[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF STANFORD UNIVERSITY]

Saponins and Sapogenins. XXVII. The Structure of the Triterpenoids

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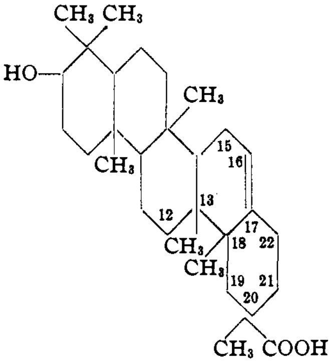
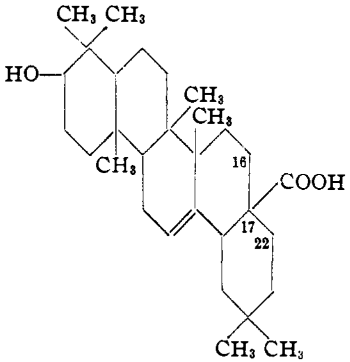
The most recent modification of the structure tentatively assigned to oleanolic acid is that represented by formula I.[1] The older formulation, II, was first suggested by R. D. Haworth[2] and still is considered to be the most satisfactory by Ruzicka.[3]



I



II

A number of triterpenoids have been shown to be closely related to oleanolic acid by interconversion reactions which have been summarized by Spring.[2] For example, conversion of the carboxyl group of oleanolic acid to a methyl group yields β-amyrin. Since both echinocystic acid[4] and siaresinolic acid[5] appear to be β-hydroxyoleanolic acids, they may be represented by formula I with the second hydroxyl group at either C-19 or C-21 or by formula II with the second hydroxyl at C-16 or at C-22.

The ultraviolet absorption spectra of the diketo methyl ester obtained by oxidation of methyl echinocystate and of norechinocystenedione, the diketone derived from the diketomethyl ester by saponification,[4a] show that neither of the carbonyl groups in either compound is conjugated with the carbon–carbon double bond.[6c] The same conclusion is reached for the diketo methyl ester derived from siaresinolic acid.[5] This diketo methyl ester, however, on saponification yields a diketo acid whose absorption spectrum is that of an α,β-unsaturated ketone, indicating that the double bond has moved to a position of conjugation with a carbonyl group. On the basis of these results, the β-hydroxyl group in echinocystic acid was assigned to C-19[1] and that in siaresinolic acid to C-21[5] in formula I.

Two new experimental facts now have indicated that the β-hydroxyl group of echinocystic acid cannot be located at C-19 in formula I. (1) Although norechinocystenedione does not contain an α,β-unsaturated ketone group, refluxing an alcoholic solution of the dione with butyl mercaptan and hydrogen chloride causes the double bond to shift to a position of conjugation.[6b] This result would be possible on the basis of structure I (C=O at C-2 and at C-19 and H replacing COOH) only by a shift of the double bond and migration of a methyl group. (2) Monoacetyl methyl echinocystate has been converted by dehydration and catalytic hydrogenation into methyl acetyloleanolate. For this reaction, structure I (OH at C-19) for echinocystic acid is wholly inadequate. If dehydration took place with the migration of a methyl group, the two double bonds would be conjugated and the rearranged product would not be expected to yield oleanolic acid on hydrogenation.

Structure II with a hydroxyl group at either C-16 or C-22 could be made to accommodate the reactions of echinocystic acid without too much difficulty but unfortunately there are other objections to this formula. Besides the results of surface film measurements on dehydroxyoleanolic acid,[7] which cannot be lightly dismissed, the reported absorption spectra of triterpenoid derivatives containing the α,β-unsaturated ketone group or the conjugated diene group do not agree with the expected values[8] for formulas based on structure II for oleanolic acid.

Several of the α,β-unsaturated ketones have been obtained by direct oxidation of the triterpenoid with chromium trioxide. Some investigators apparently have assumed[9,10] that the methylene group adjacent to the double bond is oxidized to a carbonyl group in which case the position of the double bond remains unchanged. A more likely interpretation of the reaction is given by Haworth[2] who assumes that the carbonyl group arises by a series of reactions, namely, oxidation of the double bond to the glycol, dehydration to an α,β-unsaturated secondary alcohol and oxidation

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[1] Bilham, Kon and Ross, *J. Chem. Soc.*, 532 (1942).

[2] R. D. Haworth, *Ann. Repts. Prog. Chem.*, **34**, 327 (1937). This review and that of Spring, *ibid.*, **38**, 191 (1941), cover the previous work on the structure of the triterpenoids.

[3] Ruzicka and co-workers, *Helv. Chim. Acta*, **26**, 265, 280 (1943). Only abstracts of these articles are available to us at present [cf. *Chem. Abs.*, **38**, 346, 348 (1944)].

[4] (a) White and Noller, THIS JOURNAL, **61**, 983 (1939); (b) Todd, Harris and Noller, *ibid.*, **62**, 1624 (1940); (c) Frazier and Noller, *ibid.*, **66**, 1267 (1944).

[5] Bilham, Kon and Ross, *J. Chem. Soc.*, 540 (1942).

[6] (a) Jones, Todd and Noller, THIS JOURNAL, **61**, 2421 (1939); (b) Carson, Cosulich and Noller, *ibid.*, **66**, 1267 (1944); (c) Cosulich, Thesis, Stanford University, 1943, p. 60.

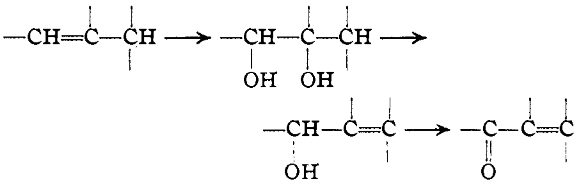
[7] Bilham and Kon, *Nature*, **147**, 745 (1941); *J. Chem. Soc.*, 552 (1941).

[8] Woodward, THIS JOURNAL, **63**, 1123 (1941); **64**, 72, 76 (1942); Evans and Gillam, *J. Chem. Soc.*, 815 (1941).

[9] Ruzicka and Jeger, *Helv. Chim. Acta*, **24**, 1236 (1941).

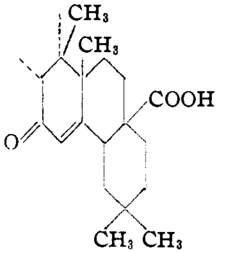
[10] Picard and Spring, *J. Chem. Soc.*, 35 (1941).

of the latter compound to the α,β-unsaturated ketone. These steps require that the double bond

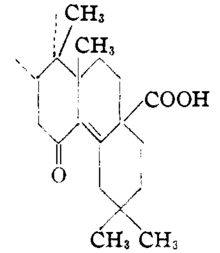


$$-CH=C-CH \longrightarrow -\underset{OH}{CH}-\underset{OH}{C}-CH \longrightarrow -\underset{OH}{CH}-C=C \longrightarrow -\underset{\overset{\|}{O}}{C}-C=C$$

shift its position.[11] On the basis of the first mechanism, formula II could give rise to partial formula III[12] while the second mechanism would lead to partial formula IV. Structure III is that



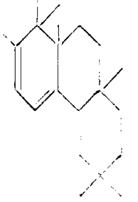
III



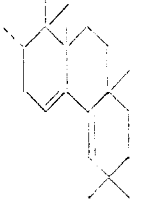
IV

of a β,β-substituted ketone with a singly exocyclic double bond for which the absorption maximum in alcohol would be expected to be at 240 mμ while structure IV is an α,β,β-substituted ketone with a doubly exocyclic double bond and presumably would give a high intensity band at 257 mμ.[8] The observed maxima for compounds which have been assigned one of the above structures are: ketoacetyloleanolic acid, 255[13]; isoketoacetyloleanolic acid, 248[14]; methyl isoketoacetyloleanolate, 249[15]; keto-β-amyrin, 245[16]; keto-β-amyrinacetate, 245[17]; β-amyrenedione, 251[18]; iso-keto-β-amyrin acetate, 247[15]; keto-α-amyrin benzoate, 245[19]; isoketo-α-amyrin, 250[20]; isoketo-α-amyrin acetate, 251[21]; hydroxyketo-α-amyrin, 250[17]; acetylglycyrrhetinic acid, 250[13]; acetyl dienone derived from glycyrrhetinic acid, 250[22]; dimethyl ketoacetylquinovate, 250[23]; methyl β-siaresinonate, 251[5]; conjugated norechinocystenedione, 252[6b]. It can be seen that with the exception of ketoacetyloleanolic acid, none of the observed positions of the absorption maxima agree with the values predicted for structure III or IV.[24]

A similar situation exists with respect to a number of conjugated dienes derived from the triterpenoids by various procedures. The most direct method is by oxidation of the triterpenoid with selenium dioxide which removes two hydrogen atoms to introduce a double bond in conjugation with that already present. On the basis of formula II, structure V or VI would be expected.[25] Structure V has both double bonds in one ring and



V



VI

would be expected to absorb in the region 255–290 mμ.[8] Triterpenoids having this structure apparently show an absorption maximum at 282 mμ.[26] Structure VI has four substituents on the conjugated system which is doubly exocyclic leading to an expected maximum of 247 mμ.[8] The observed maxima for compounds obtained by oxidation with selenium dioxide are as follows[27]: methyl acetyldehydroöleanolate, 252[28,29]; methyl

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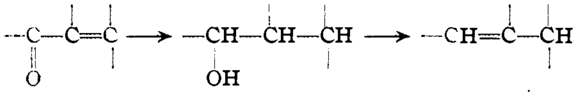
(11) The assumption that a methylene group adjacent to the double bond is oxidized to a carbonyl group probably is based on the fact that the original compounds are regenerated on catalytic hydrogenation (cf. Ref. 17). The same result would be obtained, however, by the following series of reactions



$$-\underset{\overset{\|}{O}}{C}-C=C \longrightarrow -CH-\underset{OH}{CH}-CH \longrightarrow -CH=C-CH$$

(12) β-Amyrin has a methyl group in place of the carboxyl group. In the subsequent discussion of absorption spectra, the data for derivatives of other triterpenoids have been included since analogous formulas have been proposed for these compounds.

(13) Ruzicka and Cohen, *Helv. Chim. Acta*, **20**, 804 (1937).

(14) Ruzicka, Cohen, Furter and Sluys-Veer, *ibid.*, **21**, 1735 (1938).

(15) Picard, Sharples and Spring, *J. Chem. Soc.*, 1045 (1939).

(16) Ruzicka, Müller and Schellenberg, *Helv. Chim. Acta*, **22**, 758 (1939).

(17) Beynon, Sharples and Spring, *J. Chem. Soc.*, 1233 (1938).

(18) Picard and Spring, *ibid.*, 1198 (1940). The α,β-unsaturated ketone grouping in this compound is considered to have the same structure as that in keto-β-amyrin in spite of the difference of 60 Å. in the position of the absorption maxima.

(19) Ruzicka, Müller and Schellenberg, *Helv. Chim. Acta*, **22**, 767 (1939).

(20) Seymour, Sharples and Spring, *J. Chem. Soc.*, 1075 (1939).

(21) Ewen and Spring, *ibid.*, 1197 (1940).

(22) Ruzicka and Jeger, *Helv. Chim. Acta*, **25**, 775 (1942).

(23) Ruzicka and Prelog, *ibid.*, **20**, 1570 (1937).

(24) From time to time formulas other than III or IV have been proposed for individual α,β-unsaturated compounds but none of these structures nor any derived from formula I satisfy the observed absorption maxima. The same statement applies to the following discussion of the data for the conjugated dienes.

(25) Guillemonat, *Ann. chim.*, [11] **11**, 165 (1939).

(26) Ref. 15, 17, 18 and 20; Simpson, *J. Chem. Soc.*, 230 (1940).

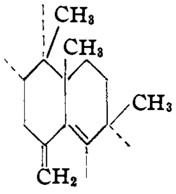
(27) The values given are those assigned by the authors. It should be noted, however, that a number of the compounds produced by oxidation with selenium dioxide show a definite fine structure in the region of the maximum. Thus methyl acetyldehydrodeoxoglycyrrhetate gives three maxima at 260, 250 and 240 mμ (log ϵ 4.30, 4.52 and 4.46, respectively[22,29]). Unpublished values for the maxima shown by the oxidation product of the monoketo methyl ester, $C_{31}H_{48}O_4$, derived from echinocystic acid, are 258, 248, 241 mμ (log ϵ 4.31, 4.47, 4.42). While methyl acetyldehydroöleanolate gives only two distinct maxima at 261 and 252 mμ (log ϵ 4.22, 4.38) there is an indication of a third maximum at 246 mμ (log ϵ 4.36).[29] β-Amyradienol-11 has been reported,[10,19] to show maxima at 260 and 251.5 mμ (log ϵ 4.26, 4.46). Although no fine structure appears in the absorption curve reported for methyl acetyldehydrosumaresinonate,[28] the curve for methyl acetyldehydroöleanolate given in the same article does not show fine structure either and it may be that the secondary maxima have not been recognized. The same statement applies to dehydro-β-amyrene for which only a single maximum has been reported.[19] It appears possible, at any rate, that oxidation with selenium dioxide may give rise to a special type of structure which we are not justified in predicting on the basis of the rules formulated by Woodward.

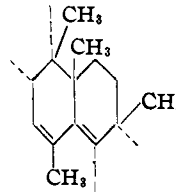
(28) Ruzicka, Grob and Sluys-Veer, *Helv. Chim. Acta*, **22**, 788 (1939).

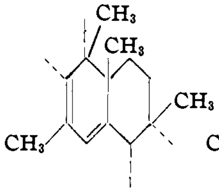
(29) Bilham, Kon and Ross, *J. Chem. Soc.*, 535 (1942).

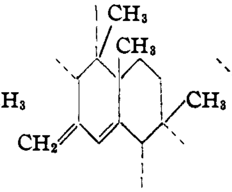
acetyldehydrodeoxoglycyrrhetate, 250[22,29]; β-amyradienol-II, 252[10,19]; dehydro-β-amyrene, 250[19]; methyl acetyldehydrosumaresinonate, 252.[28]

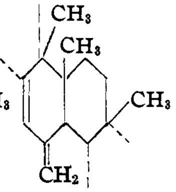
Two conjugated dienes have been obtained by dehydrating the alcohols formed by the reaction of methylmagnesium iodide with keto-α-amyrin and keto-β-amyrin. Assuming formulas III and IV to be the possible structures of the carbonyl compounds on the basis of formula II (CH_3 in place of COOH), IV would be expected to give rise to either VII or VIII while III would give either IX or X. Structure XI also has been postulated for the product derived from keto-α-amyrin.[20]


VII


VIII

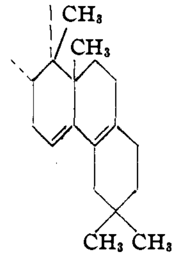

IX

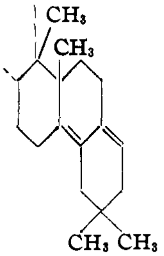

X

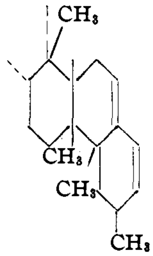

XI

Both VII and VIII would be expected to show intense absorption at 252 mμ. For IX the absorption should be at wave lengths greater than 255 mμ while X and XI should absorb at 242 mμ. The observed maxima are: homo-α-amyradienol, 245 mμ[19]; homo-α-amyradienyl acetate, 240 mμ[19,30]; homo-β-amyradienyl acetate, 240 mμ.[19] Either structure X or XI is compatible with the absorption data but there seems to be no good reason for thinking that this agreement is not fortuitous in view of the lack of agreement in the case of the α,β-unsaturated ketones from which they are derived.

Two other conjugated dienes may be considered. Norechinocystadienol, obtained by the decarboxylation and dehydration of echinocystic acid,[31] may be expected on the basis of formula II (OH at C-16 or C-22) to have partial structure XII, XIII or possibly VI. For a diene hydrocarbon isolated as a by-product in the reduction of norsiaresinone, partial formula XIV has been suggested.[5] The positions of the absorption maxima for these four structures would be expected to be: XIV, 237; VI and XII, 247; XIII, 257 mμ. Norechinocystadienol and the diene from norsiaresinone absorb at 241[31] and 240 mμ,[5] respectively.


XII


XIII


XIV

While we have not succeeded in devising a formula which will fit all of the chemical reactions and the absorption data, it seems to us that Woodward's correlations between absorption spectra and structure cannot be ignored and that the following conclusions may be drawn: ketoacetyl oleanolic acid (max. 255 mμ) is an α,β,β-substituted ketone conjugated with a doubly exocyclic double bond (expected value 257 mμ); that the eight α,β-unsaturated ketones with absorption maxima between 250 and 252 mμ are α,β,β-substituted with a singly exocyclic double bond (expected value 252 mμ); that the five compounds with maxima between 245 and 248 mμ are α,β,β-substituted ketones in which the conjugated double bond is not exocyclic (expected value 247 mμ). Of the conjugated dienes, those showing a maximum absorption in the neighborhood of 252 mμ have either six substituents and one exocyclic double bond or five substituents and two exocyclic double bonds or five substituents and one doubly exocyclic double bond (expected value 252 mμ). It is possible that those showing fine structure in the absorption band may not fall under Woodward's classification. The dienes with maxima at 240 to 241 mμ must have either four substituents and one exocyclic double bond or three substituents with both double bonds singly exocyclic (expected value, 242 mμ).

New methods of attack are needed to assist in the solution of this problem. It is hoped that anhydroechinocystic acid, in which a double bond has been introduced in the vicinity of the carboxyl group, may be useful for this purpose. The double bond can be hydrogenated readily and hence appears to be sufficiently reactive to be a point of attack for further degradation.

Summary

Currently proposed formulas for the β-amyrin group of triterpenoids are not consistent with the chemical behavior of echinocystic acid or of norechinocystenedione. Moreover, there is a general lack of correlation between the absorption spectra and the structures proposed for the α,β-unsaturated ketones and conjugated dienes derived from the triterpenoids. It is suggested that anhydroechinocystic acid should be a valuable starting point for further degradation reactions.

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(30) The difference of 50 Å. in the positions of the maxima of the alcohol and the acetate seems too large to be ascribed to the difference in solvents used and would indicate that the double bonds may not occupy the same positions in the two compounds. The value of 250 mμ for homo-α-amyradienol as given in the text (Ref. 19, p. 768) appears to be a typographical error, since 245 mμ is given in two places in the experimental part (pp. 776, 777).

(31) Noller and Carson, THIS JOURNAL, 63, 2338 (1941).