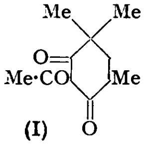
670. *β-Triketones. Part I. The Structures of Angustione, Dehydroangustione, Calythrone, and Flavaspidic Acid.*

By Arthur J. Birch.

New formulæ are advanced for angustione (I),* dehydroangustione (II), calythrone (III),* and flavaspidic acid (XX), chiefly on the basis of published evidence assisted by some spectra and model reactions.

Various alkali-soluble substances have been isolated from plants which owe their acidity to the presence of three carbonyl groups attached to the same methine group. Among those about which considerable information is available are: leptospermone (IV) (Briggs, Hassall, and Short, *J.*, 1945, 706; Briggs, Hassall, and Taylor, *J.*, 1948, 383); calythrone, formulated as (V) by Penfold and Simonsen (*J.*, 1940, 412); angustione and dehydroangustione, formulated as (VI) and (VII) respectively (Gibson, Penfold, and Simonsen, *J.*, 1930, 1184; Cahn, Gibson, Penfold, and Simonsen, *J.*, 1931, 286); humulone and lupulone (Wöllmer, *Ber.*, 1925, **58**, 672; Wieland and Martz, *Ber.*, 1926, **59**, 2352); usnic acid (Curd and Robertson, *J.*, 1937, 898); and a number of substances from male-fern, among them albaspidin (XXI) and flavaspidic acid which was formulated as (XVII) (Boehm, *Annalen*, 1898, **302**, 171; 1899, **307**, 250; 1901, **318**, 230 *et seq.*; 1903, **329**, 310). Most of these substances have biological activity and they include anthelmintics, insecticides, and antibiotics.



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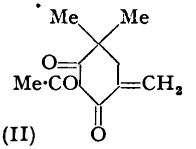

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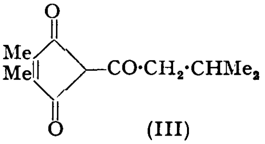

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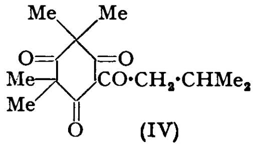

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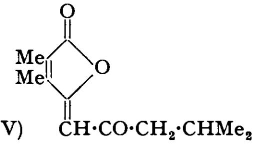

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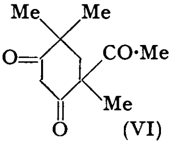

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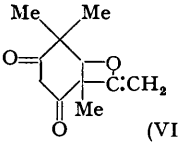

(VII)

Angustione and Dehydroangustione.—Angustione, $C_{11}H_{16}O_3$, and dehydroangustione, $C_{11}H_{14}O_3$, occur in admixture in the oil of *Backhousia angustifolia* and are separated with some difficulty by crystallisation of their imines, from which they can be regenerated with alkali (Simonsen *et al.*, *locc. cit.*). They give intense orange-red colours with ferric chloride and form copper salts which are soluble in some organic solvents. They react with one molecule of reagents such as hydroxylamine, phenylhydrazine, or semicarbazide with elimination of two molecules of water. Their principal transformations are shown in the annexed scheme.

There seems little doubt that (VIII) and (IX) are correctly formulated. They both react with piperonaldehyde in the manner characteristic of *cyclo*hexane-1 : 3-diones in the proportion of two molecules of ketone to one of aldehyde, giving products of the type (X). Angustione and dehydroangustione on the contrary give condensation products in molar proportions, which throws doubt on formulæ (VI) and (VII) since the CO·CH₂·CO system should be

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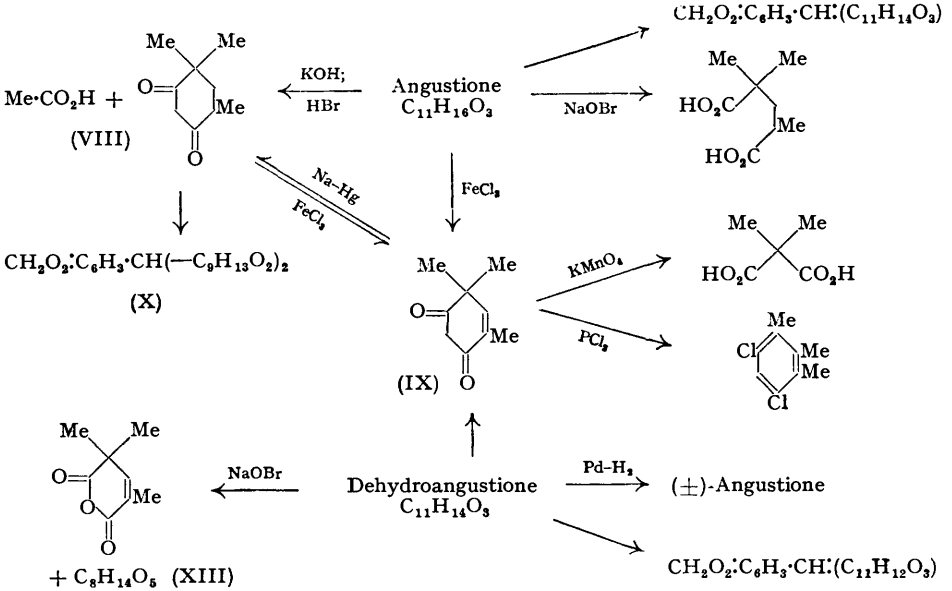
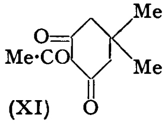
* Professor C. H. Hassall informs the author that he has independently derived the same formulæ for these two substances.

the reactive one (compare the action of formaldehyde on butanofilicinic acid; Boehm, *loc. cit.*). A study of the reaction of (XI) with piperonaldehyde showed that it forms a compound, similar to the derivatives of angustione and dehydroangustione, and formulated as (XII) since it is soluble in alkali and gives a deep brown colour with ferric chloride. Furthermore, copper salts and ferric colours of any intensity are not to be expected from (VI) and (VII) because the 1 : 3-diketo*cyclo*hexane system, although highly enolised, is *trans* and incapable of chelation; 5 : 5-dimethyl*cyclo*hexane-1 : 3-dione (dimedon) does not in fact show this behaviour. The reactions and properties of substances such as (XI) are closely similar to those of angustione and dehydroangustione (cf. Dieckmann and Stein, *Ber.*, 1904, **37**, 3370; Crossley and Renouf, *J.*, 1912, **101**, 1529): they give deep ferric colours, form bright blue copper salts soluble in chloroform, produce anhydro-derivatives with ketone reagents like hydroxylamine, and form crystalline imines from which they can be regenerated by alkali. The infra-red absorption spectrum of (XI) is very similar to those of angustione and dehydroangustione, showing in particular a series of strong bands in the region 6—7·5 μ. probably connected with the ketonic groupings and related structures. There seems little doubt that (I) correctly represents angustione, and its synthesis by standard methods is in hand.



Some difficulties remain in formulating dehydroangustione. It is obviously very closely related to angustione, and the presence in the infra-red absorption of a strong band at 11·75 μ. and an indication of a peak at 6·1 μ (partly obscured by the carbonyl band at 5·95 μ.) points to a $>C{:}CH_2$ group in the molecule. Formula (II) is therefore highly probable, but it contains



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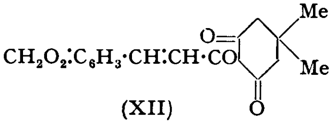

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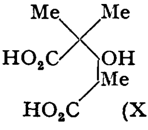
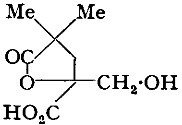


(XIV)



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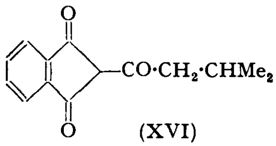


(XVI)

no asymmetric centre, and dehydroangustione is reported to be optically active. The rotation is low, however, and of the same sign as that of angustione, and Cahn *et al.* (*loc. cit.*) have pointed out that their dehydroangustione probably contained 20—25% of angustione. Another difficulty is the nature of the substance (XIII) obtained in the hypobromite oxidation. This was formulated as (XIV) on the basis of its reduction with hydriodic acid to ααγ-trimethylglutaric acid, and the closeness of its melting point (156—157°) to that (154—156°) reported by Perkin and Smith (*J.*, 1903, 776) for (XIV). However, if dehydroangustione is optically active, as was assumed on the basis of (VII), then (XIV) should also be optically active and its melting point is not a good criterion of comparison with the (±)-acid of Perkin and Smith. The compound was found to titrate as a monobasic acid in cold solution, and as a dibasic acid only with hot alkali. A more likely formulation is (XV), derived from (II), which would require $C_8H_{12}O_5$ instead of $C_8H_{14}O_5$. The ready conversion of itaconic acid into citraconic anhydride shows that a bond migration of the type required to give trimethylglutaconic anhydride might readily occur; similarly the formation of (IX) could easily occur through bond shift. If dehydroangustione is in fact optically active the only likely alternative formulation involves the presence of a *cyclo*propane ring. The parachors calculated on the basis of (I) and (II) are both about twenty units higher than the values found (Evans and Soper, *J.*, 1931, 289), but such anomalies are frequent with hydrogen-bonded substances. On the old formulæ angustione showed the anomaly and dehydroangustione did not.

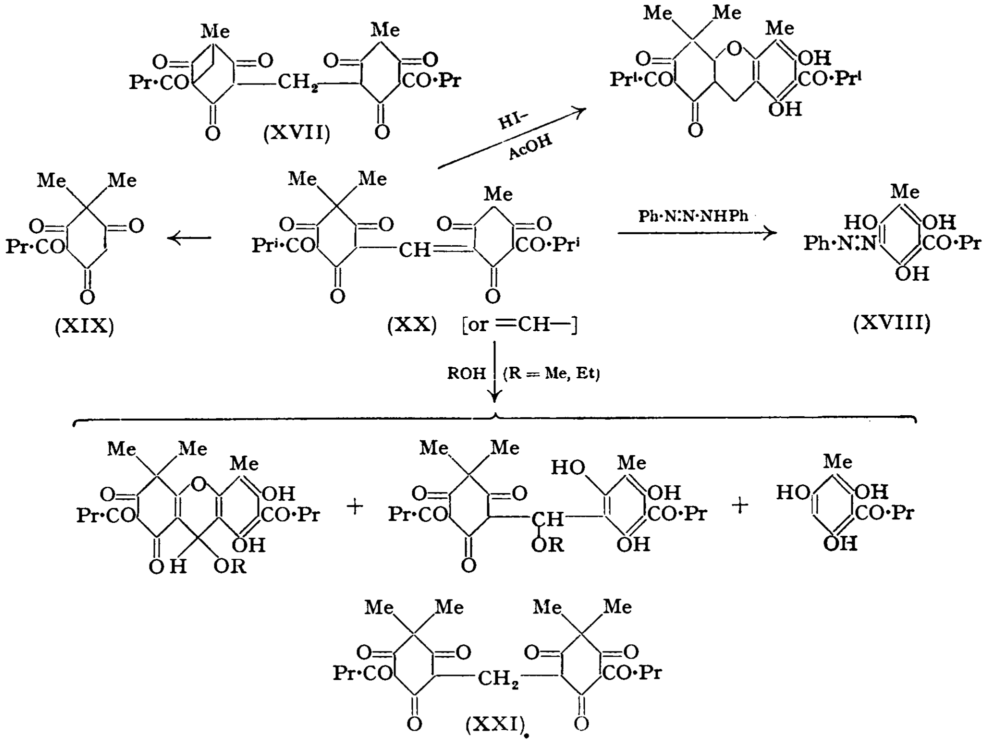
Calythrone.—Calythrone, $C_{12}H_{16}O_3$, from the oil of *Calythrix tetragona*, on oxidation with hypobromite gives dimethylmaleic anhydride, *iso*valeric acid, and bromoform. The green copper salt, $(C_{12}H_{15}O_3)_2Cu$, is soluble in chloroform; the ketone gives a red ferric colour, is soluble in aqueous ammonia, and gives an orange sodium salt, $C_{12}H_{17}O_4Na$, which can be crystallised from water. The copper salt corresponds to an unhydrated form, and is therefore unlikely to be derived from (V), while the sodium salt contains a molecule of water not removed at 100°, and was assumed to be derived from the ring-opened form of (V). However, it is known that salts of triketones $(\cdot CO)_3CH$ often retain a molecule of water or alcohol with great tenacity (Schwerin, *Ber.*, 1894, **27**, 104) (see also below), and the acid regenerates calythrone from the salt, an unlikely event if it is the salt of a ring-opened diketocarboxylic acid.

The properties of calythrone agree with those to be expected from (III), and for comparison (XVI) was made by the method of Kilgore, Ford, and Wolfe (*Ind. Eng. Chem.*, 1942, **34**, 494). This compound is readily soluble in ammonia or sodium hydrogen carbonate solution and yields a bright yellow sodium salt which can be crystallised from water. This salt contains an additional molecule of water not removed by drying at 0·1 mm. for 48 hours. The bright green copper salt gives analytical figures correct for the unhydrated form, and the substance gives a deep red colour with ferric chloride. The synthesis of (III) by analogous methods is in hand.

The above ketones have been formulated for convenience in the keto-forms, but there is little doubt that they exist as enols. The infra-red spectra show carbonyl bands displaced to longer wave-lengths, and there is a general absorption in the region of 3·3 μ. on both sides of the C–H band, both indicative of hydrogen-bonded enols. The ultra-violet absorption of (XVI) shows a series of high intensity bands in the region 230—320 mμ., and (XI) possesses high-intensity bands at 273 and 231 mμ., which indicate that both substances exist in enolic forms.

Flavaspidic Acid.—The thoroughness and competence of the work of Boehm (*locc. cit.*) on the constituents of male-fern have tended to obscure the fact that his structures for substances such as flavaspidic acid (XVII) and filicic acid, although undoubtedly correct in general outline are far from certainly established in detail. Flavaspidic acid, $C_{24}H_{28}O_8$, is a yellow substance existing in two forms, which are readily interconvertible but apparently are not just different crystalline forms. The substance is soluble in sodium hydrogen carbonate solution and titrates as a monobasic acid towards litmus. With diazoaminobenzene it gives (XVIII), a type of reaction shown by Boehm to be characteristic of methylenediphloroglucinols having all positions occupied by substituents. The action of zinc and sodium hydroxide leads to mono-, 1 : 1- and 1 : 3-di-, and 1 : 3 : 5-tri-methylphloroglucinol together with two molecules of butyric acid; under milder conditions one molecule of butyric acid and the 1 : 1-dimethylphloroglucinol are replaced by butanofilicinic acid (XIX). The four-membered ring in (XVII) (Boehm, *locc. cit.*) was invoked to explain the formation of trimethylphloroglucinol in amounts comparable with the mono- and di-methyl compounds and at the same time the formation of (XIX), the ring being opened by reduction in two directions. One objection to formula (XVII) is that the substance would not be expected to show higher acidity than albaspidin (XXI) and similar compounds which are soluble only with difficulty in sodium carbonate and cannot be titrated with litmus. There is also no explanation of the bright yellow colour, since albaspidin and similar compounds are colourless. A more likely formulation on the evidence available is (XX) the methine bridge giving rise to quinonoid properties. The two forms may then arise owing to the ready shift of the double bond from one nucleus to the other, although in the pyrromethene series this shift is so easy that such isomers have not been isolated, and in a system with so many tautomeric possibilities other explanations are possible. The other transformations shown below are much more rationally formulated on the new than on the old formula, especially the addition of alcohols, a type of reaction known to occur with pyrromethenes and methylenequinones (cf. Zincke, *Annalen*, 1903, **329**, 61). The exact structures of the xanthen derivatives depend on the unknown direction of ring-closure.

A similar formula can also be assigned to filicic acid; this will be considered in a later communication.



The chief difficulty in formulating both flavaspidic acid and filicic acid is the formation, by zinc and alkali reduction, of notable amounts of trimethylphloroglucinol, which, however, may be explicable on the basis of (XX) on the following grounds. It can be assumed that the first stage of the reduction is the formation of the methylenediphloroglucinol derivative of the type $R–CH_2–R'$ and these are known to undergo reactions in which R^- or R'^- appear—the reductive fission is one example—the negative charge being stabilised by resonance forms in which it appears on an oxygen atom. Equilibria of the type $R–CH_2–R' + H_2O \rightleftharpoons R·CH_2·OH + R'H$ are therefore likely to be set up, especially under alkaline conditions, the reverse reaction occurring, not only with R'H, but also with products already formed by reduction, *e.g.*, dimethylphloroglucinol. In the last case the ultimate reduction product will contain trimethylphloroglucinol. This view is supported by Boehm's observation (*Annalen*, 1903, **329**, 269) that methylenediphloroglucinol gives rise on reduction, not only to methyl- and dimethyl-, but also to trimethyl-phloroglucinol. This type of equilibrium also explains the ready disproportionation which occurs with many unsymmetrical pyrromethenes and with rottlerin (Backhouse, McGookin, Matchet, Robertson, and Tittensor, *J.*, 1948, 113).

Synthetic work is in hand in connection with a number of problems raised in this paper.

EXPERIMENTAL.

2-*Acetyl*-5 : 5-*dimethyl*cyclo*hexane*-1 : 3-*dione*.—This was prepared according to Crossley and Renouf (*loc. cit.*) and purified through its copper salt. The ultra-violet absorption (in ethanol) shows bands at 273 (ε = 10,800) and 231 mμ. (ε = 10,620). The infra-red absorption bands are recorded below, together with those of angustione and dehydroangustione taken from curves kindly supplied by Professor Sir John Simonsen, F.R.S.

Strong bands, 3·43, 6·0, 6·39, 6·93, 9·55, 10·55 μ.; medium bands; 8·10, 8·73, 8·90, 10·25, 10·82 μ.; weak bands, 11·25, 12·2, 14·2 μ.; side-bands, 7·05, 7·12, 7·20, 7·30, 7·50, 7·77, 7·96, 8·6, 9·73 μ.

Angustione: strong bands, 3·35, 5·95, 6·4, 6·95, 8·2, 8·55, 9·7, 10·08 μ.; medium bands, 8·92, 9·95, 10·6, 11·2, 11·5 μ.; weak bands, 12·2, 12·9, 13·6 μ.; side-bands, 7·2, 7·3, 7·43, 7·60, 8·0 μ.

Dehydroangustione: strong bands, 3·35, 5·95, 6·08, 6·45, 6·95, 7·7, 8·05, 8·54, 9·72, 9·95, 10·63, 11·30 μ.; medium bands, 8·75, 10·35, 11·87, 1272 μ.; weak bands, 13·5, 14·1 μ.; side-bands, 3·41, 7·2, 7·34, 8·94, 11·41 μ.

The *piperonylidene* derivative was obtained by heating 2-acetyl-5 : 5-dimethyl*cyclo*hexane-1 : 3-dione (100 mg.) with piperonaldehyde (200 mg.) and piperidine (20 mg.) on the steam-bath for 30 minutes, followed by the addition of methanol (2 c.c.). The product was recrystallised from methanol and formed bright yellow needles, m. p. 116° (Found : C, 69·0; H, 5·8. $C_{18}H_{18}O_5$ requires C, 68·8; H, 5·7%).

2-iso*Valerylindane*-1 : 3-*dione* (XVI).—This was prepared by the method of Kilgore, Ford, and Wolfe (*loc. cit.*). It showed the following bands in the ultra-violet (in ethanol) : 323 (ε = 8170), 311 (ε = 11,150), 283 (ε = 32,680), 274 (ε = 22,800), and 237 mμ. (ε = 17,270). The infra-red absorption curve showed very strong bands at 5·85 and 6·09 μ. in the region of normal carbonyl bands and a broader band at 6·29 μ. which probably corresponds to a carbonyl group involved in hydrogen-bonding. The dark green *copper* salt, m. p. 274°, was best crystallised by partial evaporation of its solution in chloroform (Found : C, 64·0; H, 5·3; Cu, 11·9. $C_{28}H_{26}O_6Cu$ requires C, 64·3; H, 5·0; Cu, 12·2%). The *sodium* salt was obtained by dissolving the substance in hot N-sodium carbonate and cooling, followed by recrystallisation from water. It formed long bright yellow needles which sintered at 200° and melted at 215°. After drying at 0·1 mm. for 48 hours it still contained 1 mol. of water (Found : C, 62·0; H, 5·45. $C_{14}H_{13}O_3Na,H_2O$ requires C, 62·2; H, 5·5%. The combustion was carried out in presence of potassium dichromate).

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