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THE TRITERPENES OF COMMIPHORA—II

THE STRUCTURES OF COMMIC ACID C AND COMMIC ACID D

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Abstract—Evidence is presented to show that commic acid C is probably 2β,3β-dihydroxyolean-12-ene-23-oic acid (I); commic acid D is shown to be the ursane analogue, 2β,3β-dihydroxyurs-12-ene-23-oic acid (II).

THE isolation of triterpene acids from *Commiphora pyracanthoides* Engl. (= *C. glandulosa* Schinz[2]) has been described in part I of this series, where it was also shown that methyl commates C and D were esters having two hydroxyl groups and one double bond.[3]

Both methyl commate C and D form isopropylidene derivatives, and both react with one equivalent of periodic acid, so that the two hydroxyl groups must be present in a *cis*-oriented α-glycol. Hydrolysis of the methyl esters occurs with surprising ease, suggesting that the carboxyl group, if tertiary, is in an equatorial position, though some reservation must be made in the light of the fact that the presence of a β- or γ-hydroxyl group can affect the ease of hydrolysis of methyl esters.[4] Neither acid formed a lactone, and only commic acid C crystallized, thus providing an excellent method of separating it from traces of commic acid D by recrystallization from methanol. It is interesting that halolysis of diacetyl methyl commate C with lithium iodide in dry lutidine[5] was found to give a good yield of commic acid C, a repetition of the experiment of Eschenmoser *et al.* using acetyl methyl oleanolate yielding almost pure acetyl oleanolic acid as they report.[6] The acids were oxidized with chromic acid in acetone solution, and the resulting ketoacids not isolated but treated directly with base, when compounds were obtained that gave a blue-green colour with ferric chloride, and had infra-red and ultra-violet spectra typical of diosphenols with oxygens at C-2 and C-3. The diosphenol from commic acid C was not identical with that from acid D, and their acetates were also clearly different, so that the difference between the two acids must lie in the carbon skeleton. The loss of carbon dioxide on diosphenol formation shows that the acids have hydroxyl groups at the β- and γ-positions to the carboxyl group.

Commic acid C is most probably a derivative of olean-12-ene, as was shown by the reaction of diacetyl methyl commate C with selenium dioxide in acetic acid, when a product was obtained displaying the ultra-violet triple absorption maxima associated with the oleana-11,13(18)-dienes. In a similar experiment diacetyl methyl commate D failed to react, so acid C was allocated structure I, while acid D was

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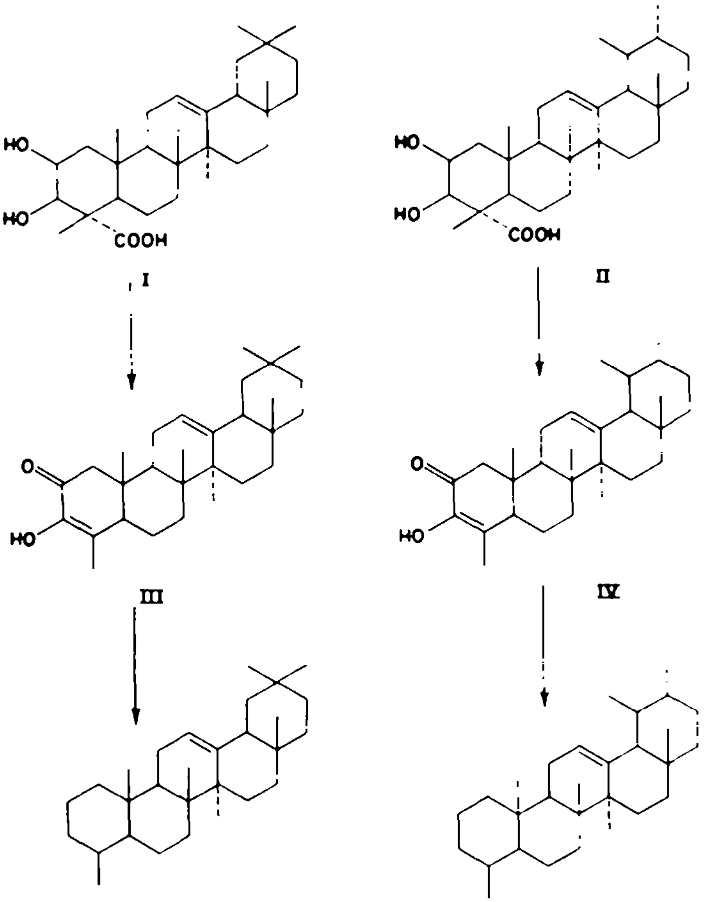
[2] H. Wild, *Bol. da Sociedade Broteriana* [Série 2] **33**, 67 (1959). I am indebted to Dr. H. Hürlimann, CIBA, Basle, Switzerland, for drawing my attention to this reference.
[3] A. F. Thomas and J. M. Müller, *Experientia* **62**, 16 (1960).
[4] C. Djerassi and J. S. Mills, *J. Amer. Chem. Soc.* **80**, 1236 (1958).
[5] F. Taschner and B. Liberek, *Rocz. Chem.* **30**, 323 (1956).
[6] F. Elsinger, J. Schreiber and A. Eschenmoser, *Helv. Chim. Acta* **43**, 113 (1960).

placed in the urs-12-ene series (structure II) and the diosphenols were ascribed structures III and IV respectively. The diosphenols were reduced by the Wolff-Kishner method, when C_{29} hydrocarbons were obtained (V and VI) respectively, the one derived from commic acid D (II) having the properties reported for 23-norolean-12-ene (VI).[8] This hydrocarbon obtained from commic acid D was found to be identical with the C_{29} hydrocarbon produced by the Wolff-Kishner reduction of nor-β-boswellinone,[9] so commic acid D is therefore a 2,3-dihydroxyurs-12-ene-23(or 24)-oic acid. The corresponding hydrocarbon in the oleanene series is not known, so a direct comparison was not possible, but in view of the similarity between the derivatives of acid C and acid D, especially in their molecular rotational differences, the formulation of commic acid C as the corresponding 2,3-dihydroxyolean-12-ene-23(or 24)-oic acid seems justified.

Series C Series D



I II III IV V VI

The occurrence of 2α,3α-dihydroxy-triterpenes has not been observed,[7] and an

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[7] C. Djerassi, D. B. Thomas, A. L. Livingstone and C. R. Thompson, *J. Amer. Chem. Soc.* **79**, 5292 (1957).
[8] L. Ruzicka, O. Jeger and W. Ingold, *Helv. Chim. Acta* **27**, 1859 (1944).
[9] I am indebted to Dr. T. G. Halsall for a generous sample of nor-β-boswellinone.

attempt was made to confirm the nature of the glycol as 2β,3β by measuring the rate of oxidation with lead tetraacetate in acetic acid.[10] The results were unsatisfactory, both methyl commate C and D being oxidized very slowly. Since no substance suitable for comparison was available, it was felt that these measurements were not reliable, and that the 2β,3β-conformation for the hydroxyl groups—and therefore, in view of the resistance to lactonization by the acids, the positioning of the carboxyl at C-23—represents the most plausible conformation for both acids.

In the case of methyl commate C, some experiments were undertaken with a view to attacking one of the hydroxyl groups preferentially, and though they were not pursued further, they will be briefly described. Methyl commate C formed a monoethylcarbonate very easily (incidentally supporting the assignment of the glycol with one axial and one equatorial hydroxyl group) but attempted oxidation of this with chromic-pyridine complex yielded only starting material—as, indeed, did every experiment in this series using this reagent. Methyl commate C does not form a *p*-toluenesulphonate, and methylsulphonyl chloride in pyridine yields only a dimethylsulphonate, reduction of which with lithium aluminium hydride gave a mixture of diols and triols from which only commol C[3] could be isolated with any certainty.

EXPERIMENTAL

M.p.s. are corrected. Rotations were measured at concentrations of 1% in chloroform. Alumina for chromatography was Woelm, neutral, grade III.

Commic acid C. Methyl commate C[3] (5 g) was heated under reflux with methanol (200 ml) and potassium hydroxide (20 g). After about 15 min the potassium salt of the acid began to crystallize, and after 4 hr no ether-soluble material could be isolated from the mixture. The salt was removed on a sinter and converted to *commic acid* C with methanol-conc hydrochloric acid; after crystallization from methanol, this had m.p. 343–345° (evac. tube). It was insufficiently soluble in chloroform, alcohol, dioxan or pyridine for its optical rotation to be measured in these solvents. (Found: C, 76·0; H, 10·2. $C_{30}H_{48}O_4$ requires: C, 76·2; H, 10·2%.) λ_{max}^{Nujol} 5·86 μ, unchanged after treatment with conc. sulphuric acid dioxan.

In another experiment, diacetyl methyl commate C[3] (0·9 g) was heated in dry 2,6-lutidine with anhydrous lithium iodide (1·4 g) under nitrogen for 7 hr then worked up as described by Eschenmoser *et al.*[9] to give commic acid C, identical in all respects with that described above. Methylation of this sample with diazomethane in ether resulted in methyl commate C, identical with previously described material.

Commic acid C reacted with one equivalent of periodic acid in dioxan solution.

Reaction of methyl commate C *with acetone.* The resin from *C. pyracanthoides* was worked up as described previously[3] to the point at which the crude ester mixture was obtained after methylating the crude acids with diazomethane. Crystallization of this several times from chloroform removed most of the methyl commate D and E (see below), and the remainder (5 g) was allowed to stand at room temp. overnight with acetone (100 ml) and conc sulphuric acid (2 ml). The reaction mixture was poured into excess saturated sodium carbonate solution, and the product isolated with ether and chromatographed. Crystals (1 g) were eluted with benzene at first, but later fractions gave resins that appeared to be mixtures of the isopropylidene derivatives of methyl commates C and D and which crystallized only with difficulty. The first fractions, crystallized from methanol, had m.p. 168–169, $[\alpha]_D^{19°}$ + 65° (Found: C, 77·0; H, 10·2. $C_{34}H_{54}O_4$ requires: C, 77·5; H, 10·3%). Some difficulty was experienced in drying this sample. Hydrolysis of the isopropylidene derivative with methanol-conc hydrochloric acid yielded methyl commate C, identical in all respects with the ester previously described.[3]

Reaction of diacetyl methyl commate C *with selenium dioxide.* Diacetyl methyl commate C[3] (0·2 g) and selenium dioxide (0·2 g) were heated under reflux in glacial acetic acid (30 ml) for 2 hr, then poured into water and the product isolated with ether. The ether was washed with sodium

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[10] C. Djerassi and R. Erlich, *J. Org. Chem.* **19**, 1351 (1954).

bicarbonate, and the residue after evaporation chromatographed. Benzene–light petroleum (9:1) eluted a substance, which, after crystallization from light petroleum had m.p. 157–159°, $[\alpha]_D^{19°}$ − 38° (Found: C, 73·9; H, 9·3. $C_{35}H_{52}O_6$ requires: C, 73·9; H, 9·2%) $\lambda_{\text{max}}^{\text{EtOH}}$ 240, 251, 260 mμ ε 14,800, 11,600, 6,800 respectively, $\lambda_{\text{max}}^{CS_2}$ 13·17 μ (*cis*-disubstituted double bond).

Treatment of methyl commate D in the same way yielded only unchanged starting material.

Diosphenol C (III). Commic acid C (0·25 g) was suspended in acetone (100 ml) and treated dropwise at room temp over 30 min with chromic oxide in sulphuric acid and water (0·4 ml of a mixture from 2·67 g CrO_3, 2·3 ml. conc H_2SO_4 and 7·7 ml water) when it was poured into water (500 ml). The product, isolated as usual with ether, was heated under reflux for one hr with potassium hydroxide in methanol (10%, 10 ml). Dilution with water and acidification with hydrochloric acid enabled the product to be isolated with ether. It was chromatographed, and elution with benzene and crystallization from methanol gave *diosphenol* C, m.p. 228–230°, $[\alpha]_D^{20°}$ −132° (Found: C, 81·9; H, 10·4. $C_{29}H_{44}O_2$ requires: C, 82·0; H, 10·4%). $\lambda_{\text{max}}^{\text{EtOH}}$ 281 mμ ε 9,000; ${}_{\text{max}}^{\text{EtOH-KOH}}$ 329 mμ, ε 3,500. $\lambda_{\text{max}}^{CH_2Cl_2}$ 2·90, 5·99, 6·08 μ.

Diosphenol C acetate. This was prepared from acetic anhydride in pyridine and crystallized from methanol, m.p. 220–221°, $[\alpha]_D^{20°}$ +156° (Found: C, 79·7; H, 9·9. $C_{31}H_{46}O_3$ requires: C, 79·8; H, 9·9%). $\lambda_{\text{max}}^{CHCl_3}$ 5·67, 5·95, 6·07 μ, $\lambda_{\text{max}}^{\text{EtOH}}$ 250 mμ, ε 7,900.

Wolff-Kishner reduction of diosphenol C (*23-norolean-*12*-ene*). Diosphenol C (80 mg), diethylene glycol (15 ml), ethanol (15 ml) and hydrazine hydrate (10 ml) were heated under reflux together for 15 min. Potassium hydroxide (5 g) was added and the mixture concentrated by distillation until the temperature attained 200–220°, where it was maintained for 3 hr. The mixture was poured into water and the product isolated with pet ether. The petroleum solution was filtered through alumina and the product obtained on evaporation was crystallized from acetone, m.p. 150°, $[\alpha]_D^{20°}$ + 106° (Found: C, 87·7; H, 12·2. $C_{29}H_{48}$ requires: C, 87·8; H, 12·2%).

It was found that Clemmenson reduction of diosphenol C using zinc amalgam (made from 10 g zinc wool and 0·75 g mercuric chloride), glacial acetic acid (20 ml) and conc hydrochloric acid (4 ml) heated for 20–30 min gave a good yield of the same 23-norolean-12-ene. Longer periods of reflux (over 2 hr) yielded mostly non-crystalline material.

Ethoxycarbonyl methyl commate C. This was made by dissolving the triterpene ester (0·5 g) in dioxan (10 ml) and pyridine (1·6 ml) at 0° and adding dropwise ethyl chloroformate (2 ml). After 2 hr the mixture was diluted with water and the product isolated with ether. Chromatography on alumina gave first, a small amount of gum (eluted with benzene) with no I.R. absorption between 2·5–3·0 μ, then the *ethoxycarbonyl* derivative which was crystallized from 90% methanol to m.p. 196–198°, $[\alpha]_D^{21°}$ +38° (Found: C, 73·1; H, 9·7. $C_{34}H_{54}O_6$ requires: C, 73·1; H, 9·7%). $\lambda_{\text{max}}^{CHCl_3}$ 2·93 (v. broad), 5·81 μ.

Dimethylsulphonyl methyl commate C. This was prepared with methyl sulphonyl chloride in pyridine, and after chromatography on alumina (eluted with benzene), crystallized from ethanol–pet ether, m.p. 222–224° $[\alpha]_D^{20°}$ + 41°, (Found: C, 62·1; H, 8·6; S, 10·0. $C_{33}H_{54}O_8S_2$ requires: C, 61·7; H, 8·5; S, 10·0%). $\lambda_{\text{max}}^{CHCl_3}$ 5·78, 8·47 μ, no band at 2·5–3·0 μ.

Treatment with sodium iodide in acetone[11] left this compound unchanged.

Commic acid D. This was prepared by hydrolysis of the methyl ester with potassium hydroxide in methanol exactly as described for commic acid C. Commic acid D did not crystallize, but had $\lambda_{\text{max}}^{\text{nujol}}$ 5·86 μ, unchanged after treatment with conc sulphuric acid–dioxan.

Methyl commate D reacted with one equivalent of periodic acid in dioxan solution.

Isopropylidene methyl commate D. This was most easily obtained by treatment of the part of the crude ester mixture that was insoluble in chloroform with acetone–sulphuric acid (2%) as described for the isopropylidene derivative of methyl commate C. Chromatography of the product yielded on elution with benzene *isopropylidene methyl commate* D, which, after crystallization from methanol had m.p. 153–154°, $[\alpha]_D^{19°}$ + 88° (Found: C, 77·3; H, 10·2. $C_{34}H_{54}O_4$ requires: C, 77·5; H, 10·3%). $\lambda_{\text{max}}^{CHCl_3}$ 5·79 μ.

Continued elution of the column with benzene–ether (1:1) yielded a substance subsequently shown to be *isopropylidene methyl commate* E, since hydrolysis with methanol–conc hydrochloric acid yielded methyl commate E.[3] Crystallization from methanol gave leaflets of m.p. 240–241°, $[\alpha]_D^{20°}$ − 53° (Found: C, 75·1; H, 10·0. $C_{34}H_{54}O_5$ requires: C, 75·2; H, 10·0%). $\lambda_{\text{max}}^{CH_2Cl_2}$ 2·77, 5·78, 9·57, 11·66 μ.

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[11] H. L. Slates and N. L. Wendler, *J. Amer. Chem. Soc.* 78, 3749 (1959).

The isopropylidene methyl commate D obtained in this experiment was hydrolysed to methyl commate D with methanol–conc hydrochloric acid.

Diosphenol D (IV). This was obtained in a manner completely analogous to that described above for diosphenol C. After chromatography and crystallization from methanol, diosphenol D had m.p. 233-235° (admixture with diosphenol C, m.p. 180 185°) $[\alpha]_D^{18°}$ +150° (Found: C, 81·8; H, 10·6. $C_{29}H_{44}O_2$ requires: C, 82·0; H, 10·4%). λ_{max}^{EtOH} 282 mμ, ε 13,800, $\lambda_{max}^{EtOH-KOH}$ 329 mμ, ε 9,500. $\lambda_{max}^{CH_2Cl_2}$ 2·90, 5·99, 6·08 μ.

Diosphenol D *acetate*. This, made with acetic anhydride in pyridine and crystallized from methanol had m.p. 210–212°, $[\alpha]_D^{18°}$ +156° (Found: C, 79·8; H, 9·8. $C_{31}H_{46}O_3$ requires: C, 79·8; H, 9·9%). λ_{max}^{EtOH} 250 mμ, ε 8,500; $\lambda_{max}^{CHCl_3}$ 5·66, 5·98, 6·08 μ.

23-*Norurs*-12-*ene*. A. From Diosphenol D. The Wolff–Kishner reduction was carried out exactly as described above for diosphenol C, yielding a product of m.p. 172 173° $[\alpha]_D^{20°}$ +106°.

B. Similar treatment of nor-β-boswellinone[8] yielded 23-norurs-12-ene of identical m.p. and mixed m.p. On admixture with the compound obtained by Wolff Kishner reduction of diosphenol C, the m.p. was found to be 120 125°.

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