102. *Sapogenins. Part XIII. The Position of the Double Bond in Acids of the β-Amyrin Group.*

By Philip Bilham, George A. R. Kon, and Walter C. J. Ross.

A new structural formula is put forward to explain the chemistry of the β-amyrin group of triterpenes.

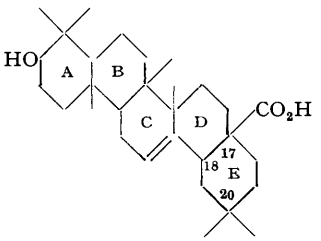
The experiments described in the accompanying papers were primarily undertaken in continuation of the programme outlined in Part XII (this vol., p. 35), which had for its object the determination of the position of the carboxyl group in a number of sapogenins. It was thought desirable to include in this survey certain triterpene acids which are clearly related to the sapogenins, although they occur in the free state and not in the form of saponins. Such compounds are siaresinolic and sumaresinolic acid occurring in gum benzoin, and the acids of elemi resin.

Whilst the work on the acids of elemi resin described in Part XVI is still of a preliminary character, the investigation of glycyrrhetic acid (Part XIV) and siaresinolic acid (Part XV) has led to the almost complete elucidation of their constitution; and it soon became apparent that this could not be satisfactorily interpreted with the aid of the structural formulæ for the triterpenes which are current at the present time.

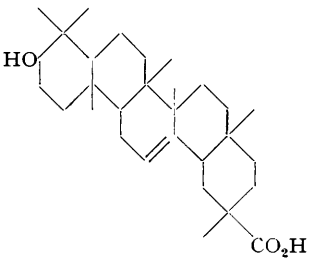
It has already been shown that the carboxyl group of oleanolic acid must occupy a position in one of the terminal rings of the hydropicene skeleton, leading to a modification of the current structural formula (I), in which this group was placed on C_{20} in ring E, but the remaining functional groups retained their original positions, as in (II) (Bilham and Kon, *Nature*, 1941, **147**, 745; J., 1941, 552).

It was foreseen at the time that the new formulation might give rise to difficulties, more especially as the formation of lactones from (II) appeared to require certain definite configurations of rings C, D, and E. The existence of two epimeric acids of the same formula, which is described in Part XIV, is possible according to this formula, but only one of these should be capable of lactone formation; a study of models shows that in the other form the carboxyl group is too remote from the unsaturated centre to allow interaction to take place.

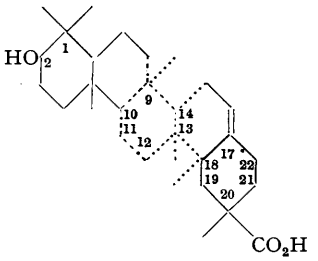
This, and other facts discovered in the course of the present work, have led us to consider afresh the position of the double bond in the acids of the β-amyrin group.



(I.)



(II.)



(III.)

Oleanolic acid being taken as typical, the requirements which have to be met are as follows : the unsaturated centre consists of a secondary and a tertiary carbon atom to allow the formation of a keto-lactone on oxidation, and there must be a methylene group next to it to account for the formation of αβ-unsaturated ketones, such as keto-oleanolic acid, thus :

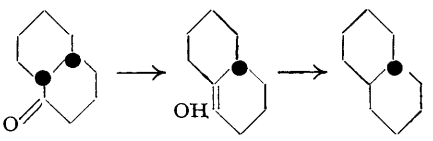
$$>C{:}CH{\cdot}CH_2— \quad \text{or} \quad —CH{:}C{\cdot}CH_2—$$

The task is simplified by the additional requirements, besides that already mentioned above, due to the new observations recorded in Parts XIV and XV which are that two methylene groups should be adjacent to the unsaturated centre. These represent the oxygen-bearing atoms of keto-oleanolic and of siaresinolic acid. Both these atoms are in proximity to the carboxyl group, as shown by the facilitation of hydrolysis of esters when either of the methylene groups is replaced by a carbonyl group. Neither of these groups can be situated in the same ring as the double bond, because when a double bond is introduced between them, this is conjugated with the double bond originally present and gives rise to selective absorption of light at a wave-length of *ca.* 2500 A., which is typical of a diene with conjugated double bonds distributed between two rings (compare, *e.g.*, Picard and Spring, J., 1941, 35). For the formulation of quillaic and echinocystic acid it is necessary that yet another methylene group, not identical with either of those already mentioned, should be situated next to the carbon atom bearing the carboxyl group. The unsaturated centre is thus part of the system

$$—CH{:}\underset{\gamma}{C}{\cdot}CH_2{\cdot}CH_2{\cdot}CR(CO_2H){\cdot}CH_2—$$

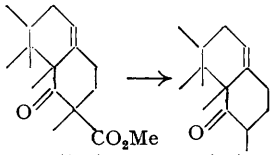
This has to be introduced into the 1 : 8-dimethylperhydropicene skeleton, which must be assumed to constitute the framework of the triterpene structure. It will be seen that, quite apart from the evidence of surface-film measurements which indicates the position of the carboxyl group in a terminal ring,* the only position in which the above system can be introduced is with the carboxyl group on C_{20} and the double bond in ring D. All the constituent atoms of ring E are thus accounted for, also a part of ring D. The parts of the molecule which had been completely elucidated by previous work included the whole of ring A and a part of ring B (the evidence for this has been fully summarised by Haworth, *Ann. Reports*, 1937, **34**, 327, and need not be recapitulated here; compare also the structure of bassic acid, J., 1940, 713); these have been embodied in formula (III) and shown in full lines. Our knowledge of the remainder of the molecule, which is shown in (III) by means of dotted lines, is derived from the dehydrogenation experiments of Ruzicka and his school (these also are summarised, *loc. cit.*); it includes ring C and three carbon atoms, assumed to belong to angular methyl groups, for which five positions are available. The arrangement shown in (III) is based on the isoprene hypothesis and the position of a methyl group on C_9 is retained from the older formulation. Another methyl group is placed on C_{13}, rather than on C_{14} as in the older formulæ (both arrangements are in agreement with the isoprene rule); the evidence for this is not yet complete and a discussion of it is reserved for a future communication, but it may be stated that such an arrangement appears to be required for the formulation of amyradienol I (Picard and Spring, *loc. cit.*), in which there are two double bonds in one ring, probably ring D.

The evidence for a methyl group on C_{18} is not conclusive, but it appears necessary in order to explain several characteristic features of quillaic and echinocystic acid. For instance, the existence of two series of mono- and di-ketones derived from echinocystic acid has been interpreted as due to stereoisomerism of the *cis-trans* α-decalone type (Bilham and Kon, J., 1940, 1469). The labile dextrorotatory ketones, *e.g.*, *iso*norechinostynenedione, pass into the stable lævorotatory compounds, such as norechinocystenedione, on treatment with alkali; a similar change is known to take place when *cis*-α-decalone is treated with alkali and is interpreted as involving enolisation towards the bridge head, for which the presence of a hydrogen atom is prerequisite :

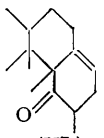


* It is hoped shortly to submit independent proof of this, based on purely chemical evidence.

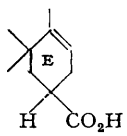
The new position for the double bond now put forward is not incompatible with stereoisomerism of this type, but it becomes necessary to explain why these ketones show no tendency to pass into their αβ-unsaturated isomerides as might be expected (compare James, Todd, and Noller, *J. Amer. Chem. Soc.*, 1939, **61**, 2421); such a change occurs very readily in derivatives of siaresinolic acid (Part XV, p. 541). An angular methyl group on C_{18} affords a natural explanation of this difference, and also of the hydrolysis of the ketonic esters (partial structure IV) derived from quillaic and echinocystic acid with loss of the carbomethoxy-group (Elliott, Kon, and Soper, J., 1940, 612; Noller and White, *J. Amer. Chem. Soc.*, 1939, **61**, 983), giving ketones (V), in contrast to derivatives of siaresinolic acid. The carbonyl group in the former series of compounds can only enolise by displacement of the carbomethoxy-group, whereas in the latter an alternative mechanism is available.



(IV.) (V.)



(VI.)

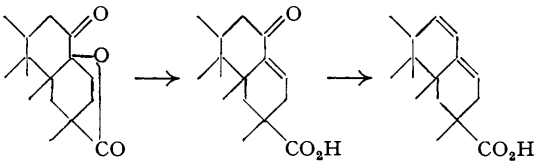


(VII.)

The precise nature of the isomerism between the two series of ketones still awaits an explanation; it may be due to the wandering of the double bond into ring E, in which case the marked lævorotation of the alkali-stable ketones of the partial structure (VI) would find a parallel in that of similarly constituted derivatives of siaresinolic acid.* An alternative explanation would be epimerisation about C_{20}, through the intermediate formation of an enol.

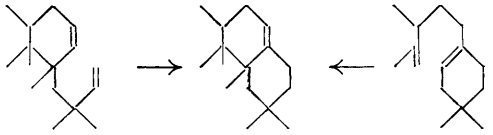
An apparent obstacle to the formulation discussed above is the decarboxylation of echinocystic acid with loss of water and formation of norechinocystadienol (Part XIV, p. 536); this must involve a retropinacolic change, in which case this compound should afford a valuable point of attack on the structural problem under discussion.

The formula (III) does not afford such an easy explanation of the results of dehydrogenation, notably of the formation of sapotalene (1 : 2 : 7-trimethylnaphthalene) from triterpenes, as the older formulation with a methyl group on C_{14}; it may, however, be pointed out that the mechanism by which this and other naphthalene derivatives are produced is in any case not fully understood. A cursory survey of the principal reactions of the triterpenes of the β-amyrin group shows that the new formula explains them adequately, with the possible exception of the experiments of Ruzicka, Cohen, and Sluys-Veer (*Helv. Chim. Acta*, 1939, **22**, 350). For example, the formation of the *iso*-keto-acids, and of the dehydro-compounds derived from them, from keto-lactones (Kitasato, *Acta Phytochim.*, 1935, **8**, 315) is readily formulated:



The structure of the isomeric keto-acids is discussed in Part XIV. It appears likely that β-oleananic acid, which is lævorotatory like the derivatives of siaresinolic acid with a double bond in ring E, may be represented by a structure analogous to that of the *iso*-keto-acid; the difference in the sign of rotation still remains to be explained.

Finally, the conversion of basseol into β-amyrin acetate (Beynon, Heilbron, and Spring, J., 1937, 989), which constituted one of the difficulties of the older formulæ, can be pictured by one of the following schemes:



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* A similar reversal of the sign of rotation takes place on decarboxylation of quinovic acid (Wieland, Schmitt, and Hrubesch, *Annalen*, 1939, **539**, 219). Many reactions of the resulting pyroquinovic acid are in good agreement with the partial structure (VII).