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Tannins and Related Compounds. VIII.[1] A New Type of Proanthocyanidin, Cinchonains IIa and IIb from *Cinchona succirubra*. (2)

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Together with known proanthocyanidins B-2 (**7**), B-5 (**8**), A-2 (**9**) and C-1 (**10**), consisting exclusively of (−)-epicatechin (C_2, C_3: *cis*) units, cinchonains IIa and IIb were isolated from red cinchona, the bark of *Cinchona succirubra* (Rubiaceae). They have been established on the basis of degradative studies, and ^{1}H- and ^{13}C-NMR evidence to be novel proanthocyanidin dimers containing a phenylpropanoid substituent.

Keywords——*Cinchona succirubra*; red cinchona; Rubiaceae; cinchonains; phenylpropanoid-substituted proanthocyanidins; flavan-3-ols; thiolysis; ^{1}H-NMR; ^{13}C-NMR

In the preceding paper,[1] the isolation and structure elucidation of phenylpropanoid-substituted flavan-3-ols, cinchonains Ia (**3**), Ib (**4**), Ic (**5**) and Id (**6**), from the bark of *Cinchona succirubra* PAVON *et* KLOTZSCH were reported. Further chemical examination of the phenolic constituents of this plant has resulted in the isolation of two new phenylpropanoid-substituted proanthocyanidins, designated as cinchonains IIa (**1**) and IIb (**2**), to which **3** and **4** may be related biosynthetically. In addition, we have also isolated and characterized known proanthocyanidin dimers, B-2 (**7**),[2] B-5 (**8**)[2a] and A-2 (**9**),[3] and the trimer C-1 (**10**),[2a] all consisting exclusively of epicatechin (C_2, C_3: *cis*) units. This paper deals with the isolation and structure determination of these compounds.

Fraction II,[1] obtained previously by Sephadex LH-20 chromatography (EtOH) of the ethyl acetate-soluble portion, was rechromatographed over Sephadex LH-20 using acetone as an eluent to yield a trimeric proanthocyanidin C-1 (**10**) and a complex mixture consisting of proanthocyanidin dimers. Separation of the dimers could be achieved by chromatography over high-porous polystyrene gel (Diaion HP-20, H_2O–MeOH) giving cinchonains IIa (**1**) and IIb (**2**), together with proanthocyanidins B-2 (**7**), B-5 (**8**) and A-2 (**9**).

Cinchonain IIa (**1**), an off-white amorphous powder, $[\alpha]_D$ −47.5° (acetone), $C_{39}H_{32}O_{15}\cdot 2H_2O$, was shown to be a proanthocyanidin since, on treatment with acids, it afforded an anthocyanidin-like red pigment. The occurrence of two flavan-3-ol units with epicatechin stereochemistry (C_2, C_3: *cis*) was deduced from the proton nuclear magnetic resonance (^{1}H-NMR) signals; a pair of singlets at δ 5.24 and 5.03 characteristic of the epicatechin C_2-H,[4] and two multiplets at δ 4.31 and 4.02 due to C_3-H. A singlet signal at δ 4.86 attributed to the C_4-methine proton indicates the presence of a β-linkage of the two flavan units. These ^{1}H-NMR data are consistent with those of proanthocyanidin B-2, a C_4,C_8-linked epicatechin dimer (**7**),[2] or B-5, the alternative C_4,C_6-linked dimer (**8**).[2a] The ^{1}H-NMR spectrum also shows signals due to a methine (δ 4.63, dd, J=2, 6 Hz), a methylene (centered at δ 3.02, m) and aromatic protons (δ 6.50, dd, J=2, 8 Hz; δ 6.64, d, J=8 Hz; δ 6.70, d, J=2 Hz). These results coupled with the appearance of two singlet signals at δ 5.97 and 6.19 arising from the flavan A-rings, suggests the existence of a phenylpropanoid substituent linked to the A-ring in the upper flavan unit. This was confirmed by the carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectrum which shows, in addition to the presence of two epicatechin units, signals attributed to a carbonyl (δ 169.2), a methylene α to the carbonyl (δ 38.0, t), a β-methine carbon (δ 34.0, d) and an aromatic ring[5] with a 3,4-dihydroxy substitution pattern.

Treatment of **1** with benzylmercaptan in the presence of acetic acid,[2a,6] followed by

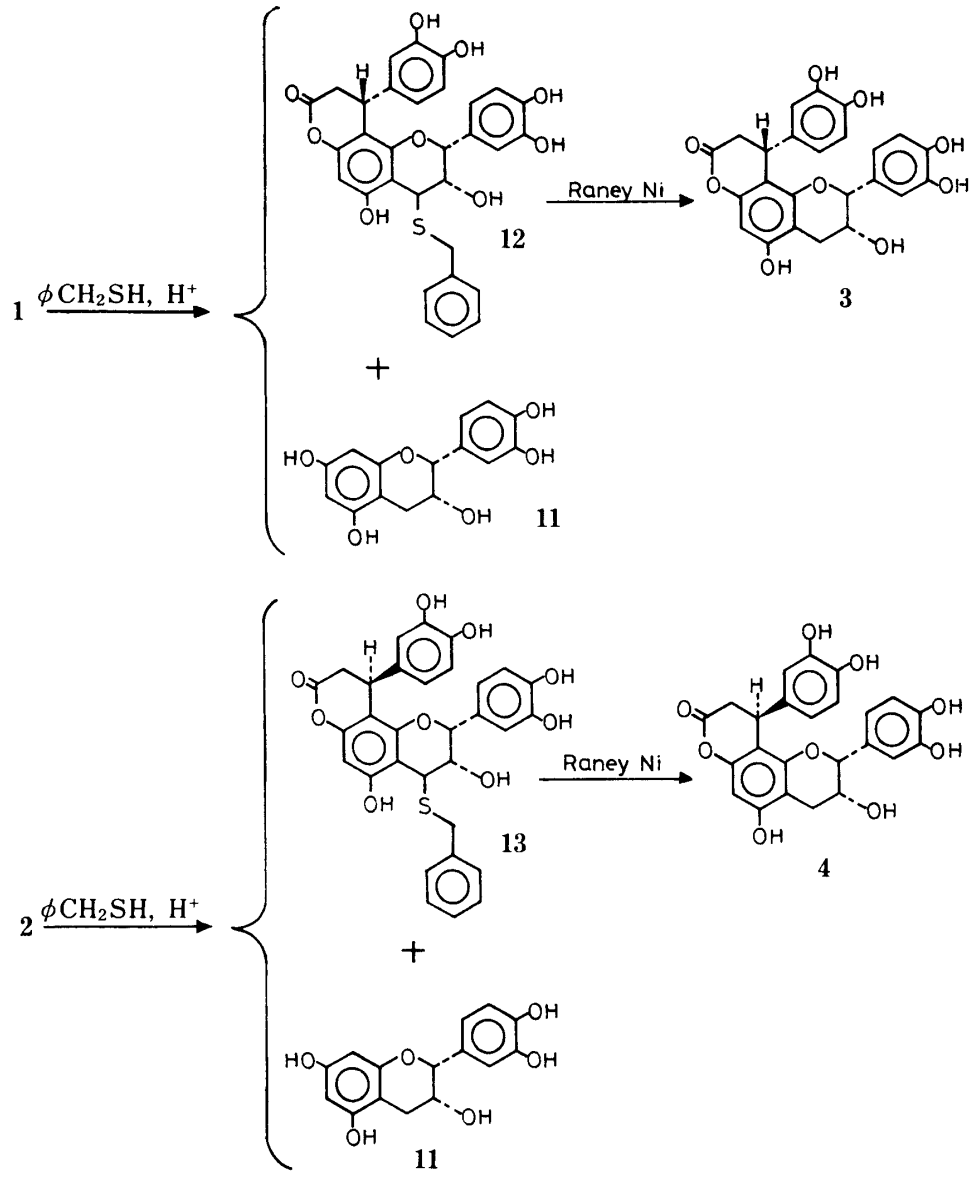

Chart 1

chromatographic separation on Sephadex LH-20 using acetone, afforded two main products; one was identical (—)-epicatechin (**11**),[1,4] and the other was shown to be a benzylthioether (**12**) by analysis of the ^{1}H-NMR spectrum (δ 4.04, s, $-CH_2S-$; δ 7.2—7.5, 5H, aromatic protons). Desulfurization of **12** with Raney nickel yielded a compound identical with cinchonain Ia (**3**), thus establishing the position of the phenylpropanoid moiety in **1**, together with the configuration of the methine carbon β to the carbonyl group.

The position of a carbon-carbon linkage between the two flavan units was determined by comparison of the ^{1}H-NMR spectrum of **1** with those of proanthocyanidins B-2 (**7**) and B-5 (**8**) (Fig. 1). In the aromatic B-ring region, **1** exhibits, along with ABX-type signals derived from the phenylpropanoid moiety, a complicated signal pattern similar to that of **7**. On the other hand, **8** shows two sets of ABX-type signals easily assignable to the respective B-ring protons, clearly indicating the absence of non-bonded interaction between these two aromatic rings. In the spectra of **1** and **7**, one of the signals attributable to $C_{2'}$- and $C_{2'''}$-H is observed distinctly as a broad singlet (δ 7.11 in **1** and δ 7.08 in **7**) in contrast to the appearance of sharp singlets (δ 7.00 and 7.07) in **8**, and this may be interpreted in terms of slower rotation of the

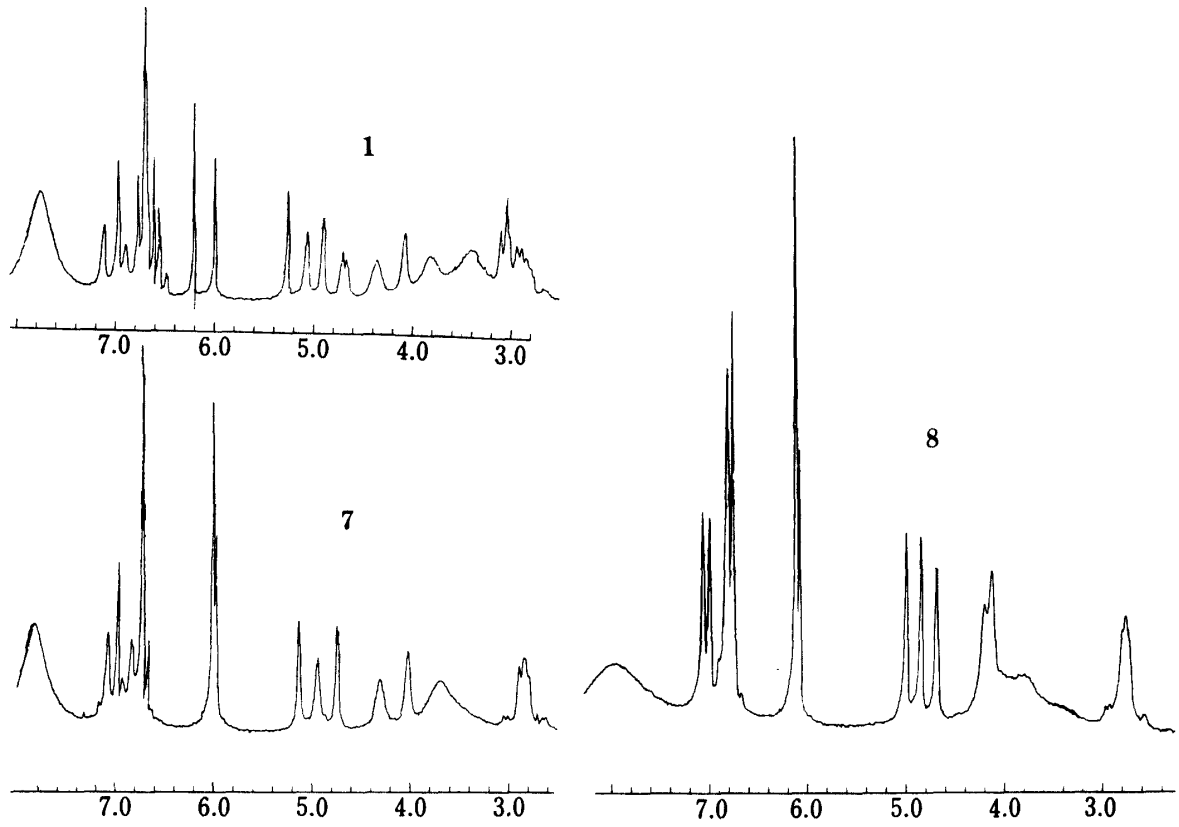

Fig. 1. ^{1}H-NMR Spectra of **1**, **7** and **8** (acetone-d_6)

aromatic ring caused by steric interaction between the two B-rings. From these findings the interflavan linkage was concluded to be at the C_4- and $C_{8''}$-positions. Thus, the structure of cinchonain IIa was established as **1**.

Cinchonain IIb (**2**), an off-white amorphous powder, $[\alpha]_D$ +134.7° (acetone), $C_{39}H_{32}O_{15}\cdot 2H_2O$, is closely related to **1**, giving rise to a similar anthocyanidin on treatment with acids. The ^{13}C-NMR spectrum reveals the presence of two epicatechin units (δ 76.4, d, C_2-H; δ 79.6, d, $C_{2''}$-H; δ 72.2, d, C_3-H; δ 66.6, d, $C_{3''}$-H; δ 36.4, d, C_4-H; δ 29.9, t, $C_{4''}$-H)[2] and a phenylpropanoid substituent (δ 36.6, t, α-C; δ 34.3, d, β-C; δ 169.6, s, –COO–). The ^{1}H-NMR spectrum, showing two singlet signals at δ 5.99 and 6.20 derived from the flavan A-rings, is consistent with the ^{13}C-NMR data. In this spectrum the appearance of a singlet signal due to C_2-H (δ 5.66) shifted considerable, is rather unusual, and this implies the presence of steric interaction between this hydrogen atom and the aromatic rings in the phenylpropanoid and lower flavan units.[4]

Specific cleavage of the linkage between two flavan units was attempted, as with **1**, by reaction with benzylmercaptan and acetic acid to give a benzylthioether (**13**) and a free flavan-3-ol, the latter being derived from the lower half and identified as (−)-epicatechin (**11**). The thioether (**13**) was then treated with Raney nickel, yielding a product which was shown to be identical with cinchonain Ib (**4**).

The ^{1}H-NMR spectrum of **2** shows a more complicated signal pattern in the aromatic filed than that found in **1**, suggesting the presence of a greater steric interaction between the aromatic rings. Furthermore, a singlet signal (δ 4.72) assignable to C_2-H in the lower flavan unit appears somewhat upfield as compared with that of epicatechin (δ 4.88), and this implies that this C_2-H is magnetically affected by the upper unit.[4] Based on these ^{1}H-NMR findings the position of a linkage between the two flavan units was determined to be at the C_8-position of the lower flavan unit. Accordingly, cinchonain IIb is assigned the struture **2**.

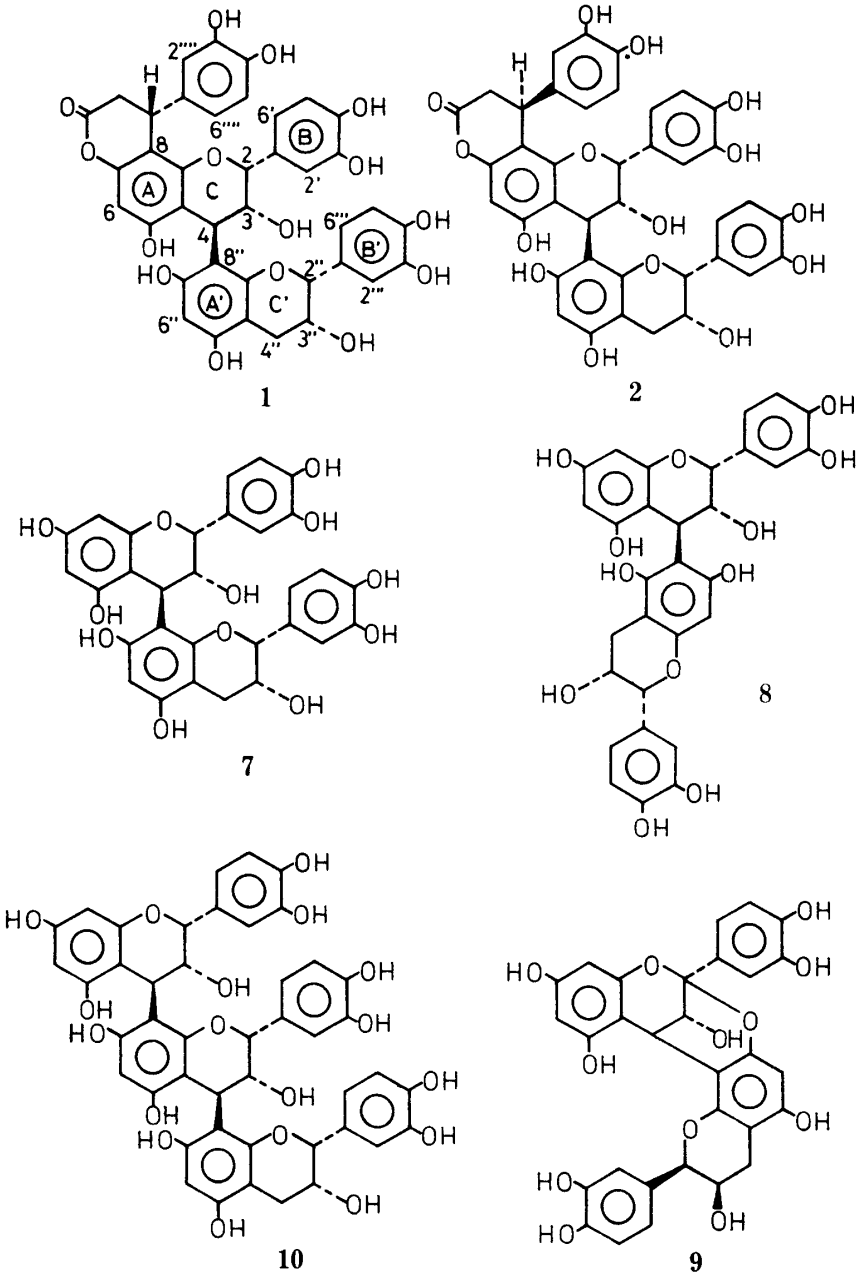

Chart 2

Cinchonains IIa and IIb are examples of a new type of proanthocyanidin containing a phenylpropanoid moiety. Since these compounds have been isolated from a variety of plant sources such as *Kandelia candel* L. (Rhizophoraceae), *Uncaria rhynchophylla* Miquel (Rubiaceae) and *Raphiolepis umbellata* Makino (Rosaceae), it is probable that cinchonain-type proanthocyanidins occur widely in plant tissues. We have detected the presence of higher oliqomers of cinchonain-type proanthocyanidins in this plant, and isolation of these compounds is currently under way.

Experimental

All melting points were determined on a Yanagimoto micromelting point apparatus (hot stage-type) and are uncorrected. Optical rotations were taken with a JASCO DIP-4 digital polarimeter using a 0.5 dm cell. ^{1}H- and ^{13}C-NMR spectra were measured with JEOL PS-100 and JEOL FX-100 machines, respectively,

and the chemical shifts are given on a δ (ppm) scale relative to an internal standard (tetramethylsilane). Column chromatography was performed on Sephadex LH-20 (25—100 μ, Pharmacia Fine Chemical Co., Ltd.) and Diaion HP-20 AG (75—150 μ, Mitsubishi Chemical Industries Ltd.). Thin-layer chromatography (TLC) was conducted on precoated Kieselgel 60 F_{254} plates (0.20 mm, Merck) with benzene–ethyl formate–formic acid (2: 7: 1), and the spots were visualized by spraying anisaldehyde-sulfuric acid and ferric chloride reagents.

Isolation——Fraction II (5.2 g),[1] previously obtained by chromatography of the ethyl acetate-soluble portion, was subsequently chromatographed on Sephadex LH-20 with acetone as an eluent to give proanthocyanidin C-1 (**10**) (0.1 g) and fractions containing dimeric proanthocyanidins. These fractions were combined, and applied to a Diaion HP-20 column. Elution with increasing amounts of MeOH in H_2O (3: 7→1: 1) gave proanthocyanidins B-2 (**7**) (1.9 g), B-5 (**8**) (0.5 g) and A-2 (**9**) (0.03 g), and cinchonains IIa (**1**) (0.9 g) and IIb (**2**) (0.8 g).

Cinchonain IIa (**1**)——An off-white amorphous powder, $[\alpha]_D^{18}$ −47.5° (c=0.98, acetone). *Anal.* Calcd for $C_{39}H_{32}O_{15}\cdot 2H_2O$: C, 60.31; H, 4.67. Found: C, 60.52; H, 4.71. ^{1}H-NMR (acetone-d_6): 2.6—3.2 (4H, m, C_4''-H, α-H), 4.02 (1H, m, C_3-H), 4.31 (1H, m, C_3''-H), 4.63 (1H, dd, J=2, 6 Hz, β-H), 4.86 (1H, s, C_4-H), 5.03 (1H, s, C_2''-H), 5.24 (1H, s, C_2-H), 5.97 (1H, s, C_6''-H), 6.19 (1H, s, C_6-H), 6.50 (1H, dd, J=2, 8 Hz, C_6''''-H), 6.64 (1H, d, J=8 Hz, C_5''''-H), 6.70 (1H, d, J=2 Hz, C_2''''-H), 6.64—7.12 (6H, m, B, B′-ring). ^{13}C-NMR (acetone-d_6+D_2O): 28.8 (t, C_4''), 34.0 (d, β-C), 36.4 (d, C_4), 38.0 (t, α-C), 66.1 (d, C_3''), 72.0 (d, C_3), 76.4 (d, C_2), 78.9 (d, C_2''), 95.4, 96.7 (each d, $C_{6,6''}$), 99.7 (s, $C_{4a''}$), 104.5 (s, C_{4a}), 106.9, 107.6 (each s, $C_{8,8''}$), 114.5, 114.7 (2C), 115.4 (2C), 115.9 (each d, $C_{2',2''',2'''',5',5''',5''''}$), 118.4, 118.9 (2C) (each d, $C_{6',6''',6''''}$), 131.2, 131.8 (each s, $C_{1',1'''}$), 134.3 (s, C_1''''), 143.9, 144.5, 144.6, 144.7, 144.8, 145.1 (each s, $C_{3',3''',3'''',4',4''',4''''}$), 151.2, 153.4, 153.8, 155.2, 155.4, 156.0 (each s, $C_{5,5'',7,7'',8a,8a''}$), 169.2 (–COO–).

Treatment of 1 with Benzylmercaptan and Acetic Acid——A mixture of **1** (120 mg), benzylmercaptan (2 ml), acetic acid (1 ml) and EtOH (4 ml) was refluxed for 11 h. After removal of the solvent by evaporation under reduced pressure, the oily residue was subjected to Sephadex LH-20 chromatography. Elution with acetone afforded a benzylthioether (**12**) (44 mg) as an off-white amorphous powder, $[\alpha]_D^{29}$ −142.3° (c=0.43, acetone). ^{1}H-NMR (acetone-d_6): 2.83 (1H, dd, J=2, 16 Hz, α-H), 3.10 (1H, dd, J=16, 6 Hz, α-H), 4.02 (1H, m, C_3-H), 4.04 (2H, s, –CH_2S–), 4.16 (1H, d, J=2 Hz, C_4-H), 4.34 (1H, dd, J=2, 6 Hz, β-H), 5.26 (1H, s, C_2-H), 6.24 (1H, s, C_6-H), 6.46 (1H, dd, J=2, 8 Hz, C_6-H in the C_6–C_3 unit), 6.57 (1H, d, J=2 Hz, C_2-H in the C_6–C_3 unit), 6.64 (1H, d, J=8 Hz, C_5-H in the C_6–C_3 unit), 6.74 (1H, dd, J=2, 8 Hz, C_6'-H), 6.80 (1H, d, J=8 Hz, C_5'-H), 7.02 (1H, d, J=2 Hz, C_2'-H), 7.2—7.5 (5H, m, aromatic H). Further elution of the column with acetone, followed by crystallization from H_2O, furnished (−)-epicatechin (**11**) as colorless needles (10 mg), mp 243—244°C, $[\alpha]_D^{28}$ −55.4° (c=0.35, acetone). ^{1}H-NMR (acetone-d_6): 2.68 (1H, dd, J=3, 16 Hz, C_4-H), 2.92 (1H, dd, J=4, 16 Hz, C_4-H), 4.19 (1H, m, C_3-H), 4.88 (1H, s, C_2-H), 5.90 (1H, d, J=2 Hz, C_6-H), 6.02 (1H, d, J=2 Hz, C_8-H), 6.76 (1H, d, J=8 Hz, C_5'-H), 6.86 (1H, dd, J=2, 8 Hz, C_6'-H), 7.04 (1H, d, J=2 Hz, C_2'-H).

Desulfurization of 12——A solution of **12** (37 mg) in EtOH was added dropwise to an EtOH slurry of Raney Ni (W-4, 1 ml), and the mixture was refluxed for 30 min. After cooling, the reaction mixture was filtered and the filtrate, after evaporation of the solvent, afforded a reddish powder, which was purified by Sephadex LH-20 column chromatography. Elution with $CHCl_3$–MeOH (3: 1) yielded colorless needles (2 mg), mp 172—174°C, the ^{1}H-NMR spectrum of which was shown to be identical with that of cinchonain Ia (**3**).

Cinchonain IIb (**2**)——An off-white amorphous powder, $[\alpha]_D^{18}$ +134.7° (c=0.96, acetone). *Anal.* Calcd for $C_{39}H_{32}O_{15}\cdot 2H_2O$: C, 60.31; H, 4.67. Found: C, 60.43; H, 4.62. ^{1}H-NMR (acetone-d_6): 2.5—3.0 (4H, m, C_4''-H, α-H), 3.88 (1H, m, C_3''-H), 4.03 (1H, m, C_3-H), 4.04 (1H, m, β-H), 4.36 (1H, s, C_4-H), 4.72 (1H, s, C_2''-H), 5.66 (1H, s, C_2-H), 5.99 (1H, s, C_6''-H), 6.20 (1H, s, C_6-H), 6.5—7.0 (9H, aromatic H). ^{13}C-NMR (acetone-d_6+D_2O): 34.3 (d, β-C), 36.4 (d, C_4), 36.6 (t, α-C), 66.6 (d, C_3''), 72.2 (d, C_3), 76.4 (d, C_2), 79.6 (d, C_2''), 94.9, 96.2 (each d, $C_{6,6''}$), 99.8 (s, $C_{4a''}$), 104.9 (s, C_{4a}), 108.0 (2C, s, $C_{8,8''}$), 114.8 (2C), 115.0 (2C), 115.4, 115.8 (each d, $C_{2',2''',2'''',5',5''',5''''}$), 118.7 (2C), 119.1 (each d, $C_{6',6''',6''''}$), 132.0, 132.1 (each s, $C_{1',1'''}$), 135.1 (s, C_1''''), 144.0, 144.6 (2C), 144.9 (2C), 145.3 (each s, $C_{3',3''',3'''',4',4''',4''''}$), 150.2, 152.9, 154.5, 155.1 (2C), 155.4 (each s, $C_{5,5'',7,7'',8a,8a''}$), 169.6 (–COO–).

Treatment of 2 with Benzylmercaptan and Acetic Acid——A mixture of **2** (150 mg), benzylmercaptan (2 ml), acetic acid (2 ml) and EtOH (6 ml) was refluxed for 12 h. The reaction mixture was concentrated under reduced pressure to give an oily residue, which was chromatographed over Sephadex LH-20. Elution with $CHCl_3$–EtOH (2: 1) furnished a benzylthioether (**13**) as an off-white amorphous powder (56 mg), $[\alpha]_D^{18}$ +99.6° (c=0.92, acetone). ^{1}H-NMR (acetone-d_6): 2.82 (1H, dd, J=2, 16 Hz, α-H), 3.08 (1H, dd, J=16, 6 Hz, α-H), 4.01 (1H, m, C_3-H), 4.04 (1H, s, –CH_2S–), 4.16 (1H, d, J=2 Hz, C_4-H), 4.42 (1H, dd, J=2, 6 Hz, β-H), 5.36 (1H, s, C_2-H), 6.26 (1H, s, C_6-H), 6.5—7.5 (11H, m, aromatic H). ^{13}C-NMR (acetone-d_6+D_2O): 34.2 (d, β-C), 37.3 (t, –SCH_2–), 37.6 (t, α-C), 43.0 (d, C_4), 70.1 (d, C_3), 75.5 (d, C_2), 96.4 (d, C_6), 104.8, 105.4 (each s, $C_{8,4a}$), 114.7, 115.0, 115.7, 116.2 (each d, $C_{2,5}$ in the C_6–C_3 unit, $C_{2',5'}$), 118.7, 119.0 (each d, C_6 in the C_6–C_3 unit, $C_{6'}$), 127.7, 129.2 (2C), 129.6 (2C) (each d, aromatic C), 130.9 (s, $C_{1'}$), 134.4 (s, C_1 in the C_6–C_3 unit), 139.5 (s, aromatic C), 144.4, 145.0, 145.1, 145.6 (each s, $C_{3,4}$ in the C_6–C_3 unit, $C_{3',4'}$), 152.6, 152.7, 157.1 (each s, $C_{5,7,8a}$), 169.3 (s, –COO–). Further elution with the same solvent system yielded (−)-epicatechin (**11**)

as colorless needles (H_2O) (7 mg), mp 241—242°C, $[\alpha]_D^{22}$ −52.0° (c=0.54, acetone).

Desulfurization of 13——A solution of **13** (50 mg) in EtOH (1 ml) was treated as described for **12**, with an EtOH slurry of Raney Ni (W-4, 1 ml). After filtration of the catalyst the filtrate was concentrated under reduced pressure. The reddish powder thus obtained was applied to a Sephadex LH-20 column. Elution with $CHCl_3$–EtOH (2 : 1) afforded colorless needles (H_2O) (3 mg), mp 240—242°C, $[\alpha]_D^{22}$ +11.8° (c=0.2, acetone), which were shown to be identical with cinchonain Ib (**4**) by comparison of the ^{1}H-NMR spectra.

Procyanidin B-2 (**7**)[2]——An off-white amorphous powder, $[\alpha]_D^{25}$ +35.5° (c=1.0, acetone). ^{1}H-NMR (acetone-d_6): 2.84 (2H, m, $C_{4''}$–H), 4.01 (1H, m, C_3–H), 4.30 (1H, m, $C_{3''}$–H), 4.74 (1H, s, C_4–H), 4.96 (1H, s, $C_{2'}$–H), 5.12 (1H, s, C_2–H), 5.99 (1H, s, $C_{6''}$–H), 6.02 (2H, $C_{6,8}$–H), 6.6—7.2 (6H, aromatic H).

Procyanidin B-5 (**8**)[2a]——An off-white amorphous powder, $[\alpha]_D^{18}$ +121.7° (c=1.0, acetone). ^{1}H-NMR (acetone-d_6): 2.5—3.0 (2H, m, $C_{4''}$–H), 4.12, 4.19 (each 1H, m, $C_{3,3''}$–H), 4.68 (1H, s, C_4–H), 4.84 (1H, s, $C_{2'}$–H), 5.00 (1H, s, C_2–H), 6.08 (1H, s, $C_{6'}$–H), 6.11 (2H, s, $C_{6,8}$–H), 6.68—7.08 (6H, aromatic H). ^{13}C-NMR (acetone-d_6+D_2O): 37.1 (d, C_4), 66.6 (d, $C_{3''}$), 71.8 (d, C_3), 76.7 (d, C_2), 78.9 (d, $C_{2''}$), 95.6, 96.1, 96.3 (each d, $C_{6,8,8''}$), 98.7 (s, $C_{4a''}$), 100.2 (s, C_{4a}), 107.3 (s, $C_{6''}$), 114.8, 115.3 (each 2C, d, $C_{2',2''',5',5'''}$), 118.9 (2C, d, $C_{6',6'''}$), 131.5, 131.7 (each s, $C_{1',1'''}$), 144.8, 145.0 (each 2C, $C_{3',3''',4',4'''}$), 154.6, 154.7, 155.4, 157.3, 158.5, 158.8 (each s, $C_{5,5'',7,7'',8a,8a''}$).

Proanthocyanidin A-2 (**9**)[3]——Colorless needles (H_2O), mp >300°C, $[\alpha]_D^{24}$ +63.5° (c=0.8, acetone). ^{1}H-NMR (acetone-d_6): 2.7—3.1 (2H, m, $C_{4''}$–H), 4.13 (1H, d, J=4 Hz, C_3–H), 4.32 (1H, m, $C_{3''}$–H), 4.33 (1H, d, J=4 Hz, C_4–H), 4.96 (1H, s, C_2–H), 5.97 (1H, d, J=2 Hz, C_6–H), 6.08 (1H, d, J=2 Hz, C_8–H), 6.14 (1H, s, $C_{6''}$–H), 6.8—7.3 (6H, aromatic H).

Procyanidin C-1 (**10**)[2a]——An off-white amorphous powder, $[\alpha]_D^{28}$ +75.2° (c=0.87, acetone). ^{1}H-NMR (acetone-d_6): 2.7—3.1 (2H, m, C_4 in C''-ring), 4.10 (2H, C_3 in C- and C'-ring), 4.34 (1H, m, C_3 in C''-ring), 4.80 (2H, br s, C_4 in C- and C'-ring), 5.04, 5.12, 5.19 (each 1H, s, C_2–H in C-, C'- and C''-ring), 5.96—6.04 (4H in total, $C_{6,8}$ in A-, A'- and A''-ring), 6.6— 7.2 (9H, aromatic H).

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