t*		47.4 *t*	47.4 *t*	47.4 *t*	47.3 *t*
C(14)	7.0 *q*	7.3 *q*		7.2 *q*	6.9 *q*	6.8 *q*	7.0 *q*
C(15)	63.1 *t*	63.6 *t*		64.2 *t*	63.3 *t*	64.3 *t*	63.0 *t*
C(16)	22.9 *q*	22.8 *q*		22.9 *q*	22.9 *q*	22.9 *q*	22.9 *q*
C(1′)	174.3 *s*	167.4 *s*		174.5 *s*	[f])	167.8 *s*	166.0 *s*
C(2′)	73.8 *d*	58.0 *d*		75.3 *d*	76.6 *d*	57.9 *d*	119.0 *d* [c])
C(3′)	32.9 *d*	61.1 *s*		36.7 *d*	32.9 *d*	62.9 *s*	154.4 *s*
C(4′)	31.9 *t*	36.9 *t*		33.0 *t*	33.7 *t*	39.4 *t*	47.7 *t*
C(5′)	60.8 *t*	60.4 *t*		69.5 *t*	68.2 *t*	67.3 *t*	100.8 *d*
C(6′)	9.8 *q*	15.8 *q*		83.7 *d*	79.1 *d* [b])	85.3 *d*	81.9 *d* [e])
C(1″)	165.8 *s* [b])	165.8 *s* [b])	C(7′)	139 0 *d*	137.6 *d*	138.1 *d*	134.6 *d*
C(2″)	127.2 *d* [a])	127.2 *d* [a])	C(8′)	126.0 *d*	126.9 *d*	126.2 *d*	126.2 *d*
C(3″)	138.6 *d*	138.0 *d*	C(9′)	143.6 *d*	142.8 *d*	142.9 *d*	142.5 *d*
C(4″)	138.6 *d*	138.0 *d*	C(10′)	117.2 *d*	117.6 *d* [c])	117.8 *d* [c])	118.9 *d* [c])
C(5″)	125.5 *d* [a])	125.6 *d* [a])	C(11′)	166.3 *s*	166.3 *s*	166.1 *s*	166.0 *s*
C(6″)	165.1 *s* [b])	164.9 *s* [b])	C(12′)	14.4 *q*	14.6 *q* [d])	17.2 *q* [d])	18.2 *q* [d])
			C(13′)	70.4 *d*	70.5 *d*	70.5 *d*	76.8 *d* [e])
			C(14′)	18.0 *q*	14.1 *q* [d])	17.9 *q* [d])	16.3 *q* [d])
			CH_3(Ac)		20.1 *q*		

[a]) [b]) [c]) [d]) [e]) These assignments could be reversed.
[f]) C(1′) and two acetate carbonyls between 168.9 ppm and 170.3 ppm.

The support of these investigations by the *Schweizerischer Nationalfonds zur Förderung der wissenschaftlichen Forschung* (Project No. 2.0550.73) and by *Sandoz A.G.*, Basel, is gratefully acknowledged.

Experimental Part

1. General Methods. – The melting points were determined on a *Kofler*-block and are corrected. Elemental analyses were carried out in the micro-analytical laboratories of the Institute (*E. Thommen*). The infrared (IR.) spectra were recorded with a *Perkin-Elmer* Model 125 IR. grating spectrophotometer in the spectral laboratories of the Institute (*K. Aegerter*).

The 100 MHz ^{1}H-NMR. spectra were determined by *E. Wullschleger* and *R. Wiessler* in the Physikalisch-Chemisches Institut der Universität Basel on a *Varian* HA-100D spectrometer. The spectral laboratory of our Institute (*K. Aegerter*) recorded the 60 MHz ^{1}H-NMR. spectra on a *Varian* A-60, and the 90 MHz ^{1}H-NMR. spectra on a *Bruker* WH-90 instrument. The 22,63 MHz ^{13}C-NMR. spectra were recorded with a *Bruker* FT spectrometer, equipped with a 10 mm probe. Abbreviations used are: *s* = singlet; *d* = doublet; $d \times d$ = double doublet, *t* = triplet; *q* = quartet.

The mass spectrum (MS.) was measured by *A. Raas* in the Physikalisch-Chemisches Institut der Universität Basel on an *AEI*-MS 30 instrument. The optical rotations were measured with a *Perkin-Elmer* Model 141 polarimeter. For column chromatography, silica gel 0.05–0.2 mm from *E. Merck* A.G., Darmstadt, was employed. Preparative thin-layer chromatography (TLC.) was carried out on silica gel PF 254 (*Merck*), and ordinary TLC. was carried out on silica gel G (*Merck*). Usual work-up means: extraction with the solvent stated, washing with 2N HCl, 2N $NaHCO_3$ and water; drying with Na_2SO_4.

2. Synthesis of hydroxy-aldehyde 13. – 2.1. *4-O-Acetyl-verrucarol* (**11**). Acetylchloride was added in three 0.01 ml portions at intervals of 2 h to a cooled solution of 106 mg verrucarol (**9**) in 0.8 ml of abs. pyridine. The mixture was kept at 25° for 24 h, poured onto ice and extracted with methylene chloride. After usual work up, the combined organic extracts were evaporated to give 120 mg crude product. Preparative TLC. with methylene chloride/methanol 95:5 yielded, after crystallization from ether/petrol ether, pure **11** of m.p. 138–140°. $[\alpha]_D^{23} = +7° \pm 1°$ ($c = 0.97$, chloroform). – IR. (methylene chloride): bands at 3620, 3500, 1720 (C=O, broad), 1680 (C=C, weak), 1370, 1222, 1085 cm^{-1}. – NMR. (60 MHz, $CDCl_3$): *cf.* table 1.

2.2. *Aldehyde* **12**. A solution of 1.21 g **11** in 200 ml of acetone was treated with 3 ml of CrO_3/H_2SO_4 solution[6]) at 25° for 5 min. After addition of 50 ml of H_2O, the acetone was removed *in vacuo*. Usual work up with methylene chloride yielded after crystallization from ether 550 mg of pure **12** of m.p. 124–126°. $[\alpha]_D^{23} = -80° \pm 2°$ ($c = 1.22$, chloroform). – IR. (KBr): bands at 1732, 1708, 1672 (C=C, weak), 1238, 1078, 960 cm^{-1}. – NMR. (90 MHz, $CDCl_3$): *cf.* table 1.

$C_{17}H_{22}O_5$ (306.4) Calc. C 66.65 H 7.24% Found C 66.50 H 7.16%

2.3. *Hydroxy-aldehyde* **13**. – A solution of 520 mg of **12** in 40 ml of methanol was stirred with a solution of 1.5 g K_2CO_3 in 5 ml of H_2O at 25° for 14 h. After dilution with 30 ml of H_2O and usual work up with methylene chloride, a colourless oil was obtained. The crude product was chromatographed on silica gel with methylene chloride/methanol. Crystallization from acetone/ether/petrol ether yielded 380 mg **13** of m.p. 135–137°. $[\alpha]_D^{24} = -112° \pm 2°$ ($c = 1.53$, chloroform). – IR. (KBr): bands at 3460, 1710 (C=O), 1672 (C=C, weak), 962 cm^{-1}. – NMR. (100 MHz, $CDCl_3$): *cf.* table 1.

$C_{15}H_{20}O_4$ (264,3) Calc. C 68.16 H 7.63% Found C 67.95 H 7.65%

3. Synthesis of keto-ether 16. – 3.1. *Hydroxy-ether* **14**. A solution of 1.53 g **11** and 3.02 g *m*-chloroperbenzoic acid in 90 ml of chloroform was stirred at 50° for 30 h. After usual work up, the organic phase was evaporated to produce a colourless oil. Chromatography on silica gel with methylene chloride/methanol and crystallization from acetone yielded 700 mg pure **14** of m.p. 168–170°. $[\alpha]_D^{23} = -46° \pm 2°$ ($c = 1.02$, chloroform). – IR. (methylene chloride): bands at 3550 (OH), 1735 (C=O), 1232, 968 cm^{-1}. – NMR. (90 MHz, $CDCl_3$): *cf.* table 1.

$C_{17}H_{24}O_6$ (324.4) Calc. C 62.95 H 7.46% Found C 63.21 H 7.53%

3.2. *Keto-ether* **15**. A solution of 650 mg **14** in 100 ml acetone was treated with 1.5 ml of CrO_3/H_2SO_4 solution[6]) at 25° for 8 min. After addition of 50 ml of H_2O, the acetone was removed *in vacuo*. Usual work up with methylene chloride and crystallization from acetone yielded 350 mg **15** of m.p. 249–251°. $[\alpha]_D^{23} = -12° \pm 2°$ ($c = 1.28$, chloroform). – IR. (methylene chloride): bands at 1750, 1735, 1080, 968 cm^{-1}. – NMR. (100 MHz, $CDCl_3$): signals at 5.65 ($d \times d$, 1 H, C(4), $J_1 = 8$ Hz, $J_2 = 4$ Hz); 2.92 (*AB*, 2 H, C(13), $J_{gem} = 4$ Hz); 2.08 (*s*, 3 H, CH_3CO); 1.23 (*s*, 3 H, C(16)); 0.69 (*s*, 3 H, C(14)) ppm.

$C_{17}H_{22}O_6$ (322.4) Calc. C 63.34 H 6.88% Found C 63.28 H 7.01%

[6]) 2.67 g CrO_3, 2.3 ml conc. H_2SO_4 and H_2O *ad* 10 ml.

3.3. *Hydroxy-keto-ether* **16**. A solution of 340 mg of **15** in 30 ml of acetone/methanol 1:1 was stirred with a solution of 1.5 g of K_2CO_3 in 5 ml of H_2O at 25° for 4 h. After dilution with 20 ml of H_2O and usual work up with methylene chloride, 290 mg of a colourless product was obtained. Crystallization from methylene chloride/ether yielded 250 mg pure **16** of m.p. 234–236°. $[\alpha]_D^{28}$ = – 14° ± 2° (*c* = 0.71, chloroform). – IR. (methylene chloride): bands at 3580, 1750 (C=O), 1075, 962 cm^{-1}. – NMR. (90 MHz, $CDCl_3$): *cf.* table 1. – MS.: M^+ at *m/e* 280.

$C_{15}H_{20}O_5$ (280.3) Calc. C 64.27 H 7.19% Found C 63.98 H 7.27%

REFERENCES

[1] 32nd. Commun.: *W. Knöll & Ch. Tamm*, Helv. *58*, 1162 (1975).
[2] *cf. U. Séquin & A. I. Scott*, Science *186*, 101 (1974).
[3] *cf. Ch. Tamm*, Progr. in the Chemistry of Org. Nat. Prod. *31*, 63 (1974).
[4] *D. Arigoni, D. E. Cane, B. Müller & Ch. Tamm*, Helv. *56*, 2946 (1973); *R. Achini, B. Müller & Ch. Tamm*, ibid. *57*, 1442 (1974); *B. Müller, R. Achini & Ch. Tamm*, ibid. *58*, 453, 471 (1975); *B. Müller & Ch. Tamm*, ibid. *58*, 483 (1975).
[5] *E. Härri, W. Loeffler, H. P. Sigg, H. Staehelin, Ch. Stoll & Ch. Tamm*, Helv. *45*, 839 (1962); *B. Böhner, E. Fetz, E. Härri, H. P. Sigg, Ch. Stoll & Ch. Tamm*, ibid. *48*, 1079 (1965).
[6] *B. Böhner & Ch. Tamm*, Helv. *49*, 2527 (1966).
[7] *J. Gutzwiller & Ch. Tamm*, Helv. *48*, 157 (1965).
[8] *J. Gutzwiller, R. Mauli, H. P. Sigg & Ch. Tamm*, Helv. *47*, 2234 (1964).
[9] *W. Zürcher, J. Gutzwiller & Ch. Tamm*, Helv. *48*, 840 (1965).
[10] *J. R. Hanson, T. Marten & M. Siverns*, J. chem. Soc. Perkin I, *1974*, 1033.
[11] *J. B. Stothers*, 'Carbon-13 NMR.-Spectroscopy', Academic Press, New York 1972, p. 186.
[12] *H. Fuhrer*, Helv. *56*, 2377 (1973); *E. Martinelli, R. J. White & G. G. Gallo*, Tetrahedron Letters *1974*, 1367.
[13] *B. Milavetz, K. Kakinuma, K. L. Rinehart, Jr., J. P. Rolls & W. J. Haak*, J. Amer. chem. Soc. *95*, 5793 (1973).
[14] *R. D. Johnson, A. Haber & K. L. Rinehart Jr.*, J. Amer. chem. Soc. *96*, 3316 (1974).

---

124. Die *Diels-Alder* Reaktion von Furan und 2-Methylfuran mit Acrylnitril

von **Frank Kienzle**

Chemische Forschungsabteilung der F. Hoffmann-La Roche & Co. AG, Basel

(24. IV. 75)

Summary. Diels-Alder reaction between furan or 2-methylfuran and acrylonitrile furnished the expected adducts in good yields. The ratio of the various products was determined.

Mit besonders aktivierten Dienophilen wie Maleinsäureanhydrid und Acetylendicarboxylaten [1] geben Furan und seine Derivate leicht *Diels-Alder*-Addukte. Mit weniger reaktiven Dienophilen wie Acrolein, Methylvinylketon oder Nitroäthylen ist der bevorzugte Reaktionsweg jedoch eine Addition-Substitution [1], wenn das Furan selbst nicht durch geeignete Substituenten aktiviert wird. So gibt Acrylnitril mit 3,4-Dimethoxyfuran leicht ein *Diels-Alder*-Addukt [2]; mit Furan und Methylfuran hingegen war eine solche Reaktion lange unbekannt [3]. Kürzlich wurde nun berichtet, dass sowohl von Furan, wie auch von 2-Methylfuran nach einmonatigem Kochen unter Rückfluss mit Acrylnitril *Diels-Alder*-Addukte erhältlich sind [4]. Im Falle des