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ABSOLUTE CONFIGURATIONS OF CHEBULIC, CHEBULINIC AND CHEBULAGIC ACID

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The absolute configuration of chebolic acid (**3**) has been determined by CD spectral comparison of its methyl derivative (**4**) with a bergenin derivative (**11**). This result led to establishment of the absolute configurations of chebulinic acid (**1**), chebulagic acid (**2**) and trilloic acid trilactone (**15**).

KEYWORDS — myrobalans; *Terminalia chebula*; tannin; chebulinic acid; chebulagic acid; chebolic acid; valonia tannin; trilloic acid trilactone; absolute configuration; CD spectrum

We reported in a previous paper¹⁾ the revised structures of chebulinic acid (**1**) and chebulagic acid (**2**) which are the tannins of myrobalans, the dried fruits of *Terminalia chebula* Retz. We also tentatively assigned the absolute configuration at C-3 in **1** and **2**, the same as that in terchebin,²⁾ based on the conceivable biogenetic correlation. This paper deals with the determination of the absolute configurations at C-2~C-4 of chebolic acid (**3**), and the resulting establishment of the absolute structures of **1**, **2** and trilloic acid trilactone (**15**).

The *cis*-arrangement of H-2 and H-3 in chebolic acid (**3**), a hydrolysis product

from **1** and **2**, was previously proposed based on their small coupling constant (ca. 1.5 Hz) in the ^1H -NMR spectra of chebolic acid derivatives,³⁾ assuming a quasi-equatorial orientation of one of the bulky substituents at C-2 and C-3. A recent X-ray crystallographic analysis,⁴⁾ however, revealed that the relative configuration at C-2~C-4 is as in the formula (**3**) in which the substituents at C-2 and C-3 are *trans*-diaxially oriented. The absolute configuration of **3** then should be either (2*S*, 3*S*, 4*S*) or (2*R*, 3*R*, 4*R*).⁵⁾

In the present study, the absolute configuration of **3** was determined by the comparison of the CD spectra of trimethyl tri-*O*-methylchebulate (**4**) prepared from **3** with a trimethyl ester (**11**) derived from bergenin (**5**) whose absolute configuration is known.⁶⁾

An initial attempt to prepare a dialdehyde (**7**) by sodium metaperiodate oxidation of dimethylbergenin (**6**) failed as an α,β -unsaturated aldehyde (**8**) was produced upon the isolation, by the β -elimination in **7**. Then, according to the procedure of Takano *et al.*,⁷⁾ **6** was oxidized with sodium metaperiodate in MeOH containing a small amount of water and sodium bicarbonate, and without isolating labile **7**, the reaction mixture was treated with sodium borohydride at 0°C for 10 min. Preparative thin-layer chromatography gave a triol (**9**), $\text{C}_{16}\text{H}_{22}\text{O}_9$ (m/z 358 (M^+); $[\alpha]_{\text{D}} +45^\circ$ (MeOH); IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} 3350, 1710}, in 50% yield. Acetylation of **9** yielded a triacetate (**10**), $\text{C}_{22}\text{H}_{28}\text{O}_{12}$ (m/z 484 (M^+); $[\alpha]_{\text{D}} +56^\circ$ (CHCl_3); IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm^{-1} 1730, 1595}. Its ^1H -NMR spectrum (90 MHz, CDCl_3) exhibited a doublet of H-3 (δ 4.89, $J=1.3$ Hz) and a double triplet of H-2 (δ 5.00, $J=1.3$, 6 Hz). The substituents at C-2 and C-3 in **10** are therefore *trans*-diaxially oriented in a way similar to that of **4** (^1H -NMR, δ 5.25, d, $J=1.4$ Hz, H-2). Upon oxidation with Jones reagent followed by methylation with diazomethane, triol (**9**) furnished a trimethyl ester (**11**) as a colorless syrup, $\text{C}_{19}\text{H}_{22}\text{O}_{12}$ (m/z 442 (M^+); $[\alpha]_{\text{D}} +68^\circ$ (CHCl_3); IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm^{-1} 1740, 1598, 1510; ^1H -NMR (CDCl_3) δ 7.48 (1H, s), 5.58 (1H, d, $J=1.8$ Hz, H-2), 5.31 (1H, d, $J=1.8$ Hz, H-3), 4.71 (1H, s, H-5), 3.95-3.68 (6 x OMe)}.

The CD spectrum of **11** showed four Cotton effects at 268 ($\Delta\epsilon +7.2$), 241 ($\Delta\epsilon -2.2$), 224 ($\Delta\epsilon +8.7$) and 205 nm ($\Delta\epsilon -11.8$), attributable to the chiral dihydroisocoumarin chromophore, and was nearly superimposable on that of **4** as shown in Fig. 1.⁹⁾ This result unequivocally established the (2*S*, 3*S*, 4*S*) configuration of **4**, and hence of **3**.

In order to determine the absolute configuration of **1** and **2** based on that of **3**, retention of the absolute configurations at C-2~C-4 upon the production of **3** from **1** and **2** was confirmed as follows. Methanolysis of methyl undeca-*O*-methylchebulate (**12**) with NaOMe in MeOH gave trimethyl di-*O*-methylchebulate (**13**)¹⁾ which was methylated with diazomethane to give a tri-*O*-methyl congener. This derivative was identical with **4** obtained by hydrolysis of **1** and **2** with boiling water followed by methylation. When an analogous methanolysis of **12** was carried out in CD_3OD containing sodium, no hydrogen-deuterium exchange at C-3~C-5 was observed in the ^1H -NMR spectrum of the product. The proton at C-2 was partially substituted by deuterium. However, the retention of about 60% of H-2 in the product, and the fact that **3** and **13** have never been contaminated by a diastereomer upon the hydrolysis and the methanolysis as shown by TLC and ^1H -NMR spectra, disprove the occurrence of epimerization at C-2 upon the formation of **3** from **1** and **2**. The observed vicinal coupling constants of H-2 ($J_{2,3}=7$ Hz) and H-3 ($J_{3,4}=0$) in the

3 R=R'=H
4 R=R'=Me
13 R=Me, R'=H

7 R=CHO, R'=H
9 R=CH₂OH, R'=H
10 R=CH₂OAc, R'=Ac

5 R=H
6 R=Me

8

11

15

16

3

Fig. 1. CD and UV Spectra of **4** (---) and **11** (—) in EtOH

^1H -NMR spectra of **1**, **2** and their derivatives are also consistent with those expected for stereostructure (1a) of the dihydrocoumarin moiety.

The absolute configurations of chebulinic acid and chebulagic acid are therefore exhibited by the formulae **1** and **2**. The identity of the absolute configuration at C-3 in **1** and coexisting terchebin (**14**) verifies their biogenetic correlation which can be illustrated by Chart 1.

Chart 1

The present study also establishes the absolute configuration of trilloic acid trilactone (**15**) which is a hydrolysate of valonia tannins, valolaginic acid¹⁰⁾ and isovalolaginic acid,¹¹⁾ as in the formula. The identity of the absolute configurations of **3** and **15** was already proved by the production of (+)-3,4-dicarboxy-2-hydroxyadipic-2,4-lactone (**16**) upon oxidation of both **3** and **15** with potassium permanganate in acidic medium, without determining the absolute configuration of **16**.^{12,13)}

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- 8) This numbering is based on that of **3**.
- 9) It is notable that the CD spectrum of **6** which has diequatorial substituents at C-2 and C-3, showed the Cotton effects of reversed sign to those of **11**; $\Delta\epsilon_{274} -3.9$, $\Delta\epsilon_{244} +3.6$ and $\Delta\epsilon_{223} -10.9$.
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