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AN UNUSUAL REACTION OF FLAVAN–3–OLS WITH ACETONE OF RELEVANCE TO THE FORMATION OF THE TETRACYCLIC RING SYSTEM IN PELTOGYNOIDS

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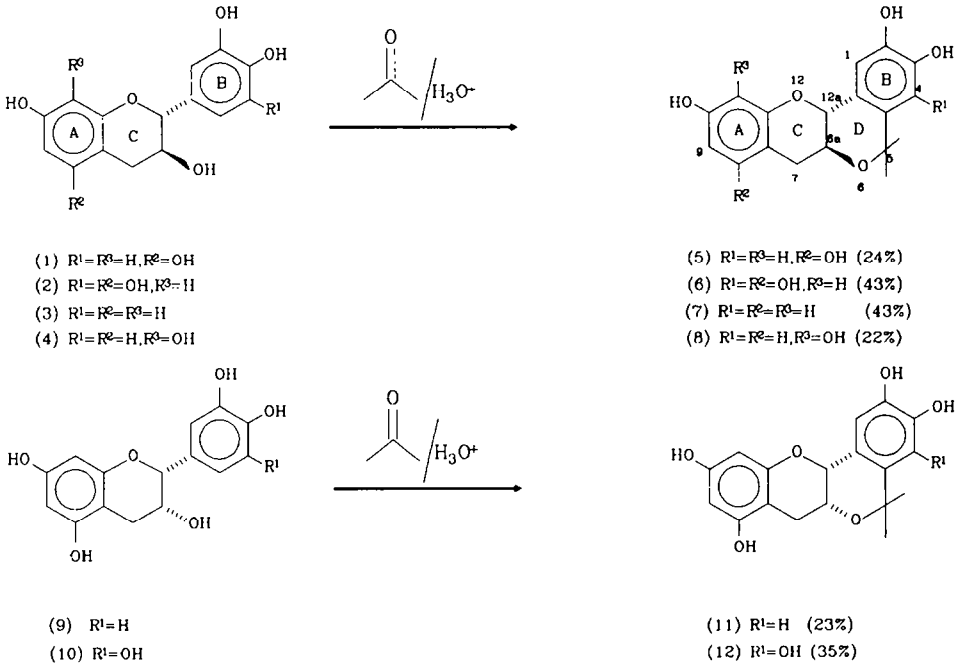
Abstract —— Flavan–3–ols are in moist acetone subject to acid-catalyzed incorporation of an 1–methylethylidene fragment between 3–OH and C–2 (B-ring) to give a tetracyclic ring system reminiscent of the peltogynoid series of flavonoids.

Tetrabromomethane (CBr_4) serves as a source of bromine radicals under extremely mild conditions[1,2]. Our programme of converting the C-4-benzylic methylene group of readily available flavan-3-ols into an electrophilic centre for utilization in the semi-synthetic approach[3] towards condensed tannins thus prompted assessment of the potential of CBr_4 for introducing functionality *via* bromination of the flavan-3-ols in their free phenolic form. Treatment of the flavan-3-ols with CBr_4 in moist acetone under photolytic conditions, however, did not lead to bromination but instead resulted in the incorporation of the carbon framework of acetone with concomitant formation of a tetracyclic ring system reminiscent of the peltogynoid series[4,5] of naturally occurring flavonoids.

Irradiation of a solution of (+)-catechin 1 [(2*R*,3*S*)-2,3-*trans*-flavan-3,3',4',5,7-pentaol] and CBr_4 (1:1 molar ratio) in moist acetone at 354 nm for 6 h under nitrogen and subsequent chromatography on silica afforded unreacted starting material 1 (*ca.* 15%), the dimethyltetracyclic compound 5 (*ca.* 25%), and a considerable proportion (*ca.* 60%) of products with high polarity (*vide infra*). Similar reactions were obtained for the flavan-3-ols, (+)-gallocatechin 2, (−)-fisetinidol 3, (+)-mesquitol 4, (−)-epicatechin 9, and (−)-epigallocatechin 10 in the yields indicated in scheme 1.

Comparison of the 300 MHz ^{1}H NMR spectra of (+)-catechin 1 and the tetracyclic compound 5 in $(CD_3)_2CO$ (Table) revealed replacement of the aromatic ABX spin system (B-ring) in 1 by two one-proton signals (δ6.65, s; δ7.07, d, J1.0 Hz) in 5 as well as the presence of two methyl resonances (δ1.45, 1.51) in the spectrum of the latter compound. In addition the spectra of both 1 and 5 exhibited very similar AMXY-systems for the heterocyclic proton resonances. When taken in conjunction with the formation of a tetra-acetate on acetylation and the observed molecular mass of 330 ($C_{18}H_{18}O_6$), the ^{1}H NMR features collectively indicated the incorporation of the carbon skeleton of acetone between 3–OH and C–2 (B-ring) of (+)-catechin 1 and hence structure 5 for the novel tetracyclic compound. Similar arguments were utilized to eluci-



(1) $R^1=R^3=H, R^2=OH$
(2) $R^1=R^2=OH, R^3=H$
(3) $R^1=R^2=R^3=H$
(4) $R^1=R^2=H, R^3=OH$

(5) $R^1=R^3=H, R^2=OH$ (24%)
(6) $R^1=R^2=OH, R^3=H$ (43%)
(7) $R^1=R^2=R^3=H$ (43%)
(8) $R^1=R^2=H, R^3=OH$ (22%)

(9) $R^1=H$
(10) $R^1=OH$

(11) $R^1=H$ (23%)
(12) $R^1=OH$ (35%)

Scheme 1 Acid catalyzed reaction of flavan-3-ols with moist acetone

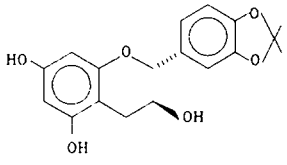
Table. ^1H NMR peaks (p.p.m.) of the dimethyltetracyclic compounds 5, 6, 7, 8, 11, and 12 in $(CD_3)_2CO$ (23°C) at 300 MHz. Splitting patterns and J–values (Hz) are given in parentheses.

Ring	Proton	5	6	7	8	11	12
A	8	-	-	6.93(br.d,8.5)	6.48(dd,1.0,8.5)	-	-
	9	6.05(d,2.5)	5.94(d,2.5)	6.41(dd,2.5,8.5)	6.43(d,8.5)	5.77(d,2.5)	5.76(d,2.5)
	11	5.97(d,2.5)	6.05(d,2.5)	6.39(d,2.5)	-	5.97(d,2.5)	5.97(d,2.5)
B	4	6.65(s)	-	6.65(s)	6.65(s)	6.81(s)	-
	1	7.07(d,1.0)	6.73(d,1.5)	7.08(d,1.0)	7.25(d,1.0)	6.69(d,1.0)	6.46(s)
C	12a	4.45(dd,1 0,9.5)	4.40(dd,1.5,9.5)	4.50(dd,1.0,9.5)	4.53(dd,1.0,9.5)	4.49(br.s)	4.41(br.s)
	6a	3.82(m)	3.79(m)	3.85(m)	3.89(m)	4.26(m)	4.23(m)
	7 ax.	2.49(dd,11.0,15.0)	2.41(dd,10.5,15.5)	2.73(dd,10.5,15.0)	2.76(dd,11.0,15.5)	2.77(dd,2.0,16.0)	2.76(dd,2.0,17,5)
	7 eq.	2.96(dd,6.0,15 0)	2.96(dd,6.0,15.5)	2.90(dd,6.0,15.0)	2.91(dd,6.0,15.5)	2.90(dd,5.5,15.0)	2.86(dd,5.0,17.0)
D	5-CH_3	1.45,1.51(each s)	1.65,1.63(each s)	1.45,1.51(each s)	1.45,1.51(each s)	1.37,1.46(each s)	1.55,1.60(each s)

date the structures of the remaining tetracyclic analogues 6, 7, 8, 11, and 12 (see the table for their ^{1}H NMR data).

The same reactions also occurred when the flavan-3-ols were simply treated with a solution of CBr_4 in acetone at ambient temperature. Reactions were, however, inhibited by addition of solid sodium bicarbonate under either of the two different sets of conditions. These results thus indicate a simple acid-catalyzed reaction of the respective flavan-3-ols with acetone, the hydrogen bromide presumably originating *via* the action of bromine radical with an active hydrogen of the solvent system. Separate treatment of a solution of the respective flavan-3-ols in acetone at ambient temperature with a variety of acids, *e.g.* sulphuric acid (98%), concentrated hydrobromic– and hydrochloric acid, and toluene-*p*-sulphonic acid all gave product distributions and yields similar to those described above.

The observed incorporation of the 1-methylethylidene fragment between 3-OH and C–2(B) in the flavan-3-ols contrasts with the more common formation of a dimethylacetal 13 at the *o*-dihydroxy functionality of the pyrocatechol B-ring of (+)-catechin 1 under anhydrous conditions[6]. Such a difference in the course of acid catalyzed reaction of acetone and the flavan-3-ols with pyrocatechol B-rings is presumably attributable to differences in the solvent systems. Under anhydrous conditions in the polar aprotic solvent the preference of a 'hard base' for a 'hard acid' will dictate attack of the phenolic hydroxy group at the protonated carbonyl carbon atom of acetone thus leading to formation of the dimethylacetal 13. Formation of



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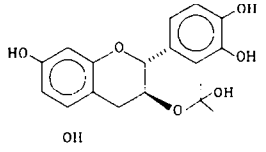

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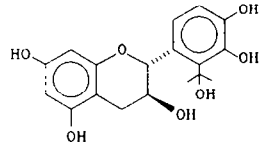

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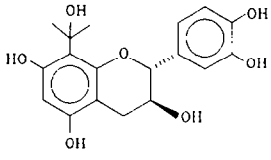

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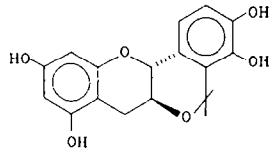

(17)

the tetracyclic compounds, *e.g.* 5, may occur *via* either of the intermediates 14 or 15. Under the conditions which we employed, the presence of water presumably leads to predominant C-alkylation[7,8] and hence to

the formation of the dimethylmethylol compound 15. This derivative could then serve as intermediate for the tetracyclic compound 5. Such a sequence closely parallels the course of the reactions usually employed for the synthesis[9–11] of the peltogenoids.

Initial electrophilic substitution of the dimethylmethylol group at the more nucleophilic positions of the A-rings in the flavan-3-ols may be anticipated to compete with substitution at C–2(B). Evidence for such a competition was found by regular monitoring of the reaction by ^{1}H NMR which indeed indicated the simultaneous disappearance of the A-ring protons of (+)-catechin 1 used in this experiment. Our method of work-up and purification *i.e.* removal of the excess of acetone by a nitrogen current followed by subjection of the mixture to PLC on silica, presumably resulted in acid catalyzed polimerization of A-ring substituted analogues of type 16 hence also explaining the considerable loss of material in the form of unidentified products with high polarity (*vide supra*).

Monitoring of the reaction of (+)-catechin 1 by ^{1}H NMR could not differentiate between the intermediates 14 and 15 since the full set of signals of the tetracyclic compound 5 was evident after 30 min. This nonetheless indicated a rapid second step involving protonation/cyclization of either of the intermediates 14 or 15. Although the available evidence does not permit differentiation, the exclusive formation of the peltogynoid type tetracyclic compounds, *e.g.* 5, presumably indicates a preference for initial substitution at C–2(B) and hence the formation of the dimethylmethylol compound 15. The alternative intermediate 14 is anticipated to give rise to both the peltogynoid– and mopanoid-type tetracyclic compounds 5 and 17. The genesis of these peltogynoid-type analogues bears a strong resemblance with the formation of bisphenol-A and related compounds derived from 2,6-diphenylphenol[12–14].

Notable in the formation of the series of tetracyclic analogues is the increased yields observed for (+)-gallocatechin 2 and (−)-epigallocatechin 10 in comparison to those for the remaining flavan-3-ols. This is presumably attributable to the pyrogallol-type B-ring in 2 and 10 acting as the more potent nucleophile compared to the pyrocatechol-type B-rings of the other analogues. Although these yields appear to be low they compare very favourably with those reported for a series of (+)-catechin dialkylacetals, prepared to assess their phytoalexin properties[6].

The apparent ease of electrophilic substitution at C–2(B) of the flavan-3-ols with pyrocatechol-type B-rings is in contrast with the exclusive substitution at the more potent nucleophilic positions of the A-ring in the biomimetic sequence to condensed tannins under ionic conditions[15]. Substitution at the B-ring under similar conditions is indeed limited to a single example[16] involving the flavan-3-ol, (−)-robinetinidol, the 5-deoxy analogue of (+)-gallocatechin 2. Collectively these results indicate that electrophilic substitution at the A– or B-rings is presumably dictated by the polarity of the reaction medium. Experiments aimed at verifying such an assumption are presently being investigated. These results will be published separately.

EXPERIMENTAL

^1H and ^{13}C NMR spectra were recorded on a Bruker AM–300 spectrometer in $(CD_3)_2CO$ with Me_4Si as internal standard. Mass spectra were obtained with a Kratos MS 80 instrument. TLC was performed on precoated Merck plastic sheets (DC-Plastikfolien Kieselgel 60 F_{254}, 0.25 mm) and compounds were located by H_2SO_4-HCHO (40:1) spray reagent. Preparative plates (PLC), 20x20 cm, Kieselgel PF_{254} (1.0 mm) were air-dried and used without prior activation.

Owing to the similarity of the procedures leading to the dimethyltetracyclic analogues, full detail is given for the (+)-catechin analogue 5 only.

(+)-Catechin 1 (30 mg) was dissolved in Me_2CO (1 cm^3) containing *ca.* 2% H_2O (v/v). *p*-Toluenesulphonic acid (20 mg) was added and the solution left for 3 days at room temperature (*ca.* 22°C). The solvent was evaporated with N_2 gas and the mixture subjected to PLC in C_6H_6-Me_2CO-MeOH (70:25:5) to give two compounds at R_f 0.15 (4 mg) and 0.35 (5 mg). The former band gave unchanged (+)-catechin 1 and the R_f 0.35 band (6*a*S, 12*a*R)-6*a*,12*a*-trans-2,3,8,10-*tetrahydroxy*-5,5-*dimethyl*-5,6*a*,7,12*a*-*tetrahydro*-[1]*benzopyrano*[3,2–*c*][2]*benzopyran* 5 as a white solid (Found: M^+, 330.1119. $C_{18}H_{18}O_6$ requires M, 330.1103); ^1H NMR data (Table); δ(C) 157.5, 157.0, 156.3, 144.5, 135.3, 125.1, 113.0, 112.3, 101.0, 96.5, 96.0, 76.1, 74.1, 67.2, 32.0, 28.5, and 28.1; m/z 330 (M^+, 54%), 315 (100), 192 (8), 177 (32), 139 (37), 138 (3). Acetylation with Ac_2O-pyridine for 12 h at room temperature afforded the tetra-*O*-acetyl derivative (Found: M^+, 498.1519. $C_{26}H_{26}O_{10}$ requires M, 498.1526); δ6.53 [d, J2.5 Hz, 6–H(A)], 6.66 [d, J2.5 Hz, 8–H(A)], 6.92 [s, 3–H(B)], 7.46 [d, J1.0 Hz, 6–H(B)], 4.65 [dd, J1.0 and 9.5 Hz, 2–H(C)], 3.94 [m, 3–H(C)], 2.64 [dd, J11.0 and 16.0 Hz, 4–$H_{ax.}$(C)], 2.98 [dd, J6.0 and 16.0 Hz, 4–$H_{eq.}$(C)], and 1.51 (s, 2xCH_3); m/z 498 (M^+, 66%), 483 (21), 456 (75), 441 (74), 414 (36), 399 (100), 357 (37), 234 (43), 221 (29), 195 (25), 177 (64), 163 (32), and 139 (51).

(6*a*S,12*a*R)–6*a*, 12*a*–trans–2,3,4,8,10-*Pentahydroxy*-5,5-*dimethyl*-5,6*a*,7,12*a*-*tetrahydro*-[1]*benzopyrano*-[3,2–*c*][2]*benzopyran* 6 (Found: M^+, 346.1039. $C_{18}H_{18}O_7$ requires M, 346.1053); ^1H NMR data (Table).

(6*a*S,12*a*R)–6*a*,12*a*-trans-2,3,10-*Trihydroxy*-5,5-*dimethyl*-5,6*a*,7,12*a*-*tetrahydro*-[2]*benzopyrano*[3,2–*c*][1]-*benzopyran* 7 (Found: M^+, 314.1141. $C_{18}H_{18}O_5$ requires M, 314.1154); ^1H NMR data (Table).

(6*a*S,12*a*R)–6*a*,12*a*–trans–2,3,10,11-*Tetrahydroxy*-5,5-*dimethyl*-5,6*a*,7,12*a*-*tetrahydro*-[1]*benzopyrano*-[3,2–*c*][2]*benzopyran* 8 (Found: M^+, 330.1112. $C_{18}H_{18}O_6$ requires M, 330.1103); ^1H NMR data (Table).

(6*a*R,12*a*R)–6*a*,12*a*–cis–2,3,8,10-*Tetrahydroxy*-5,5-*dimethyl*-5,6*a*,7,12-*tetrahydro*-[1]*benzopyrano*[3,2–*c*]-[2]*benzopyran* 11 (Found: M^+, 330.1116. $C_{18}H_{18}O_6$ requires M, 330.1103); ^1H NMR data (Table).

(6*a*R,12*a*R)–6*a*,12*a*–cis–2,3,4,8,10-*Pentahydroxy*-5,5-*dimethyl*-5,6*a*,7,12*a*-*tetrahydro*-[1]*benzopyrano*-[3,2–*c*][2]*benzopyran* 12 (Found: M^+, 346.1041. $C_{18}H_{18}O_7$ requires M, 346.1053); ^1H NMR data (Table)

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