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ABSOLUTE CONFIGURATIONS OF CHEBULIC, CHEBULINIC AND CHEBULAGIC ACID

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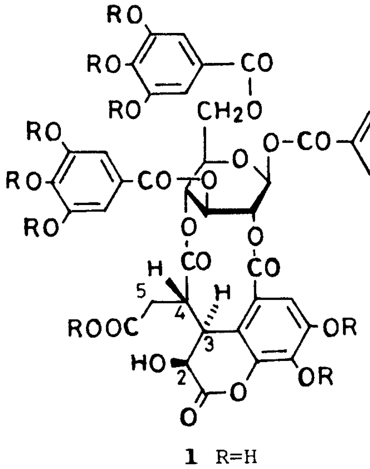
The absolute configuration of chebulic acid (**3**) has been determined by CD spectral comparison of its methyl derivative (**4**) with a bergenin derivative (**11**). This result led to establishment of the absolute configurations of chebulinic acid (**1**), chebulagic acid (**2**) and trilloic acid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

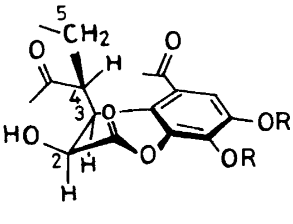
KEYWORDS —— myrobalans; *Terminalia chebula*; tannin; chebulinic acid; chebulagic acid; chebulic acid; valonia tannin; trilloic acid trilactone; absolute configuration; CD spectrum

We reported in a previous paper[1)] 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 chebulic acid (**3**), and the resulting establishment of the absolute structures of **1**, **2** and trilloic acid trilactone (**15**).

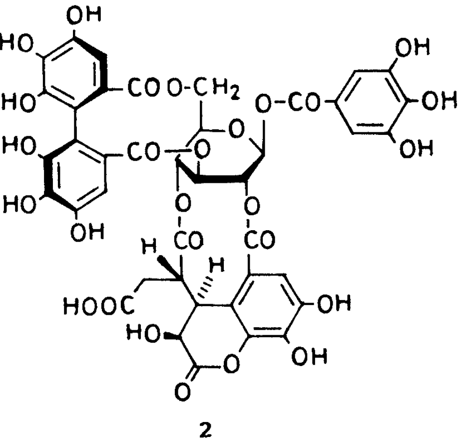
The *cis*-arrangement of H-2 and H-3 in chebulic acid (**3**), a hydrolysis product



1 R=H
12 R=Me



1a



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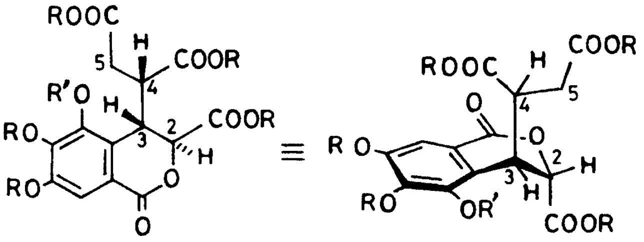
from **1** and **2**, was previously proposed based on their small coupling constant (ca. 1.5 Hz) in the ^{1}H-NMR spectra of chebulic acid derivatives,[3)] assuming a quasi-equatorial orientation of one of the bulky substituents at C-2 and C-3. A recent X-ray crystallographic analysis,[4)] however, 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 fo **3** then should be either (2*S*, 3*S*, 4*S*) or (2*R*, 3*R*, 4*R*).[5)]

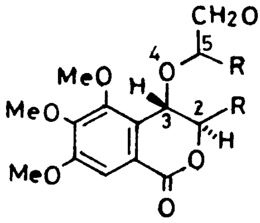
In the present study, the absolute configuration of **3** was determined by the comparison of the CD spectra of trimethyl tri-*O*-methylchebulate (**4**) prepared from **3** with a trimethyl ester (**11**) derived from bergenin (**5**) whose absolute configuration is known.[6)]

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**), $C_{16}H_{22}O_9$ {*m/z* 358 (M^+); $[\alpha]_D$ +45° (MeOH); IR ν_{max}^{KBr} cm^{-1} 3350, 1710}, in 50% yield. Acetylation of **9** yielded a triacetate (**10**), $C_{22}H_{28}O_{12}$ {*m/z* 484 (M^+); $[\alpha]_D$ +56° ($CHCl_3$); IR $\nu_{max}^{CHCl_3}$ cm^{-1} 1730, 1595}. Its ^{1}H-NMR spectrum (90 MHz, $CDCl_3$) exhibited a doublet of H-3[8)] (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** (^{1}H-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, $C_{19}H_{22}O_{12}$ {*m/z* 442 (M^+); $[\alpha]_D$ +68° ($CHCl_3$); IR $\nu_{max}^{CHCl_3}$ cm^{-1} 1740, 1598, 1510; ^{1}H-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 (Δε +7.2), 241 (Δε -2.2), 224 (Δε +8.7) and 205 nm (Δε -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*-methylchebulinate (**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 ^{1}H-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 ^{1}H-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

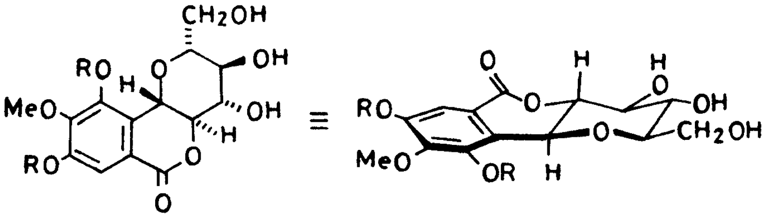
4 R=R'=Me

13 R=Me, R'=H

7 R=CHO, R'=H

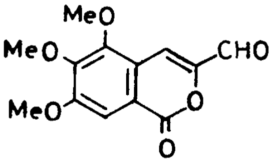
9 R=CH_2OH, R'=H

10 R=CH_2OAc, R'=Ac



5 R=H

6 R=Me



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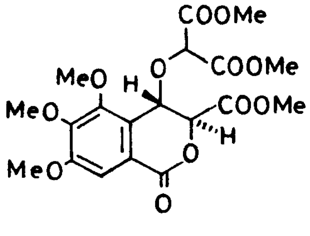

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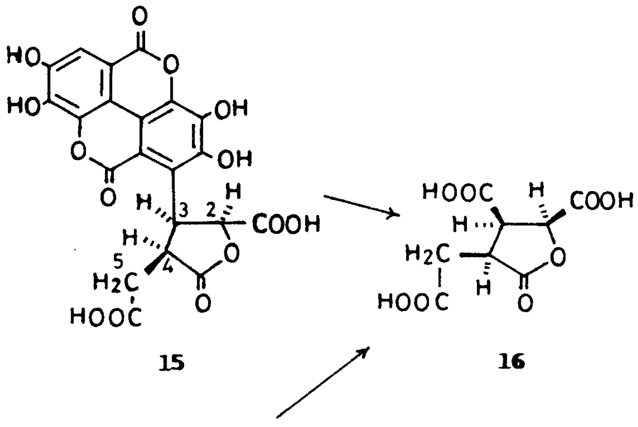

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3

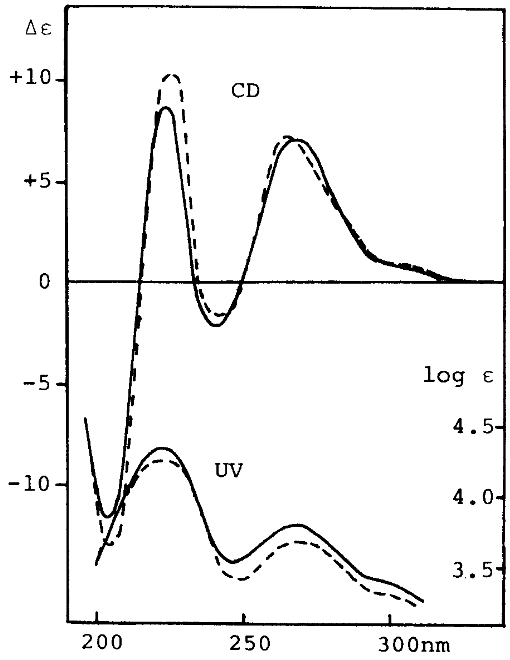
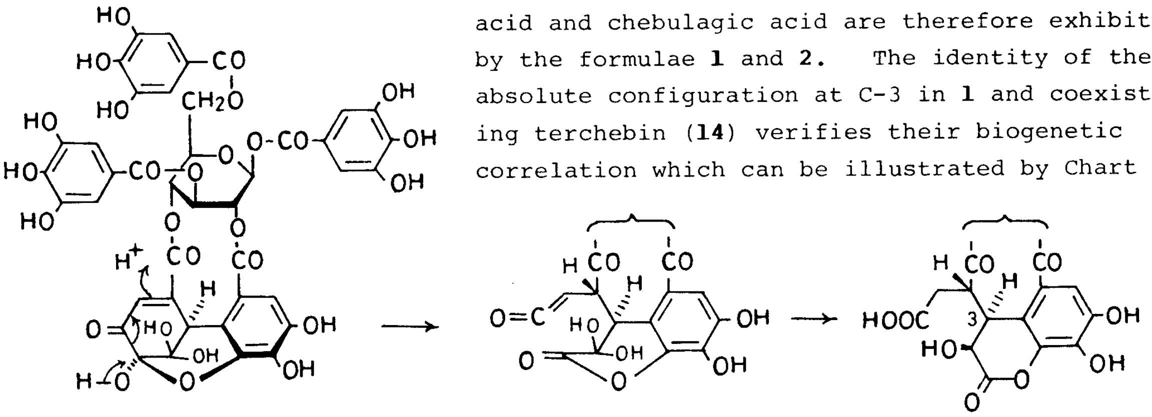


Fig. 1. CD and UV Spectra of **4** (---) and **11** (——) in EtOH

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



14 **1**

Chart 1

The present study also establishes the absolute configuration of trilloic acid trilactone (**15**) which is a hydrolysate of valonia tannins, valolaginic acid$^{10)}$ 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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5) The symbols *R* and *S* for C-3 configuration in chebulic acid in Ref. 4 does not conform to the real configuration shown in the figure.

6) J. E. Hay and L. J. Haynes, J. Chem. Soc., 1958, 2231; T. Ito, N. Harada, and K. Nakanishi, Agric. Biol. Chem., 35, 797 (1971).

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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**; $\Delta\varepsilon_{274}$ -3.9, $\Delta\varepsilon_{244}$ +3.6 and $\Delta\varepsilon_{223}$ -10.9.

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