Tetrahedron Letters No.60, pp. 5247-5250, 1970. Pergamon Press. Printed in Great Britain.

THEAFLAVIC AND EPITHEAFLAVIC ACIDS

D. T. Coxon, A. Holmes, and W. D. Ollis*

Department of Chemistry, The University, Sheffield S3 7HF

(Received in UK 7 October 1970; accepted for publication 25 November 1970)

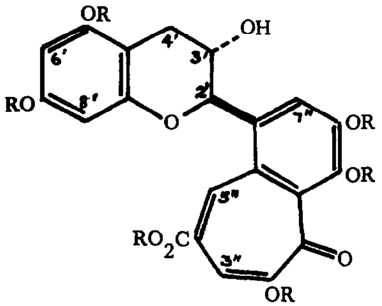
During the early phases of Roberts' investigations of the extractives of black tea, he recognised a number of substances by their paper chromatographic behaviour and labelled these fractions A, B, C, P, Q, R, S, X, Y, and Z.[1] Subsequently some of these substances have been identified as bisflavanols (A and B),[2] the anthocyanidin tricetinidin (P),[1] the thearubigins (S),[1,3] and the theaflavins (X and Y).[1,4,5,6,7] Roberts has suggested that substance Q[1,8] is a mixture possibly containing coupled oxidation products derived from natural flavan-3-ols [for example, (-)-epicatechin, (+)-catechin, (-)-epigallocatechin, (+)-gallocatechin and their gallates] and gallic acid. In connection with this suggestion[1,8] and our current interest[5,7] in the theaflavin fraction of black tea, we have examined the coupled oxidation products obtained from (+)-catechin and (-)-epicatechin with gallic acid. The results are also relevant to our investigations[9] of the constitution and configuration of theaflavin and isotheaflavin.

Oxidation by potassium ferricyanide of (+)-catechin and gallic acid in aqueous sodium bicarbonate solution at 0° yielded theaflavic acid (I), m.p. ~215° (decomp.) from ethyl acetate (lit.[10] 234 - 235.5° from acetic acid). Epitheaflavic acid (III), m.p. 232-235° (decomp.) from ethyl acetate was similarly obtained from (-)-epicatechin and gallic acid.

The molecular formulae of theaflavic and epitheaflavic acid were both established by high resolution mass spectrometry (Found: M, 428.0746. $C_{21}H_{16}O_{10}$ requires M, 428.0743). Methylation of theaflavic acid (I) with dimethyl sulphate and potassium carbonate in acetone gave the corresponding pentamethyl ether methyl ester (II), pale yellow needles, m.p. 101-103° (lit.[10] 104-105°) from aqueous methanol. Epitheaflavic acid (III) similarly yielded the derivative (IV), pale yellow needles, m.p. 132-135° from aqueous methanol.

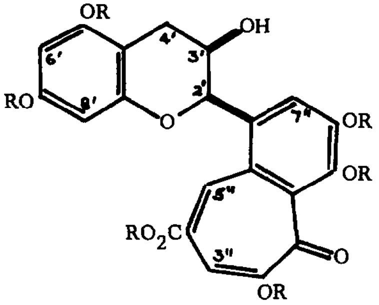
---

* To whom all correspondence should be addressed.



Theaflavic acid (I)* R = H

(II) R = Me



Epitheaflavic acid (III)* R = H

(IV) R = Me

TABLE 1. Absorption spectra λ_{max} (ε_{max}) in ethanol

(I)	208 (59,100)	280 (27,800)	404 (12,400)
(III)	208 (54,500)	280 (23,600)	400 (11,000)
(II)	207 (68,300)	273 (15,700)	346 (12,850)
(IV)	207 (72,000)	275 (16,850)	347 (13,050)

The constitutional and configurational formula proposed for theaflavic acid (I) and epitheaflavic acid (III) on the basis of their syntheses were supported by the following physical data. Their IR spectra (KBr disc) were very similar and showed carbonyl bands assignable to benztropolone (1630 cm^{-1}.) and carboxylic acid (1700 cm^{-1}.) groupings. Comparison of the absorption spectra (Table 1) with those in Table 1 of the preceding paper[9] showed a modification of the benztropolone chromophore by its direct bonding to the carboxyl group; the same effect is observed in the comparison of the absorption spectra of purpurogallin (λ_{max} 434 nm) and purpurogallin-6-carboxylic acid (λ_{max} 400 nm).[11] The compounds (I), (II), (III), and (IV) showed a fascinating internal consistency between their mass spectra and a satisfying correspondence with the mass spectra of derivatives of theaflavin[5,7] and isotheaflavin.[9]

Comparison of the NMR spectra (Table 2) for theaflavic acid and epitheaflavic acid with those given

---

* The numbering of the positions in these formulae and in Table 2 does not follow systematic nomenclature, but it has been chosen to facilitate comparison with theaflavin and isotheaflavin.[9]

TABLE 2. NMR Spectra (100 MHz.) of theaflavic acid, epitheaflavic acid, and their pentamethyl ether methyl esters

	2'	3'	4'	4*'	6', 8'	3''	5''	7''	Tropolone OH	Methoxyl groups
(I)	4.52 d $J_{2',3'} = 8$	5.70 m	6.90 dd $J_{3',4'} = 6$ $J_{4',4*'} = 16$	7.31 dd $J_{3',4*'} = 9$ $J_{4',4*'} = 16$	3.91d 4.05d $J_{6',8'} = 2.5$	2.15 d $J_{3'',5''} \sim 1$	0.85 d $J_{3'',5''} \sim 1$	2.21 s	-4.91 s	-
(II)	4.64 d $J_{2',3'} = 8$	5.82 m	6.98 dd $J_{3',4'} = 5.5$ $J_{4',4*'} = 16$	7.32 dd $J_{3',4*'} = 8$ $J_{4',4*'} = 16$	3.88 s (two H)	3.42 s	1.66 s	2.63 s	-	6.06, 6.12, 6.20, 6.20, 6.20, 6.25 All s
(III)	4.30 s	5.52 m	6.99 "t"		3.94 s (two H)	2.16 d $J_{3'',5''} \sim 1$	1.27 d $J_{3'',5''} \sim 1$	1.95 s	-4.70 s	-
(IV)	4.49 s	5.67 m	7.01 "d"		3.80d 3.87d $J_{6',8'} = 2.5$	3.40 s	1.95 s	2.30 s	-	6.01, 6.06, 6.16, 6.18, 6.21, 6.24 All s

For general notes refer to footnotes of Table 2 of preceding paper.[9]

Solvents: (I) and (III), CD_3COCD_3; (II) and (IV), $CDCl_3$.

in the preceding paper[9] (Tables 2 and 3) clearly shows that theaflavic acid (I) has, as expected, the 2', 3'-trans-configuration and epitheaflavic acid (III) has the 2', 3'-cis-configuration. Epitheaflavic acid (III) is apparently identical with the compound described as TF4,[6] but we do not understand the basis for the coupling constants assigned to the two 4'-protons of TF4.[6]

Dr. Sanderson has kindly informed us that our samples of theaflavic acid (I) and epitheaflavic acid (III) prepared by ferricyanide oxidative coupling are identical with his samples of (I) and (III) prepared from the same precursors using soluble tea enzymes.[12]

REFERENCES

(1) E. A. H. Roberts, in The Chemistry of Flavonoid Compounds (edited by T. A. Geissman), pp. 488 and 498, Pergamon Press, Oxford (1962).

(2) A. Ferretti, V. P. Flanagan, H. A. Bondarovich, and M. A. Gianturco, J.Agr.Food Chem. **16**, 756 (1968).

(3) A. G. Brown, W. B. Eyton, A. Holmes, and W. D. Ollis, Nature **221**, 742 (1969); Phytochemistry **8**, 2333 (1969).

(4) Y. Takino, A. Ferretti, V. Flanagan, M. Gianturco, and M. Vogel, Tetrahedron Letters 4019 (1965).

(5) A. G. Brown, C. P. Falshaw, E. Haslam, A. Holmes, and W. D. Ollis, Tetrahedron Letters 1193 (1966).

(6) T. Bryce, P. D. Collier, I. Fowlis, P. E. Thomas, D. Frost, and C. K. Wilkins, Tetrahedron Letters 2789 (1970).

(7) D. T. Coxon, A. Holmes, W. D. Ollis, and V. C. Vora, Tetrahedron Letters (1970).

(8) E. A. H. Roberts and M. Myers, J.Sci.Food Agr. **10**, 167 (1959); **11**, 158 (1960).

(9) D. T. Coxon, A. Holmes, and W. D. Ollis, Tetrahedron Letters (1970).

(10) H. Horikawa, Tokyo Kasei Daigaku Kenkyu Kiyo (9), 1 (1969); Chem.Abs. **72**, 80320 (1970).

(11) W. D. Crow and R. D. Haworth, J.Chem.Soc. 1325 (1951); E. A. H. Roberts and D. M. Williams, J.Sci.Food Agr. **9**, 217 (1958).

(12) G. W. Sanderson, personal communication.