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SOME DERIVATIVES OF OLEANOL

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CCXVII.—*Some Derivatives of Oleanol.*

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In a former communication (T., 1908, **93**, 896) Dr. Power and one of us described the isolation from olive leaves of a crystalline substance, which was designated oleanol. It was shown that oleanol possessed the formula $C_{31}H_{50}O_3$, and that it contained two hydroxyl groups, one of which had phenolic properties. Thus, on methylation with methyl iodide and sodium ethoxide, oleanol yielded a monomethyl derivative, and the latter, on acetylation, gave a monoacetyl compound. Oleanol itself was shown to afford a diacetyl derivative, which, on heating with dilute alcohol, lost one acetyl group, yielding monoacetyloleanol.

It was also shown (*loc. cit.*) that when diacetyloleanol (m. p. 208°) is heated above its melting point it underwent some change, gas being evolved, and a compound formed which did not melt at 310°. The analysis of the latter compound indicated it to possess the formula $C_{31}H_{48}O_3$, and, since it was not affected by alkalis, it

was concluded that it had been formed by the elimination of the two acetyl groups from diacetyloleanol.

More recently, Power and Moore (T., 1910, **97**, 1104) isolated from the leaves of *Prunus serotina* a substance isomeric with oleanol. This compound, which was strictly analogous to oleanol in its properties, was designated prunol. Diacetylprunol, on heating, underwent a change similar to that suffered by diacetyloleanol, but in this case it was conclusively shown that the reaction consisted in the elimination of one molecule of acetic anhydride from two molecules of the diacetyl compound. The product of high melting point (315°) has the composition $C_{66}H_{102}O_7$, but, since it is not affected by heating with alcoholic potassium hydroxide, it is probable that some change had occurred other than the condensation consequent upon the elimination of acetic anhydride.

A quantity of the alcoholic extract of olive leaves being available, it was considered of interest to pursue the investigation of oleanol with the hope of throwing some light on its constitution, and also to ascertain whether the behaviour of the diacetyl derivative on heating was analogous to that of diacetylprunol.

Although the amount of oleanol available did not permit of much information being gained regarding the constitution of a substance of so large a formula, a number of interesting derivatives have been prepared from it.

With regard to the change suffered by the diacetyl derivative on heating, it has now been ascertained that this reaction proceeds analogously to that undergone by diacetylprunol, and results in the formation of a substance possessing the formula $C_{66}H_{102}O_7$. The misleading analytical results previously obtained by Power and Tutin have been found to be due to the persistent retention of benzene, which was employed for the crystallisation of the compound in question.

When oleanol, $C_{31}H_{50}O_3$, is oxidised with potassium permanganate in acetic acid solution it yields a dihydroxy-compound having the formula $C_{29}H_{46}O_4$. It would appear, therefore, that oleanol contains the group $CH_3{\cdot}CH{:}C<$, and that this undergoes oxidation, yielding acetic acid and a ketone. Although no direct evidence of the ketonic character of the substance $C_{29}H_{46}O_4$ was obtained, it would appear certain that it contains a carbonyl group, and it is proposed to designate it *oleanone*. It yields *mono-* and *di-acetyl* derivatives.

The reactions which ensued on heating oleanone and diacetyloleanone with acetic acid containing water and hydrochloric acid respectively were of an unexpected nature, and serve to explain the considerable difficulty which was at first experienced in preparing any appreciable quantity of the first-mentioned compound.

Oleanone, when heated with glacial acetic acid, undergoes no change, but if the acid is slightly diluted with water a pink colour rapidly develops, which changes, first to green, and then to a dull violet colour, the latter gradually fading. On removal of the acetic acid a product is obtained which is uncrystallisable, but yields a crystalline *acetyl* derivative having the formula

$$C_{50}H_{76}O_7 \cdot CO \cdot CH_3.$$

On hydrolysis, the latter yields the corresponding *alcohol*, $C_{50}H_{76}O_5(OH)_2$. This change may be accounted for, empirically, by the condensation of 2 molecules of oleanone, accompanied by the addition of one molecule of water and the elimination of the elements $C_8H_{16}O_2$:

$$2C_{29}H_{46}O_4 + H_2O = C_{50}H_{78}O_7 + C_8H_{16}O_2.$$

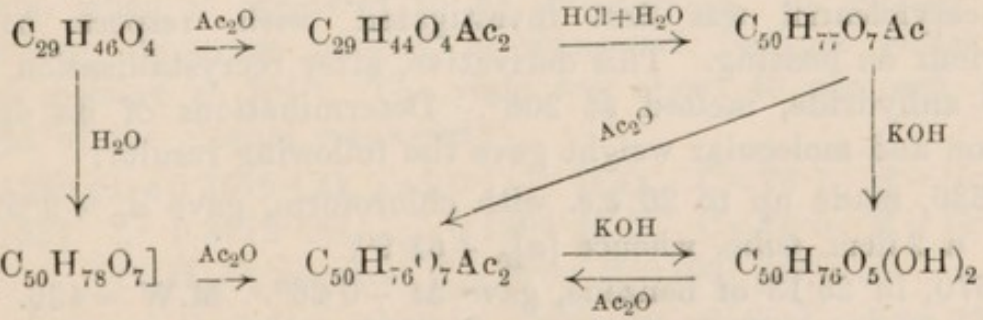
There are several ways possible in which such a change could occur, but the amount of material available was not sufficient to permit of the determination of the exact course of the reaction.

The above-described reaction is of interest inasmuch as the changes of colour closely resemble those produced by a phytosterol when treated with a drop of sulphuric acid in the presence of acetic anhydride. It is possible, therefore, that some similar condensation may take place in the case of the phytosterols.

When diacetyloleanone is heated with acetic acid containing aqueous hydrochloric acid, an analogous reaction occurs. The same change of colours takes place, and a *compound*, $C_{50}H_{77}O_7 \cdot CO \cdot CH_3$, results. The latter proved to be the monoacetyl compound corresponding with the above-mentioned diacetyl derivative,

$$C_{50}H_{76}O_7(CO \cdot CH_3)_2.$$

On acetylation it yielded the latter, and on hydrolysis with alkali it gave the dihydroxy-compound, $C_{50}H_{76}O_5(OH)_2$. These changes may be represented as follows:



The further oxidation of oleanone, $C_{29}H_{46}O_4$, could not be effected by means of potassium permanganate, and recourse was therefore had to the use of chromic acid. This resulted in the formation of a *substance*, $C_{29}H_{42}O_4$, and, since the latter yields only a *monoacetyl* derivative, it would appear that the alcoholic hydroxyl group originally present in oleanol had been oxidised to a keto-group. The other two atoms of hydrogen removed are possibly accounted

for by the oxidation of a reduced aromatic nucleus. When the substance, $C_{29}H_{42}O_4$, which melts at 275°, was submitted to the fairly prolonged action of alcoholic potassium hydroxide it was converted into an isomeride, melting at 315°. If, however, the action of the alkali was still more prolonged further, and more profound, changes occurred.

The direct oxidation of oleanol by means of a warm solution of chromic acid in acetic acid resulted in the formation of the above-mentioned compound, $C_{29}H_{42}O_4$, together with a mixture of carboxylic acids. It was ascertained that the latter contained at least three compounds, but no crystalline acid could be isolated from it.

Experimental.

The alcoholic extract of olive leaves from which the oleanol was obtained was the same as that employed for the investigation of the constituents of olive leaves (T., 1908, **93**, 891). It was mixed with water and distilled in a current of steam for the removal of the volatile constituents, after which the resin was separated from the aqueous liquid. The resin was then mixed with purified sawdust, and the thoroughly dried mixture extracted, first with petroleum (b. p. 35—50°), and then with ether. The ether extract consisted largely of crude oleanol, which separated as a green, sparingly soluble powder. The latter was collected, and crystallised from alcohol with the employment of animal charcoal, when pure oleanol was obtained in slender, colourless crystals, melting at 304°. The mother liquors from this substance gave further amounts of oleanol in an impure, amorphous condition, from which the pure compound was obtained by means of the acetyl derivative. The latter, on treatment with alcoholic potassium hydroxide, yielded pure oleanol.

Diacetyloleanol was first investigated with respect to its behaviour on heating. This derivative, after recrystallisation from acetic anhydride, melted at 208°. Determinations of its optical rotation and molecular weight gave the following results:

0·4636, made up to 20 c.c. with chloroform, gave α_D +2°52′ in a 2-dcm. tube, whence $[\alpha]_D$ +61·9°.

0·5570, in 25·13 of benzene, gave Δt −0·26°. M.W. = 426.

$C_{35}H_{54}O_5$ requires M.W. = 554.

The somewhat low result of this molecular-weight determination may be accounted for by the great readiness with which diacetyloleanol undergoes partial hydrolysis.

A quantity (2 grams) of diacetyloleanol was heated in a distillation apparatus for some time at 240°, when a volatile substance was evolved, and collected in the receiver. This distillate was

identified by its general properties and boiling point as acetic anhydride. The solid residue in the distillation flask was dissolved in a small amount of hot petroleum (b. p. 90—120°), and boiling ethyl acetate added. A substance then separated in small, colourless, flattened prisms, which melted at 315—316°:

0·0995 * gave 0·2860 CO_2 and 0·0892 H_2O. C = 78·4; H = 10·0.

$C_{66}H_{102}O_7$ requires C = 78·7; H = 10·1 per cent.

It is thus evident that the change undergone by diacetyloleanol on heating is analogous to that suffered by diacetylprunol (Power and Moore, *loc. cit.*), and proceeds according to the following equation:

$$2C_{35}H_{54}O_5 = C_{66}H_{102}O_7 + (CH_3{\cdot}CO)_2O.$$

Oxidation of Oleanol with Potassium Permanganate. Formation of Oleanone, $C_{29}H_{46}O_4$.

A quantity (10 grams) of oleanol was dissolved in glacial acetic acid, and a solution of 7 grams of potassium permanganate in a large volume of 95 per cent. acetic acid then gradually added. After keeping the mixture for an hour it was decolorised by means of sulphur dioxide, when, on pouring the solution into water, a quantity of solid was precipitated. The latter was isolated by means of ether, and the ethereal solution shaken with aqueous alkalis. This treatment, however, removed only acetic acid and relatively small amounts of amorphous products. The ethereal solution was then evaporated, and the residue crystallised from ethyl acetate. This was achieved only with considerable difficulty, owing to the great tendency of the product to separate in a colloidal condition. The material which had been once crystallised from ethyl acetate was then recrystallised several times from methyl alcohol, when it appeared to be dimorphous. It formed either glistening, colourless needles, or elongated, lustrous plates, both forms melting at 304°. The yield was about 40 per cent. of the weight of the oleanol employed:

0·1299 gave 0·3625 CO_2 and 0·1170 H_2O. C = 76·1; H = 10·0.

0·1331 „ 0·3712 CO_2 „ 0·1202 H_2O. C = 76·0; H = 10·0.

$C_{29}H_{46}O_4$ requires C = 76·0; H = 10·0 per cent.

It appears, therefore, that on oxidation oleanol suffers the loss of the elements C_2H_4 and the addition of one atom of oxygen. It is highly probable that the resulting product, $C_{29}H_{46}O_4$, is a ketone, although no oxime could be prepared from it, and it is proposed to designate it *oleanone*.

Oleanone is moderately soluble in most organic solvents, and a

* Dried at 130°.

determination of its optical rotatory power gave the following result:

0·3760, made up to 20 c.c. with chloroform, gave α_D +1°31′ in a 2-dcm. tube, whence $[\alpha]_D$ +40·4°.

Diacetyloleanone, $C_{29}H_{44}O_4(CO\cdot CH_3)_2$.—A quantity of oleanone was heated for some time with acetic anhydride, after which the mixture was poured into water, and the resulting solid collected. The latter was crystallised from a mixture of alcohol and ethyl acetate, when pure *diacetyloleanone* was obtained. This substance, like the corresponding dihydroxy-ketone, appears to be dimorphous. It forms either well-defined, colourless needles, or flat plates. Both forms melt sharply at 293°:

0·1371 gave 0·3682 CO_2 and 0·1173 H_2O. C=73·2; H=9·5.

$C_{33}H_{50}O_6$ requires C=73·1; H=9·2 per cent.

A determination of the specific rotatory power gave the following result:

0·3966, made up to 20 c.c. with chloroform, gave α_D +2°27′ in a 2-dcm. tube, whence $[\alpha]_D$ +61·8°.

Unlike diacetyloleanol, this diacetyl derivative does not undergo hydrolysis with the formation of a monoacetyl derivative when heated with 75 per cent. alcohol.

Monoacetyloleanone, $C_{29}H_{45}O_4\cdot CO\cdot CH_3$.—A considerable quantity of impure material contained in the mother liquors from the crystallisation of crude diacetyloleanone was fractionally crystallised, when, in addition to the last-mentioned compound, a small amount of another substance was obtained. The latter formed well-defined, colourless needles, melting at 260°:

0·1038 gave 0·2831 CO_2 and 0·0878 H_2O. C=74·4; H=9·4.

$C_{31}H_{48}O_5$ requires C=74·4; H=9·6 per cent.

This substance thus appeared to be *monoacetyloleanone*, and, when hydrolysed with alcoholic potassium hydroxide, oleanone was regenerated from it. It is more soluble in alcohol and less so in ethyl acetate than the corresponding diacetyl derivative, but is freely soluble in chloroform. Its optical rotatory power was determined with the following result:

0·4147, made up to 20 c.c. with chloroform, gave α_D +3°3′ in a 2-dcm. tube, whence $[\alpha]_D$ +73·5°.

When the ketone was regenerated from either of its acetyl derivatives the product obtained usually consisted of a mixture of the above-mentioned dimorphous forms.

Action of Dilute Acetic Acid on Oleanone.

The oxidation of oleanol necessitated the use of a large volume of acetic acid (3 litres for 10 grams of the alcohol), and this was

also inconvenient for the isolation of the oxidation product. In a number of experiments, therefore, it was sought to recover the greater part of the acetic acid by distillation in a vacuum before the reaction mixture containing the oxidation product had been poured into water. When this was done, however, it was found very difficult, or impossible, to isolate any pure oleanone from the oxidation product, the latter being, for the most part, uncrystallisable. It was thus evident that the evaporation of the acetic acid with the aid of heat had caused some change to take place, and it was at first thought that this might be due to the partial acetylation of the oxidation product by the acetic acid in the presence of the manganous sulphate which had been formed during the treatment of the oxidation mixture with sulphur dioxide. A quantity (1 gram) of pure oleanone was therefore dissolved in acetic acid, and such an amount of manganous sulphate added, dissolved in a little water, as would have been formed during the preparation of one gram of oleanone. The mixture was boiled for three hours, after which it was concentrated in a vacuum and poured into water. The product was then extracted with ether, when some yellow, uncrystallisable material was obtained. The latter was heated for some time with acetic anhydride, after which the mixture was poured into water, and the resulting solid collected. The latter was crystallised several times from dilute alcohol, when small, colourless plates were obtained, which, on heating, first softened, and then melted at 324°. This substance was evidently a new compound, being quite distinct from diacetyloleanone, and it was thus evident that heating with acetic acid and manganous sulphate did not cause simply partial acetylation, as had been thought, but that some more profound change had occurred.

The action of anhydrous acetic acid alone on oleanone was therefore investigated, but, after boiling for several hours, the original ketone could be recovered unchanged. When, however, a small amount of water was added to a solution of oleanone in boiling glacial acetic acid, a pink colour rapidly developed, which gradually changed to green, and finally to a faint violet tint. On isolating the resulting product, only uncrystallisable material was obtained, but, on acetylation, the latter yielded the above-described acetyl derivative, melting at 324°. It is evident, therefore, that oleanone is radically changed by the action of hot dilute acetic acid.

The *diacetyl* derivative, $C_{50}H_{76}O_7(CO\cdot CH_3)_2$ (m. p. 324°), was moderately soluble in alcohol and ethyl acetate, but more readily so in chloroform or benzene. After drying at 125°, it yielded the following results:

0·1537 gave 0·4164 CO_2 and 0·1308 H_2O. C=73·9; H=9·4.
0·1067 „ 0·2896 CO_2 „ 0·0922 H_2O. C=74·0; H=9·6.
0·5208, in 24·0 of benzene, gave Δt −0·13°. M.W.=853.
$C_{54}H_{82}O_9$ requires C=74·1; H=9·4 per cent. M.W.=874.

A quantity of the acetyl derivative was hydrolysed by means of alcoholic potassium hydroxide, and the resulting substance isolated. The latter was crystallised from ethyl acetate containing a small amount of alcohol, when it separated in very thin, colourless plates, which melted at 312°:

0·1028 gave 0·2814 CO_2 and 0·0926 H_2O. C=74·7; H=10·0.
$C_{50}H_{78}O_7$ requires C=74·7; H=9·9 per cent.

Action of Acetic and Hydrochloric Acids on Diacetyloleanone.

A quantity (4 grams) of diacetyloleanone was dissolved in glacial acetic acid, and 15 per cent. hydrochloric acid added to the hot liquid until a faint cloudiness was produced. The mixture was then boiled for some time, when the previously-described cycle of colour changes occurred, at the completion of which a substance separated from the boiling liquid in colourless, glassy plates. After recrystallisation from methyl alcohol, this substance melted at 332°:

0·1417 gave 0·3904 CO_2 and 0·1226 H_2O. C=75·2; H=9·6.
0·1316 „ 0·3626 CO_2 „ 0·1154 H_2O. C=75·2; H=9·7.
$C_{52}H_{80}O_8$ requires C=75·0; H=9·7 per cent.

This compound proved to be the *monoacetyl* derivative of the previously-described dihydroxy-compound, melting at 312°. On hydrolysis with alcoholic potassium hydroxide it yielded the latter, and on acetylation it gave the diacetyl derivative. (Found, C=74·1; H=9·6. Calc., C=74·1; H=9·4 per cent.) The melting point of the diacetyl derivative when prepared in this manner, however, could not be raised above 292°, but this was doubtless due to the persistent retention of a very small amount of impurity. In all other respects the two preparations were identical, and no lowering of the melting point occurred on mixing them.

Oxidation of Oleanone with Chromic Acid.

As oleanone could not be further oxidised by means of potassium permanganate, recourse was had to the use of chromic acid.

A quantity (10 grams) of oleanone was dissolved in 1 litre of glacial acetic acid, and a solution of 13 grams of chromic acid in 150 c.c. of 75 per cent. acetic acid gradually introduced, the mixture being stirred, and maintained at 55—60°. Sulphur dioxide was

then passed into the mixture to remove any excess of chromic acid, and the solution poured into water. The mixture was subsequently extracted with ether, and the ethereal solution deprived of acetic acid by means of aqueous potassium hydroxide, washed, dried, and concentrated. A sparingly soluble, crystalline substance then separated from the solution. This was most conveniently recrystallised by extraction with ether in a Soxhlet apparatus, when it formed thin, lustrous, colourless plates, melting at 275°. The yield of pure material was 4·5 grams from 10 grams of oleanone:

0·1272 gave 0·3586 CO_2 and 0·1062 H_2O. C = 76·9; H = 9·3.
0·1357 „ 0·3811 CO_2 „ 0·1151 H_2O. C = 76·6; H = 9·4.
$C_{29}H_{42}O_4$ requires C = 76·7; H = 9·3 per cent.

This *compound* is thus seen to be formed from oleanone by the loss of 4 atoms of hydrogen. It was found to contain only one hydroxyl group, and is probably a diketone.

A small quantity of the substance $C_{29}H_{42}O_4$ was acetylated by means of acetic anhydride, and the product crystallised from absolute alcohol. Long, colourless, hair-like needles were then obtained, which melted at 268°:

0·1027 gave 0·2815 CO_2 and 0·0842 H_2O. C = 74·8; H = 9·1.
0·3404, in 23·56 of benzene, gave Δt −0·147°. M.W. = 492.
$C_{31}H_{44}O_5$ requires C = 75·0; H = 8·9 per cent. M.W. = 496.

This *monoacetyl* derivative is moderately soluble in alcohol, somewhat more so in ethyl acetate, and readily so in chloroform or benzene.

Action of Potassium Hydroxide on the Compound $C_{29}H_{42}O_4$.

The substance $C_{29}H_{42}O_4$ could be recovered unchanged after being heated for a short time with fairly dilute alcoholic potassium hydroxide, and it could therefore be regenerated from its acetyl derivative. When, however, stronger alkali was employed, and the heating was more prolonged, further changes took place.

A quantity of the substance $C_{29}H_{42}O_4$ (m. p. 275°) was dissolved in fairly concentrated alcoholic potassium hydroxide, and the mixture heated for two hours. The liquid was then poured into water, acidified, and extracted with ether. On evaporation of the ether a product was obtained, which, when crystallised from a mixture of ethyl acetate and alcohol, separated in small, thin prisms, melting at 315°. The yield of the latter was by no means quantitative, and the mother liquors contained uncrystallisable material:

0·1017 gave 0·2867 CO_2 and 0·0849 H_2O. C = 76·9; H = 9·3.
0·1406 „ 0·3970 CO_2 „ 0·1182 H_2O. C = 77·0; H = 9·3.
$C_{29}H_{42}O_4$ requires C = 76·7; H = 9·3 per cent.

This *substance* therefore appears to be isomeric with the compound $C_{29}H_{42}O_4$ (m. p. 275°), from which it was obtained. A mixture of the two isomerides melted at 250—256°.

The new isomeride, melting at 315°, yielded a *monoacetyl* derivative on treatment with acetic anhydride. This derivative crystallised from ethyl acetate in colourless needles, melting at 308°:

0·1106 gave 0·3046 CO_2 and 0·0920 H_2O. C = 75·1; H = 9·2.

$C_{31}H_{44}O_5$ requires C = 75·0; H = 8·9 per cent.

Another portion of the original compound, $C_{29}H_{42}O_4$ (m. p. 275°), was dissolved in concentrated alcoholic potassium hydroxide, and the mixture boiled for three days, after which it was evaporated almost to dryness. The residue was then poured into water, acidified, and extracted with ether. On evaporating the ether a product was obtained, from which neither of the isomeric substances, $C_{29}H_{42}O_4$, could be obtained, and which was, for the most part, uncrystallisable. It yielded, however, a small amount of a substance, which crystallised in small leaflets, melting at 87—88°, and had the characters of a higher fatty acid:

0·0578 gave 0·1652 CO_2 and 0·0682 H_2O. C = 78·0; H = 13·1.

$C_{23}H_{46}O_2$ requires C = 78·0; H = 13·0 per cent.

The formation of a fatty acid, $C_{23}H_{46}O_2$, from the substance $C_{29}H_{42}O_4$ would account for the major portion of the molecule of oleanol, and would greatly facilitate the elucidation of the constitution of the latter. The change might take place according to the following equation:

$$C_{29}H_{42}O_4 + 4H_2O = C_{23}H_{46}O_2 + C_6H_4O_6.$$

Unfortunately, however, this point cannot be considered as definitely established, since the amount of material available only permitted of one further small experiment being conducted, and the latter did not result in the isolation of any more of the fatty acid in question. It is difficult to see, however, how the acid $C_{23}H_{46}O_2$ (m. p. 87—88°) could have been introduced from an extraneous source, particularly as no compound possessing this composition and melting point has hitherto been known. An acid possessing the same formula, but melting at 68°, has been shown to occur in olive leaves (Power and Tutin, *loc. cit.*), but it is impossible for any of this to have been occluded in the compound $C_{29}H_{42}O_4$ (m. p. 275°), which was hydrolysed, since the latter was prepared from pure oleanol, melting at 304°.

The action of concentrated alcoholic potassium hydroxide on oleanol itself was investigated, but was found to bring about no change.

Oxidation of Oleanol with Chromic Acid.

Oleanol was oxidised with chromic acid under the same conditions as those described in connexion with the oxidation of oleanone. At the completion of the oxidation the acetic acid solution was poured into water and extracted repeatedly with ether. The ethereal solution was then shaken with aqueous alkali, which removed acetic acid and a considerable amount of a mixture of solid carboxylic acids. The ethereal liquid then contained the above-described substance, $C_{29}H_{42}O_4$ (m. p. 275°), the yield of which was about 10 per cent. of the weight of the oleanol employed.

The above-mentioned mixture of carboxylic acids could not be crystallised, nor could any crystalline ester or salt be obtained from it. It was therefore converted into the barium salt, and the latter precipitated in seven fractions by concentrating its aqueous solution. The acid was then recovered from each of the fractions of barium salt, and the resulting products, all of which were amorphous, dried at 125°. Their analysis and the determination of their neutralisation values gave the following results:

Fraction.	Percentage of carbon.	Percentage of hydrogen.	Neutralisation value.
1	69·0	8·4	236
2	68·6	8·3	237
3	71·7	8·6	268
4	70·7	8·6	268
5	69·4	8·5	243
6	69·7	8·4	230
7	68·3	8·0	221

It is thus evident that the direct oxidation of oleanol by means of chromic acid results in the formation of at least three carboxylic acids, in addition to the above-described substance, $C_{29}H_{42}O_4$.

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