Tetrahedron Letters No. 12, pp 1081 - 1084, 1978. Pergamon Press. Printed in Great Britain.

REVISION OF THE STRUCTURES OF THE NATURALLY OCCURRING ACYL TETRONIC ACIDS: DEHYDROCAROLIC ACID, TERRESTRIC ACID AND CARLIC ACID.

J.P. Jacobsen[a], T. Reffstrup[a], R.E. Cox[b], J.S.E. Holker[b] and P.M. Boll[a*]

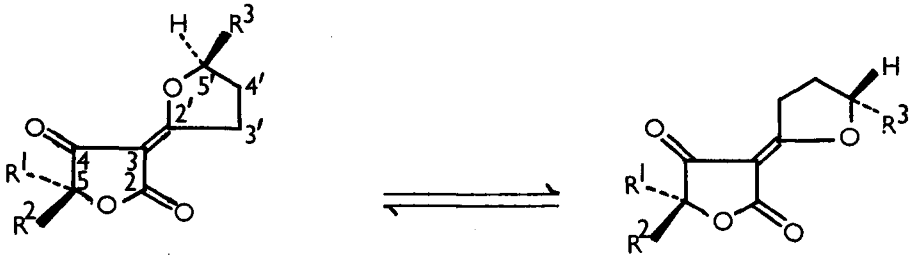
[a]Department of Chemistry, Odense University, DK 5230 Odense M, Denmark
and [b]Department of Organic Chemistry, The Robert Robinson Laboratories,
University of Liverpool, Liverpool L69 3BX, England.

(Received in UK 18 January 1978; accepted for publication 30 January 1978)

It has recently been shown (1) that carolic acid, a metabolite of Penicillium charlesii (2), exists in deuteriochloroform solution as a 4:5 mixture of the (E)- and (Z)-isomers of 5-methyl-3-(2'-tetrahydrofurylidene)tetrahydrofuran-2,4-dione (1). This conclusion was based on ^{13}C-nmr spectral measurements of both unenriched and enriched carolic acid derived by incorporation of [1-]-, [2-]-, and [1,2-^{13}C]-acetate respectively. These spectra showed two closely similar signals for each carbon atom, except C-6 and C-4', with chemical shift values which were incompatible with the earlier proposed structure (9) (3). In aqueous solution the non-lactonic ring in carolic acid is opened to give the α-acyltetronic acid structure (5).

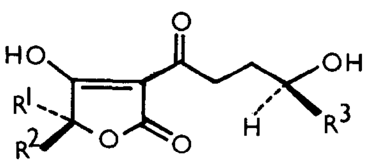
It has now been shown that when carolic acid is crystallised from ethanol and dissolved in the dark in pure acetonitrile-d_3 there is only one isomer present. Comparison of the ^{13}C-chemical shifts of this with those of methyl (E)- and (Z)-3-methoxyacrylate (4) suggest that it is the (E)-form of (1). In the presence of traces of acid, or under the influence of light, equilibration with the (Z)-isomer occurs, although the position of the equilibrium appears to be solvent dependent. The ^{13}C-chemical shifts for the pure (E)-isomer permit unambiguous assignments for the individual isomers in deuteriochloroform (cf. Table) These contrast with the earlier tentative assignments (1) which were based on relative signal intensitities in the spectrum of the mixture.

The ^{13}C-nmr spectra of the related α-acyltetronic acids: dehydrocarolic acid (**6**) from *P. cinerascens* (5), terestric acid (**7**) from *P. terrestre* (6) and carlic acid (**8**) from *P. charlesii* (2) show close parallels with that of carolic acid (*cf.* Table). In the cases of dehydrocarolic and terrestric acids in deuteriochloroform it is clear that they exist as mixtures of (*E*)- and (*Z*)-5-methylene-3-(2'-tetrahydrofurylidene)- (**2**) and 5-methyl-3-[2'-(5'-ethyltetrahydrofurylidene)]tetrahydrofuran-2,4-dione (**3**) respectively. Due to the low solubility of carlic acid in chloroform its ^{13}C-nmr spectrum was measured in methanol-$\underline{d}_4$ and the chemical shifts compared with those of carolic acid in the same solvent (*cf.* Table). The parallel again emerges and carlic acid in methanol is thus a mixture of (*E*)- and (*Z*)-5-carboxymethyl-3-(2'-tetrahydrofurylidene)tetrahydrofuran-2,4-dione (**4**). It is now clear that the original structures, (**10**) for dehydrocarolic acid, (**11**) for terrestric acid and (**12**), or other alternatives (7) for carlic acid, are no longer tenable.

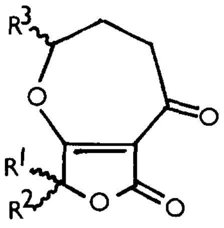


(*E*) (*Z*)

(**1**, **2**, **3**, **4**)



(**5**, **6**, **7**, **8**)



(**9**, **10**, **11**, **12**)

(**1**,**5**,**9**; $R^1 = \overset{6}{C}H_3$, $R^2 = R^3 = H$. **2**, **6**,**10**; $R^1 = R^2 = \overset{6}{C}H_2$, $R^3 = H$.
3,**7**,**11**; $R^1 = \overset{6}{C}H_3$, $R^2 = H$, $R^3 = \overset{6}{C}H_2\overset{7}{C}H_3$. **4**,**8**,**12**; $R^1 = R^3 = H$, $R^2 = \overset{6}{C}H_2.\overset{7}{C}O_2H$)

The absolute configurations of C-5 in terrestric and carlic acids have been shown to be (*R*)- and (*S*)- respectively (8,9). The recent synthesis (10) of (*S*)-(-)-4-hexanolide establishes that C-5' in terrestric acid has the (*S*)-configuration since acid hydrolysis gives (-)-4-hexanolide (from C-2' to C-7') in addition to acetoin (from C-3 to C-6) and carbon dioxide (from C-2) (6).

Acknowledgements. The authors are indebted to Dr. C.W. Hesseltine, U.S. Department of Agriculture, Agricultural Research Service, Peoria, Illinois for supplying the *P. charlesii* culture, to Professor Sir D.H.R. Barton, Imperial College, London, who kindly supplied from the Raistrick collection a sample of authentic terrestric acid, and to Dr. T.F.W. McKillop, I.C.I. Ltd., Pharmaceuticals Division, Macclesfield, who generously supplied a sample of dehydrocarolic acid.

References.

1. J.P. Jacobsen, T. Reffstrup and P.M. Boll, *Acta Chem. Scand.*, *B 31*, 505(1977).
2. P.W.Clutterbuck, W.N. Haworth, H. Raistrick, G. Smith and M. Stacey, *Biochem. J.*, *28*, 94 (1934).
3. P.W. Clutterbuck, H. Raistrick and F. Reuter, *Biochem. J.*, *29*, 300 (1936).
4. H. Brouwer and J.B. Stothers, *Canad. J. Chem.*, *50*, 601 (1972).
5. A. Bracken and H. Raistrick, *Biochem. J.*, *41*, 569 (1947).
6. J.H. Birkinshaw and H. Raistrick, *Biochem. J.*, *30*, 2194(1936).
7. F.M. Dean, *Naturally Occurring Oxygen Ring Compounds*, Butterworths, London, 1963, *p*. 74.
8. P.M. Boll, E. Sørensen and E. Balieu, *Acta Chem. Scand.*, *22*, 3251 (1968).
9. J.L. Bloomer and F.E. Kappler, *J. Chem. Soc. Perkin* I, 1485 (1976).
10. U. Ravid and R.M. Silverstein, *Tetrahedron Letters*, 423 (1977).

Table. ^{13}C NMR Chemical Shifts, δ_i(ppm)[a] of Naturally Occurring Tetronic Acid Derivatives.

Compound	Carolic acid[b] (1)		Dehydrocarolic acid[b] (2)		Terrestric acid[c] (3)		Carolic acid[b] (1)		Carlic acid[b] (4)	
Geometry	Z	E	Z	E	Z	E	Z	E	Z	E
C-2	167.24	170.29	163.54	166.85	166.94	170.33	169.90	172.70	169.97	172.63
C-3	95.05	95.64	95.38	96.09	94.28	94.77	95.38	95.90	96.42	97.00
C-4	199.01	195.70	183.15	179.91	198.82	195.13	200.44	197.65	198.82	196.15
C-5	79.66	79.27	152.30	151.91	79.26	79.03	81.02	80.50	80.50	80.11
C-6	17.02	17.02	93.17	92.84	17.03	17.03	17.15	17.15	36.32	36.32
C-7									172.63	172.63
C-2'	187.31	186.61	188.23	187.13	187.14	186.40	191.21	190.76	190.43	189.53
C-3'	33.27	33.46	33.79	33.79	33.63	33.86	34.76	34.90	34.50	34.76
C-4'	21.76	21.70	21.77	21.77	27.64	27.64	22.48	22.48	22.42	22.42
C-5'	77.51	78.03	77.97	78.49	93.03	92.50	79.46	79.98	79.33	79.85
C-6'					26.41	26.41				
C-7'					9.46	9.46				
Solvent	deuteriochloroform						methanol-d_4			

A [a] Uncertainty: ± 0.07 ppm. [b] Recorded on a Jeol FX60 spectrometer. [c] Recorded on a Varian XL-100-15FT spectrometer.