QUARTERLY REVIEWS

ACETYLENIC COMPOUNDS AS NATURAL PRODUCTS

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IN the past ten to twenty years the study of natural products has amply demonstrated the versatility of biochemical systems by bringing to light an enormous diversity of chemical structures, not only in biologically functional compounds (coenzymes, hormones, etc.), but also in that wider group of "secondary metabolites", compounds whose metabolic role, if they have any, remains obscure. In the long list of instances which could be compiled there are many new *compounds* without close parallels or with only a few near relatives, but there are also a few new *categories* of natural products, in which common features recur in numerous examples from a variety of sources. Compounds containing carbon–carbon triple bonds appear to form one such new category, and the study of the naturally derived acetylenes has reached a stage at which attempts to review the field may be profitable. Though the list of types of natural acetylenes is almost certainly incomplete, it is sufficiently long to warrant some provisional ordering and an effort to relate that ordering to the general background of metabolic studies. This account of the natural compounds is therefore drawn up in a way which it is hoped will call attention to the wider aspects of the problem. It may well be that the study of natural acetylenic compounds will play an important part in linking studies of primary and secondary metabolism, for, whilst they are quite clearly exotic substances, special features in the general pattern of Nature, they seem to be constructed on rather simple plans, unlike, *e.g.*, the alkaloids or sapogenins. In this sense they are the simplest of the more complicated natural products.

Historical

The first record of the natural occurrence of what are now known to be acetylenic derivatives appears to be the observation by Bretz and Elieson (1826) [1] of the ready crystallisation of the essential oil of *Artemisia vulgaris*. Carthaus (1907—1910) [2] isolated a compound $C_{12}H_{14}O_2$ from *Artemisia* sp. but the constitution of *A. vulgaris* oil was not thoroughly investigated until

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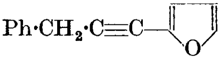
[1] Bretz and Elieson, cited in Gildmeister and Hoffmann, "Die ätherischen Öle", Schimmel, Miltitz, 1931, Vol. III, p. 1018.

[2] Carthaus, *Jaarb. Dep. Landb. in Ned.-Indie, Batavia*, 1907, 66; 1910, 55; cf. also ref. 1.

the work of Stavholt and Sörensen[3] in 1950. Meanwhile credit for the first characterisation of a natural acetylene goes to Arnaud, who isolated tariric acid (I) in 1892 and was able to determine its structure;[4] it was not

$$CH_3{\cdot}[CH_2]_{10}{\cdot}C{\equiv}C{\cdot}[CH_2]_4{\cdot}CO_2H \quad \text{(I)}$$

synthesised until 1952.[5] At about the same time Hebert[6] described unstable fatty acids from isano oil, the composition of which is still not fully understood. Semmler and Ascher had earlier isolated "Carlina oxide", from *Carlina acaulis*, for which they proposed an allenic structure on the basis of its molecular refractivity.[7] The correct, acetylenic, structure (II) was established (and synthesised) in 1935, by Pfau *et al.*, whose paper[8] provides an interesting example of the early use in structure studies of data from vibrational spectra.



(II)

The first natural product to be characterised as a polyacetylene (*i.e.*, with more than one C≡C unit) was the lachnophyllum ester (III), isolated[9] by Willjams, Goljmov, and Smirnov in 1935, and the recent increase in importance of the natural acetylenes arises primarily from work in Norway

$$CH_3{\cdot}CH_2{\cdot}CH_2{\cdot}C{\equiv}C{\cdot}C{\equiv}C{\cdot}CH{=}CH{\cdot}CO_2Me \quad \text{(III)}$$

by the Sörensens and their collaborators on this and other constituents of Compositæ, beginning in 1941 and resumed after the war. Professor Sörensen made a useful summary[10] of some aspects of this work in 1953. Parallel with this development there was rapid progress in the pure chemistry of acetylenic compounds, particularly relevant in the present connection being the work of Jones, Whiting, and their co-workers on the synthesis and properties of polyacetylenic compounds[11] and the similar work of Bohlmann.[12] At first this work assisted the study of natural polyacetylenes mainly by providing comparative data on spectroscopic properties; as more powerful synthetic methods were developed, it became possible to use the synthesis of possible structures as a direct method of establishing the identity of a natural product.

A recent development, made possible by the full use of modern methods, has been the study of polyacetylenic compounds in fungi. Antibiotics, later shown to contain triple bonds and allene units, were described by Anchel

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[3] Stavholt and Sörensen, *Acta Chem. Scand.*, 1950, **4**, 1567.

[4] Arnaud, *Compt. rend.*, 1892, **114**, 79; 1896, **122**, 1000; 1902, **134**, 473, 547, 842.

[5] Lumb and Smith, *Chem. and Ind.*, 1952, 358; *J.*, 1952, 5032.

[6] Hebert, *Bull. Soc. chim. France*, 1896, **15**, 935, 941.

[7] Semmler, *Chem. Ztg.*, 1889, **13**, 1158; *Ber.*, 1906, **39**, 726; Semmler and Ascher, *Ber.*, 1909, **42**, 2355.

[8] Pfau, Pictet, Plattner, and Susz, *Helv. Chim. Acta*, 1935, **18**, 935; cf. also Gilman, van Ess, and Burtner, *J. Amer. Chem. Soc.*, 1933, **55**, 3461.

[9] Willjams, Smirnov, and Goljmov, *Zhur. obshchei Khim.*, 1935, **5**, 1195.

[10] Sörensen, *Chem. and Ind.*, 1953, 240.

[11] Bowden, Heilbron, Jones, and Sargent, *J.*, 1947, 1579, and subsequent papers.

[12] Bohlmann, *Chem. Ber.*, 1951, **84**, 545, and subsequent papers.

and her co-workers[13] in 1950, and in 1952 Celmer and Solomons[14] elucidated the remarkable structure of the antibiotic mycomycin (IV), the first naturally occurring optically active allene to be fully characterised. The appropriate fungi promise to be the most useful material for the study of the interesting problems of the biogenesis of the natural acetylenes.

$$\mathrm{H{\cdot}C{\equiv}C{\cdot}C{\equiv}C{\cdot}CH{=}C{=}CH{\cdot}CH{=}CH{\cdot}CH{=}CH{\cdot}CH_2{\cdot}CO_2H}$$

(IV)

Previous reviews of this subject include summaries by Sörensen[10] and Anchel[15] of work on the Compositæ and Fungi respectively and an article by Bohlmann[16] which is especially useful for its summary of the synthetic methods applied in this field. The latter have also been described more generally by Jones and others.[17]

Distribution

An acetylenic component was detected[18] in a fraction, b.p. 95—105°/12 mm., from methylated butter-fat acids by the characteristic Raman bands (*ca.* 2040 and 2230 cm.$^{-1}$) ; apart from this the occurrence of acetylene derivatives in animal products has not been authenticated, and the natural acetylenes are derived from higher plants and fungi. Those from plants fall into two main groups, one comprising some acetylenic C_{18} acids occurring as glycerides in the seed-fat of certain angiosperms, and the other the acetylenic compounds found in essential oils, particularly of certain groups of Compositæ. The acetylenes of microbiological origin are produced mainly by Basidiomycetes, the so-called higher fungi, with the exception of mycomycin which is produced by an Actinomycete. A summary of the

Types of natural acetylenes

Source	Chain length	Conjugated carbon--carbon unsaturation	Functional groups
Fungi . . .	8 9 10 11 12 13	$\cdot\mathrm{CH{=}CH{\cdot}C{\equiv}C{\cdot}CH{=}CH}\cdot$ to $\cdot\mathrm{[CH{=}CH]_2{\cdot}CH{=}C{=}CH{\cdot}[C{\equiv}C]_2}$	$\mathrm{—CH_2{\cdot}OH}$, —CHO, $\mathrm{—CO_2H}$ $\mathrm{—CO_2Me}$, $\mathrm{—CO{\cdot}NH_2}$, —CN $\rangle\mathrm{CH{\cdot}OH}$, $\rangle$S (thiophen), $\mathrm{—CO{\cdot}O—}$ (γ-lactone)
Compositæ and Umbelliferæ	10 12 13 14 17	$\cdot\mathrm{[C{\equiv}C]_2}\cdot$ to $\cdot\mathrm{CH{=}CH{\cdot}[C{\equiv}C]_5}$	$\mathrm{—CH_2{\cdot}OH}$, $\mathrm{—CH_2{\cdot}OAc}$, $\mathrm{—CO_2Me}$, $\mathrm{—CO{\cdot}NHBu^i}$ $\rangle\mathrm{CH{\cdot}OH}$, $\rangle\mathrm{C{=}O}$, $\rangle$O (furan), $\mathrm{—C_6H_5}$
Seed oils . .	18	$\cdot\mathrm{C{\equiv}C}\cdot$ to $\cdot\mathrm{[C{\equiv}C]_2{\cdot}CH{=}CH}\cdot$	$\mathrm{—CO_2H}$ (as glycerides) $\rangle\mathrm{CH{\cdot}OH}$

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[13] Anchel, Polatnick, and Kavanagh, *Arch. Biochem.*, 1950, **25**, 208 ; Kavanagh, Hervey, and Robbins, *Proc. Nat. Acad. Sci.*, 1950, **36**, 1, 102.

[14] Celmer and Solomons, *J. Amer. Chem. Soc.*, 1952, **74**, 1870, 2245.

[15] Anchel, *Trans. New York Acad. Sci. U.S.A.*, 1954, **16**, 337.

[16] Bohlmann, *Angew. Chem.*, 1955, **67**, 389.

[17] Jones, *J.*, 1950, 754 ; Raphael, " Acetylenic Compounds in Organic Synthesis ", Butterworths, London, 1955.

[18] Yvernault, *Oleagineux*, 1946, **1**, 189 ; *Chem. Abs.*, 1947, **41**, 3697.

salient features of the natural acetylenes so far encountered is given in the Table on the previous page.

General Properties

Stability.—The ease with which acetylenic compounds of the types found in Nature can be handled varies within rather wide limits. A few are quite stable to heat and may be melted or steam-distilled without decomposition, and many can be recrystallised without special precautions. On the other hand most polyacetylenes are apt to polymerise, particularly on exposure to light. The effect is sometimes spectacular: for example, crystals of *iso*nemotinic acid (p. 386) become bright pink after a few seconds' exposure. This photosensitivity is shown only in condensed phases and is therefore ascribed to photocatalysed cross-linking of the carbon chains of adjacent molecules. Such a reaction would give three-dimensional networks containing various conjugated chromophores, the exact course being determined by the crystal structure of the monomer. This accords with the fact that where the acetylenic carbon atoms are particularly exposed, as in the group $H{\cdot}[C{\equiv}C]_n{\cdot}$, photosensitivity is most marked, whereas in compounds with more bulky substituents it may be quite absent.[19] Susceptibility to atmospheric oxidation appears to be less marked than with polyenes but may be considerable when a number of double bonds is also present. Extreme pH values are in general to be avoided in work with polyacetylenes since they may bring about hydration or ionotropic rearrangements; some allenic compounds undergo prototropic rearrangement even at pH 7.

Spectra.[20]—The spectroscopic properties of the polyacetylenes are very characteristic and most useful in constitutional studies. In general, the ultraviolet absorption spectra of chromophores in which triple bonds predominate show band series with a characteristic fine structure (vibration) spacing of about 2000 cm.$^{-1}$, a frequency comparable to that of the $C{\equiv}C$ stretching vibration in the ground state. These bands are in two groups, the wavelengths and relative intensities of which characterise the chromophore almost completely, though such "isomeric" chromophores as ${\cdot}CH{=}CH{\cdot}[C{\equiv}C]_2{\cdot}CH{=}CH{\cdot}$ and ${\cdot}[CH{=}CH]_2{\cdot}[C{\equiv}C]_2{\cdot}$ may not be immediately distinguishable. The individual bands are usually very sharp and their intensities may be as high as 10^5 or more, so that polyacetylenic compounds can often be detected, and to some extent characterised, in crude extracts.* Thus in Fig. 1 the spectrum of a crude extract from a fungus shows clearly the presence of a polyacetylenic compound of which the whole sample contained less than 5μg.; the absorption spectrum of the pure compound is given for comparison.

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[19] Bohlmann, *Chem. Ber.*, 1953, **86**, 657.

[20] Cf. especially Jones, Whiting, Armitage, Cook, and Entwhistle, *Nature*, 1951, **168**, 900; Bohlmann, *Chem. Ber.*, 1953, **86**, 63; also Bohlmann [16, 19] and Jones *et al.*[11]

* However, it should be noted that for *purely* acetylenic chromophores, the longer-wavelength series of bands is of very low intensity and easily masked even in relatively pure preparations. Where there are more than three triple bonds, a shorter-wavelength band series of high intensity is easily observed under normal conditions but in other cases this feature has led to confusion, as in the case of "biformin" (p. 386).

The double bonds of allene units are spectroscopically independent of each other ; when each is involved in further conjugation, as in mycomycin, the resultant absorption spectrum is approximately the sum of those of the two independent chromophores.[14]

The infrared spectra of these compounds are also of importance in structural studies, an early use of Raman spectra[8] in this connection having already been noted ; the generally simple, linear structures of most natural acetylenes are reflected in the relative simplicity of their spectra. In absorption, bands due to the triple bond itself may be rather inconspicuous ; frequently multiple, they occur between 2000 and 2200 cm.$^{-1}$, but are of variable intensity (the same vibration causes strong bands in the Raman spectrum [18]). Allene groups are associated with a sharp peak at about 1950 cm.$^{-1}$ which is the most reliable test for the presence of such a group ; free ethynyl groups are readily detected by the $\equiv$C—H stretching band at about 3300 cm.$^{-1}$, and infrared spectra are also useful in assigning configurations to double bonds. More generally, they may be used to characterise the functional groups of the molecule, whether or not these form part of a chromophore system deduced from ultraviolet absorption data. Moreover infrared spectra offer a most valuable method for comparing a synthetic and a natural product in a field where melting-point determinations are frequently impracticable. As an example of the use of spectroscopic measurements for structure-determination in this field the case of the antibiotic nemotin (p. 386) may be cited. With the added information that nemotin gives undecanoic acid on hydrogenation, the ultraviolet and

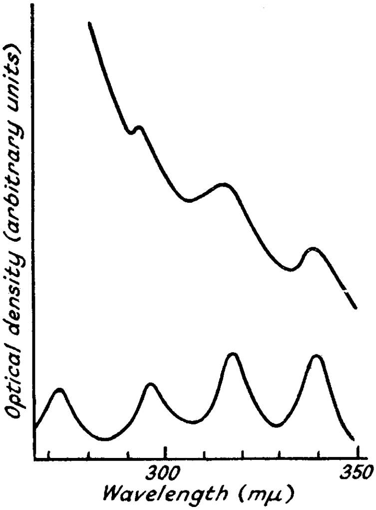

FIG. 1

Use of ultraviolet absorption spectra for the detection of polyacetylenes. Upper curve : absorption spectrum of crude ethanol extract from slope culture of a fungus. Lower curve : absorption spectrum of the acetylenic component after purification. (Reviewer's unpublished work.)

infrared spectra are sufficient to establish the structure. The former indicates the presence of an ene-diyne group as the only conjugated system, the latter fixes the remainder of the structure, as shown in Fig. 2.

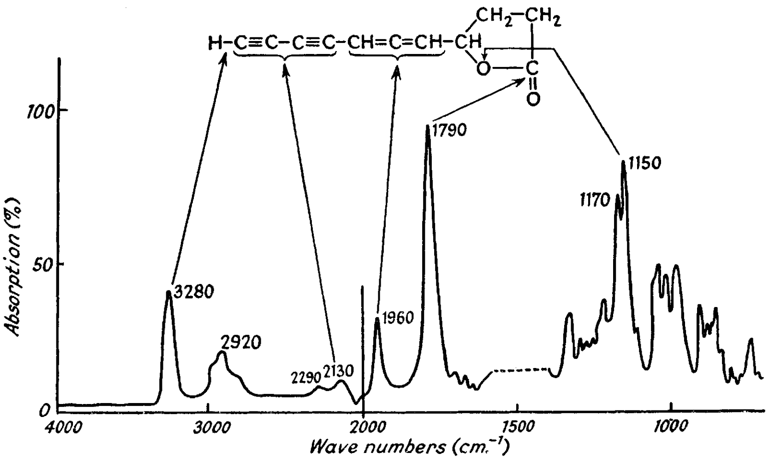

FIG. 2

Use of infrared absorption spectra for the structural determination of nemotin, a polyacetylene from fungi. With ultraviolet and hydrogenation data, the spectrum determines the structure uniquely, as shown.

Methods of Investigation

The C_{18} acids from seed oils have generally been isolated and studied by the usual techniques of fat chemistry, though recent advances have involved the use of more refined methods better suited to this class of compound. In some of the studies of essential oils, and in a recent study of volatile constituents of a fungus, compounds were isolated by steam-distillation, but the most generally used methods have involved solvent-extraction. Subsequent working-up has sometimes employed simple or fractional crystallisation, but chromatographic methods have been widely used, for example, in the separation of a number of polyacetylenes from *Polyporus anthracophilus*.[21] The use by Lythgoe and his associates of morin–alumina columns, on which light-absorbing compounds appear as dark bands under ultraviolet light, may be noted.[22] For dealing with more unstable compounds, special methods may be required. Celmer and Solomons described methods for low-temperature recrystallisation in an inert atmosphere,[14] whereas the Reviewer and his co-workers prefer techniques such as solvent-extraction and counter-current distribution which minimise the handling of solid products.[23]

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[21] Bu'Lock, Jones, and Turner, *Chem. and Ind.*, 1955, 686, and unpublished work.

[22] Anet, Lythgoe, Silk, and Trippett, *J.*, 1953, 309 ; Brockmann and Volpers, *Chem. Ber.*, 1947, **80**, 77.

[23] Bu'Lock, Jones, and Leeming, *J.*, 1955, 4270.

Provided that the compound can be obtained pure in solution, characterisation need not necessarily require its isolation as a solid. Spectroscopic and other data can be obtained by transfer to suitable solvents; electrometric titrations and the study of addition or rearrangement reactions can if necessary be carried out similarly, as can hydrogenation to a more stable product. When the compound is sufficiently stable to be manipulated in crystalline form, more precise data can, of course, be obtained. The structures of hydrogenation products are readily established by conventional means; in considering evidence so obtained, it should be remembered that some allylic alcohols and esters are susceptible to hydrogenolysis under quite mild conditions of hydrogenation. Classical methods of degradation are of little use with compounds in which the unsaturation extends over almost the entire molecule, though oxidation was used to establish the structures of some of the seed-oil acids and hydrative breakdown of the conjugated chain with alkali was used with the lachnophyllum ester.[9] The triple bond reacts rather slowly with ozone and peracids,[24] so that double bonds may be oxidised selectively, as in one determination of the structure of ximenynic (santalbic) acid.[25] In the same way, since ene-ynes give maleic anhydride adducts only under forcing conditions, the Diels–Alder reaction can be used to detect *trans-trans*-diene groups, as in *iso*mycomycin,[26] at the same time providing data on the residual chromophore of the adduct.

In many cases, the study of ultraviolet and infrared spectra and the identification of the hydrogenation product have been sufficient to justify the assignment of one or a few possible structural formulæ, decision between these being made by synthesis of the relevant compounds. As examples may be quoted syntheses by Bohlmann *et al.* of a series of related ketones in order to determine the structure of a compound from *Artemisia vulgaris* [27] and the assignment [28] of the correct structures to agrocybin and diatretyne I.

Acetylenic Acids from Seed Oils

The acetylenic acids from seed oils form a clearly defined group in that all those so far encountered have the well-known C_{18} straight chain of stearic acid; on the other hand, not all the members of this group are as well characterised as might be wished. The simplest is tariric acid (I), the structure of which was unambiguously established at an early date.[4] Glycerides of this acid make up about 95% of the seed fat of *Picramnia sow*, and also occur in *P. camboita*, *P. carpinteræ* and *P. lindeniana*, but not, apparently, in other genera of the group (Simarubaceæ) to which *Picramnia* belongs.[29]

Another acid with a species-specific distribution is ximenynic acid (V),

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[24] Bohlmann and Sinn, *Chem. Ber.*, 1955, **88**, 1869.

[25] Gunstone and McGee, *Chem. and Ind.*, 1954, 1112.

[26] Celmer and Solomons, *J. Amer. Chem. Soc.*, 1952, **74**, 3838.

[27] Bohlmann, Mannhardt, and Viehe, *Chem. Ber.*, 1955, **88**, 361.

[28] Bu'Lock, Jones, Mansfield, Thompson, and Whiting, *Chem. and Ind.*, 1954, 990.

[29] Steger and van Loon, *Rec. Trav. chim.*, 1933, **52**, 593; Grimme, *Chem. Rev. Fett.-Harz-Ind.*, 1910, **17**, 158; 1912, **19**, 51.

octadec-11-en-9-ynoic acid.[30] The seed oils of several South African *Ximenia* species contain up to 25% of the glycerides of this acid. The genus belongs to the order Santalales, and ximenynic acid appears to be characteristic of *Santalum* sp. The so-called santalbic acid, from *S. album*,[31] is in fact ximenynic acid [32] (the name santalbic acid is therefore redundant), and the same acid constitutes over 40% of the seed-fat acids of *S. acuminatus* and *S. murrayana.*

$$CH_3\cdot[CH_2]_5\cdot CH{=}CH\cdot C{\equiv}C\cdot[CH_2]_7\cdot CO_2H$$

(V)

The seed-oil of a species belonging to another genus of the Santalales, *Ongueka gore* Engler (" isano ", " boleko "), presents a more complex picture. Isano oil was first studied by Hebert,[6] who in 1896 isolated from it an unsaturated, photosensitive fatty acid, isanic acid, which was not fully characterised. Later investigations by Steger and van Loon [33] and Castille [34] were complicated by the isolation of artefacts, the failure to obtain homogeneous products, and the use of two different names, isanic and erythrogenic acid, for the main constituent of the fatty acid mixture. In the Reviewer's opinion the name isanic acid should be retained, to refer to the acid for which structure (VI) [33, 34] was finally established, by degradation by Seher [35] and by synthesis by Black and Weedon.[36] Castille's " erythrogenic acid " consisted mainly of the acid (VI) but its ultraviolet absorption spectrum shows it to have contained about 10—15% of a conjugated ene-diyne.[37] The oil also contains hydroxystearic acid derivatives,[38] and Seher [35] ascribes to one such component (not isolated) the ene-diyne structure (VII). This structure bears no obvious relation to that of isanic acid, and since there is also evidence for the existence of both 8-hydroxyisanic acid [38] and a non-hydroxylated ene-diyne acid [39] in isano oil, it is apparent that the detailed constitution of this oil remains unsettled.

$$CH_2{=}CH\cdot[CH_2]_4\cdot C{\equiv}C\cdot C{\equiv}C\cdot[CH_2]_7\cdot CO_2H$$

(VI)

$$CH_3\cdot[CH_2]_2\cdot CH{=}CH\cdot C{\equiv}C\cdot C{\equiv}C\cdot CH_2\cdot CH(OH)\cdot[CH_2]_6\cdot CO_2H$$

(VII)

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[30] Lighthelm and Schwartz, *J. Amer. Chem. Soc.*, 1950, **72**, 1868; Lighthelm and von Holdt, *J.*, 1952, 1088, 5039.

[31] Madhuraneth and Manjunath, *J. Indian Chem. Soc.*, 1938, **15**, 389.

[32] Hatt and Szumer, *Chem. and Ind.*, 1954, 962; Grigor, MacInnes, McLean, and Hogg, *ibid.*, p. 1112; *J.*, 1955, 1069; also ref. 25.

[33] Steger and van Loon, *Fette u. Seifen*, 1937, **44**, 243; *Rec. Trav. chim.*, 1940, **59**, 1156; 1941, **60**, 107.

[34] Castille, *Annalen*, 1939, **543**, 104; *Bull. Acad. roy. Med. Belg.*, 1941, **6**, 152.

[35] Seher, *Annalen*, 1954, **589**, 222.

[36] Black and Weedon, *J.*, 1953, 1785.

[37] Cf. Jones *et al.*, ref. 20.

[38] Steger and van Loon, *Fette u. Seifen*, 1937, **44**, 243; *Rec. Trav. chim.*, 1941, **60**, 107; Kaufmann, Balter, and Herminghaus, *Fette u. Seifen*, 1951, **53**, 537; Riley, *J.*, 1951, 1346.

[39] Meade, personal communication.

Acetylenic acids thus occur in the seed oils of the order Santalales and of the genus *Picramnia.* Although the simpler chromophores of tariric and ximenynic acid would not be readily detected spectroscopically, it seems likely that the application of the spectroscopic methods used in the examination of, *e.g.*, the Compositæ essential oils, would reveal a wider distribution of more highly unsaturated acetylenic acids. The potentialities of the use of Raman spectra, in which even isolated triple bonds give rise to strong and characteristic bands, should be noted ; the method has been used by Yvernault [18] to detect acetylenic constituents in butter-fat and in dry-distilled castor oil.

Compositæ essential oils

The best-known class of natural acetylenes is that comprising compounds from the essential oils of many Compositæ and some Umbelliferæ ; they occur in many familiar wild and cultivated plants. This is at present the largest class and is of interest, not only because of the chemistry of individual compounds, but also because of the relations between them. Thus the distribution of certain compounds accords well with the taxonomy of the Compositæ and may be used in some cases to supplement the botanical classification.[10, 40] Moreover, the compounds are such that correlations can be made between their structure, so that some plausible biogenetic hypotheses can be put forward.

The occurrence of several of the Compositæ polyacetylenes has been summarised by Sörensen,[10] with whom the subject is particularly associated. In the present Review the compounds will be considered in order of their chain length (cf. Table, p. 373). The compounds are in general neutral (esters, ethers, and hydrocarbons), and the Norwegian school have in fact isolated many of them from steam-distilled oils. The amide anacyclin is a more polar compound and belongs to a different category.

C_{10} Series.—The most widely-occurring natural polyacetylenes are unsaturated esters and alcohols derived from *n*-decane. These are especially characteristic of Compositæ, though some of them also occur in fungi (p. 385). The first to be discovered was the lachnophyllum ester, shown by degradation to be the *cis*-isomer of structure (III).[9] This was first isolated from *Lachnophyllum gossypinum* Bg., but is widely distributed in Compositæ, particularly in various sections of the genus *Erigeron.*[40] The isomeric $\alpha\beta$-dihydromatricaria ester (VIII) has also been reported from several Compositæ.[41] However, this ester was characterised as the derived acid after alkaline hydrolysis,

$$\mathrm{CH_3{\cdot}CH_2{\cdot}CH_2{\cdot}C{\equiv}C{\cdot}C{\equiv}C{\cdot}CH{=}CH{\cdot}CO_2Me}$$

(III)

$$\mathrm{CH_3{\cdot}CH{=}CH{\cdot}C{\equiv}C{\cdot}C{\equiv}C{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2Me}$$

(VIII)

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[40] Tronvold, Nestvold, Holme, Sörensen, and Sörensen, *Acta Chem. Scand.*, 1953, **7**, 1375.

[41] Baalsrud, Holme, Nestvold, Pliva, Sörensen, and Sörensen, *ibid.*, 1952, **6**, 883.

and other esters giving (VIII) on alkali treatment may also have been present. Similarly in *Bellis perennis* the *trans*-isomer of the ester (III) occurs together with an ene-diyne of unknown structure which after saponification ultimately gives the conjugated diyne-ene-acid corresponding to (III) ; [42] again a more complex, possibly allenic, compound appears to have been present in the actual plant extracts. The alcohol (IX), matricarianol, occurs (principally as the acetate of the *trans*-*trans*-isomer) in some Compositæ.[40, 43]

$$CH_3{\cdot}CH{=}CH{\cdot}C{\equiv}C{\cdot}C{\equiv}C{\cdot}CH{=}CH{\cdot}CH_2{\cdot}OH$$

(IX)

The most characteristic polyacetylene of the C_{10} series from Compositæ is the matricaria ester (X), the *cis*-*cis*-isomer having been found in nearly fifty species, particularly of the genus *Erigeron* (*Tripleurospermum*).[40, 43] This isomer was first isolated from *Matricaria inodora* (scentless mayweed) and its structure established by degradative methods.[44] The assignment of the configuration originally rested upon photoisomerisation to the 2-*trans*-8-*cis*-isomer which was synthesised.[45] This isomer too has been isolated from *Matricaria inodora* and other Compositæ.[41] The more common 2-*cis*-8-*cis*-isomer has now been synthesised, as also has the *cis*-lachnophyllum ester ; [46] since there is some confusion in the literature, the melting points of the known isomers of (X) are given here. The ultraviolet absorption spectra of all the matricaria esters are somewhat anomalous in that their acetylenic fine structure is not sharp.

$$CH_3{\cdot}CH{=}CH{\cdot}C{\equiv}C{\cdot}C{\equiv}C{\cdot}CH{=}CH{\cdot}CO_2Me \quad \text{(X)}$$

2-*cis*-8-*cis*-, m.p. 37° (natural and synthetic)
2-*trans*-8-*cis*-, m.p. 2° (natural and synthetic)
2-*trans*-8-*trans*-, m.p. 61° [natural (fungi) and synthetic]

The most highly unsaturated decane derivatives so far encountered in Compositæ are the dehydromatricaria esters (XI), about which there has also been some confusion. The first to be isolated, from *Artemisia vulgaris*,[47] has m.p. 112° and is the *cis*-isomer, as was subsequently shown by Sörensen's group [48, 49] and by Bohlmann and Mannhardt ; [50] this too has recently been synthesised by Bell, Jones, and Whiting.[46] The *trans*-isomer of (XI), which melts at 105° when pure, was synthesised [48] before its isolation from *Matricaria* sp.[49]

$$CH_3{\cdot}C{\equiv}C{\cdot}C{\equiv}C{\cdot}C{\equiv}C{\cdot}CH{=}CH{\cdot}CO_2Me$$

(XI)

As well as the fully characterised polyacetylenes of the C_{10} series, there

[42] Holme and Sörensen, *Acta Chem. Scand.*, 1954, **8,** 280.
[43] *Idem*, *ibid.*, p. 34.
[44] Sörensen and Stene, *Annalen*, 1941, **549,** 80.
[45] Bruun, Christensen, Haug, Stene, and Sörensen, *Acta Chem. Scand.*, 1951, **5,** 1244.
[46] Bell, Jones, and Whiting, *Chem. and Ind.*, 1956, 548.
[47] Stavholt and Sörensen, *Acta Chem. Scand.*, 1950, **4,** 1567.
[48] Christensen and Sörensen, *ibid.*, 1952, **6,** 602.
[49] Sörensen, Bruun, Holme, and Sörensen, *ibid.*, 1954, **8,** 26.
[50] Bohlmann and Mannhardt, *Chem. Ber.*, 1955, **88,** 429.

also exist in Compositæ several apparently related compounds lacking the characteristic ultraviolet absorption spectra of polyacetylenes. Besides the compounds mentioned above as possible precursors of (III) and (VIII) there are compounds such as the " composit-cumulen I " (broad absorption maximum at *ca.* 3500 Å) from *Matricaria inodora*,[49, 51] for which a cumulene structure was proposed but now seems unlikely. Also associated with decane derivatives (in *Artemisia vulgaris*) are a C_{14} ketone (see p. 382) and a dienetriyne hydrocarbon of unknown chain length.[47] The hydrocarbon appears to be related to certain acetylenic hydrocarbons of unknown structure which occur in *Centaurea* sp. together with related polyenes.[52]

Other Compounds from Compositæ.—A hydrocarbon capillene, from the essential oil * of *Artemisia capillaris* Thunb., was assigned by Harada [53] the structure (XII), on the basis of hydrogenation to *n*-hexylbenzene, the presence of acetylenic bands in the infrared spectrum, and oxidative degradations from which phenylacetic and acetic acid were isolated, but no acetaldehyde. The physical constants of capillene (d^{20} 0·9735, n_D^{20} 1·5698) agree closely with those reported for agropyrene (d^{20} 0·9744, n_D^{20} 1·5695), one of the few acetylene derivatives from plants which are not Compositæ. Agropyrene was isolated by Treibs from a 22-year-old sample of essential oil from couch grass (*Triticum repens, Agropyrum repens*) and was also assigned structure (XII).[53] However, a synthesis of the *trans*-isomer of (XII) gave a product with properties ($d^{26·5}$ 0·9450, $n_D^{26·5}$ 1·5510) differing from those recorded for agropyrene and capillene.[54] The recorded properties of the natural products, whilst insufficient to characterise them as being the *cis*-form of (XII), rule out all phenylhexatriene structures and make the alternative formulation $Ph{\cdot}CH_2{\cdot}C{\equiv}C{\cdot}CH{=}CH{\cdot}CH_3$ appear unlikely.

$$Ph{\cdot}CH_2{\cdot}CH{=}CH{\cdot}C{\equiv}C{\cdot}CH_3 \quad \text{(XII)}$$

Whatever its structure, agropyrene would seem to be related to a group of C_{13} compounds, some of which contain also the phenyl group. The best authenticated of these are the compounds (XIII) (which occurs as the acetate in *Carlina vulgaris*),[55] (XIV) (from *Coreopsis* sp., as the acetate),[56] and (II), the " Carlina oxide " (from *Carlina acaulis*). These three isomeric compounds are thus closely related both chemically and botanically. The

$$CH_2{=}CH{\cdot}CH{=}CH{\cdot}C{\equiv}C{\cdot}C{\equiv}C{\cdot}C{\equiv}C{\cdot}CH{=}CH{\cdot}CH_2{\cdot}OH$$
(XIII)

$$trans\text{-}Ph{\cdot}C{\equiv}C{\cdot}C{\equiv}C{\cdot}CH{=}CH{\cdot}CH_2{\cdot}OH$$
(XIV)

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[51] Sörensen and Stavholt, *Acta Chem. Scand.*, 1950, **4,** 1080.

[52] Löfgren, *ibid.*, 1949, **3,** 82 ; Hellström and Löfgren, *ibid.*, 1952, **6,** 1024 ; Sörensen and Stavholt, *ibid.*, 1950, **4,** 1575.

[53] Harada, *J. Chem. Soc., Japan,* 1954, **75,** 727 (*Chem. Abs.*, 1955, **49,** 10235) ; Treibs, *Chem. Ber.*, 1947, **80,** 97.

[54] Cymerman-Craig, David, and Lake, *J.*, 1954, 1874.

[55] Sörensen and Sörensen, *Acta Chem. Scand.*, 1954, **8,** 1763.

[56] *Idem, ibid.*, p. 1741.

* This oil also contains the C_{12} ketone 1-phenylhexa-2 : 4-diyn-1-one (Imai, *J. Pharm. Soc. Japan,* 1956, **76,** 397 ; *Chem. Abs.*, 1956, **50,** 10340).

acetates of (XIII) and (XIV) were characterised spectroscopically and by hydrogenation;[55, 56] that of (XIV) and of the all-*trans* isomer of (XIII) have been synthesised.[57] Similarly "Carlina oxide" was eventually characterised by its Raman spectrum, hydrogenation and synthesis;[8] the earlier workers[7] preferred an allenic structure to the acetylenic structure (II), partly because of the molecular refractivity, and partly because they considered the acetylenic link unlikely to exist in a natural product· The biogenetic implications of the occurrence of this group of compounds, and of other arylacetylene derivatives, are considered below (p. 393).

There also exist in Compositæ a series of C_{13} hydrocarbons which may perhaps be regarded as related to the alcohols (XIII) and (XIV). These may be represented by the formulæ (XV)—(XX); all are very unstable and occur only in small amounts, so that their characterisation has been

(XV) $\mathrm{CH_2{=}CH{\cdot}CH{=}CH{\cdot}CH{=}CH{\cdot}C{\equiv}C{\cdot}C{\equiv}C{\cdot}CH{=}CH{\cdot}CH_3}$
(XVI) $\mathrm{CH_2{=}CH{\cdot}CH{=}CH{\cdot}C{\equiv}C{\cdot}C{\equiv}C{\cdot}C{\equiv}C{\cdot}CH{=}CH{\cdot}CH_3}$
(XVII) $\mathrm{CH_2{=}CH{\cdot}C{\equiv}C{\cdot}C{\equiv}C{\cdot}C{\equiv}C{\cdot}C{\equiv}C{\cdot}CH{=}CH{\cdot}CH_3}$
(XVIII) $\mathrm{CH_2{=}CH{\cdot}C{\equiv}C{\cdot}C{\equiv}C{\cdot}C{\equiv}C{\cdot}C{\equiv}C{\cdot}C{\equiv}C{\cdot}CH_3}$
(XIX) $\mathrm{Ph{\cdot}C{\equiv}C{\cdot}C{\equiv}C{\cdot}CH{=}CH{\cdot}CH_3}$
(XX) $\mathrm{Ph{\cdot}C{\equiv}C{\cdot}C{\equiv}C{\cdot}C{\equiv}C{\cdot}CH_3}$

extremely difficult.[56, 58] The structures of (XVIII), one of three highly unsaturated hydrocarbons from *Helipterum* sp.,[58] and of (XVII) have been confirmed by synthesis,[59] and an isomer of (XV) has also been synthesised.[60] The hydrocarbons (XV) and (XVII) occur together in *Coreopsis* sp.[56] as do (XVI) and (XIX);[61] (XX) was also isolated from *Coreopsis* sp.[61, 62]

The C_{14} ketone from *Artemisia vulgaris*,[47] for which the formula (XXI) was eventually established by synthesis,[27] at present remains without close parallel.

$$\mathrm{CH_3{\cdot}C{\equiv}C{\cdot}C{\equiv}C{\cdot}C{\equiv}C{\cdot}CH{=}CH{\cdot}CH_2{\cdot}CH_2{\cdot}CO{\cdot}CH_2{\cdot}CH_3}$$

(XXI)

Umbelliferæ. Acetylenic structures have been established for the toxic principles of two species of Umbelliferæ, *Cicuta virosa* (hemlock water dropwort) and *Œnanthe crocata* (cowbane, water hemlock). Earlier work on these compounds, which have some importance as stock poisons, is summarised by Lythgoe and his co-workers,[63] who succeeded in resolving the rather complex mixture of compounds in each source and showed that the

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[57] Bruun, Skatteböl, and Sörensen, *Acta Chem. Scand.*, 1954, **8,** p. 1757; Bohlmann and Inhoffen, *Chem. Ber.*, 1956, **89,** 21.

[58] Sörensen, Holme, Borlaud, and Sörensen, *Acta Chem. Scand.*, 1954, **8,** 1769.

[59] Jones, Skatteböl, and Whiting, personal communication; cf. Jones, Thompson, and Whiting, *Acta Chem. Scand.*, 1954, **8,** 1944.

[60] Bohlmann and Mannhardt, *Chem. Ber.*, 1955, **88,** 1330.

[61] Sörensen and Sörensen, personal communication; also *Tids. Kjemi*, 1955, **15,** 129; cf. Bohlmann, *Chem. Ber.*, 1955, **88,** 1755.

[62] The author is especially grateful to Professor Sörensen for advance information regarding this group of C_{13} hydrocarbons.

[63] Anet, Lythgoe, Silk, and Trippett, *Chem. and Ind.*, 1952, 757; *J.*, 1953, 309.

toxic compounds were glycols, accompanied in each case by varying amounts of related compounds. The compounds from *Œnanthe crocata* were assigned structures (XXII)—(XXIII) ; those from *Cicuta virosa*, (XXIV*a* and *b*), are clearly related but have the unsaturation differently arranged. The structures of the *Œnanthe* compounds and of cicutoxin (XXIV*a*) have been confirmed by synthesis.[64]

$$HO{\cdot}CH_2{\cdot}CH{=}CH{\cdot}C{\equiv}C{\cdot}C{\equiv}C{\cdot}CH{=}CH{\cdot}CH{=}CH{\cdot}CH_2{\cdot}CH_2R$$

(XXII*a*) : $R = CH(OH){\cdot}Pr^n$. (XXII*b*) : $R = Bu^n$.

$$CH_3{\cdot}CH{=}CH{\cdot}C{\equiv}C{\cdot}C{\equiv}C{\cdot}CH{=}CH{\cdot}CH{=}CH{\cdot}CH_2{\cdot}CH_2{\cdot}COPr^n$$

(XXIII)

$$HO{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}C{\equiv}C{\cdot}C{\equiv}C{\cdot}CH{=}CH{\cdot}CH{=}CH{\cdot}CH{=}CHR$$

(XXIV*a*) : $R = CH(OH){\cdot}Pr^n$. (XXIV*b*) : $R = Bu^n$.

Insecticidal amides. There have been isolated from a variety of plants of the Compositæ and Rutaceæ a series of *N*-*iso*butylamides of unsaturated acids, several of which show notable insecticidal activity. Some earlier confusion about the structures of certain of these amides has now been cleared up, largely by Crombie and his collaborators,[65, 66] and certain common structural features can now be discerned. The compounds are all derived from even-numbered fatty acids (C_{10}, C_{12}, C_{14}, and C_{18}) and their structures are consistent with a derivation from C_2 (acetate) units. One member of this group, in other respects typical, contains two triple bonds ; this is anacyclin, for which structure (XXV) has been established.[66] The

$$CH_3{\cdot}[CH_2]_2{\cdot}C{\equiv}C{\cdot}C{\equiv}C{\cdot}[CH_2]_2{\cdot}CH{=}CH{\cdot}CH{=}CH{\cdot}CO{\cdot}NHBu^i$$

(XXV)

insecticidal *iso*butylamides have been isolated by solvent extraction from the plant materials ; it is not yet known whether related compounds (such as esters of the corresponding acids) occur in the same or related species.

Micro-organisms

Distribution.—Versatility of secondary metabolism is characteristic of micro-organisms generally, and in the recent extensive research in this field it is scarcely surprising that a number of acetylene derivatives should have been encountered ; however, their distribution seems to be somewhat restricted. The selection of material for study has been guided mainly by the search for antibiotics and hence is not truly representative ; nevertheless some groups of micro-organisms have been quite intensively studied (*e.g.*, Streptomycetes) without any acetylenic metabolites having been encountered. Acetylene derivatives have been reported only once outside the group of Fungi proper, *viz.*, in a species of the fungus-like Actinomycetales, *Nocardia acidophilus*. In the Fungi, the known producers of acetylenic compounds are all of the class Basidiomycetes (" higher fungi "), sub-class

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[64] Hill, Lythgoe, Merrish, and Trippett, *J.*, 1955, 1770 ; Bohlmann and Viehe, *Chem. Ber.*, 1955, **88**, 1245.

[65] *E.g.* Crombie, *J.*, 1955, 995.

[66] *Idem, ibid.*, p. 999,

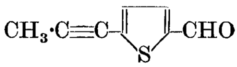
Homobasidiomycetes, order Agaricales, and all belong to only two families of the Agaricales, *viz.*, Agaricaceæ (including *Agrocybe*, *Clitocybe*, *Coprinus*, *Drosophila*, and *Marasmius* spp.) and Polyporaceæ (including *Dædalea*, *Fistulina*, *Polyporus*, and *Poria* spp.). The extent to which this distribution reflects any fundamental classification of micro-organisms can only be decided by further studies, both chemical and taxonomic.

Types of Compound.—*C_8 series.* In a few cases polyacetylenes of the same or related structures have been found in more or less closely related species of Fungi. Thus *Agrocybe dura* produces agrocybin (XXVI) [67] whilst *Clitocybe diatreta*, in a related genus, produces the two compounds (XXVII) and (XXVIII).[68] The structures of the amides (XXVI) and (XXVII) were

$$\text{(XXVI)}\quad \mathrm{HO{\cdot}CH_2{\cdot}C{\equiv}C{\cdot}C{\equiv}C{\cdot}C{\equiv}C{\cdot}CO{\cdot}NH_2}$$
$$\text{(XXVII)}\quad \mathrm{HO_2C{\cdot}CH{=}CH{\cdot}C{\equiv}C{\cdot}C{\equiv}C{\cdot}CO{\cdot}NH_2}$$
$$\text{(XXVIII)}\quad \mathrm{HO_2C{\cdot}CH{=}CH{\cdot}C{\equiv}C{\cdot}C{\equiv}C{\cdot}CN}$$

finally established by synthesis, the arrangement of the unsaturation in the latter having been previously ascertained by measuring the pK_a of the carboxyl group.[69] The nitrile (XXVIII) has also been synthesised.[70].

Though these three compounds are not dissimilar, a fourth C_8 compound from fungi bears no apparent relation to them. This is the acetylenic thiophenaldehyde, junipal (XXIX), which together with anisaldehyde is responsible for the characteristic odour of *Dædalea juniperina* cultures.

(XXIX) 

Junipal, which occurs together with a (?)vinylogous compound and *p*-anisaldehyde, was isolated by steam-distillation and characterised spectroscopically and by a two-step oxidation to thiophen-2 : 5-dicarboxylic acid.[71] The aldehyde group and sulphur atom are so far unique amongst natural acetylenes; junipal is in fact the only simple natural thiophen known.

C_{10} series. The compounds (XXVI)—(XXVIII) were originally studied because of the antibiotic activity of the metabolic liquors in which they occur, and the aldehyde (XXIX) because of its odour. Another group of fungal polyacetylenes was first encountered in a spectroscopic " screening " of wood-rotting fungi. The most interesting results so far have been obtained with *Polyporus anthracophilus*, an Australian species, from cultures of which at least twelve acetylenes have been isolated and characterised.[72] These may be represented by formulæ (XXX)—(XXXV); the acids occur free, as the methyl esters, or as esters with the alcohol groups of (XXXI) and (XXXII; R = Me).

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[67] Kavanagh, Hervey, and Robbins, *Proc. Nat. Acad. Sci. U.S.A.*, 1950, **36**, 102.

[68] Anchel, (*a*) *J. Amer. Chem. Soc.*, 1952, **74**, 1588; 1953, **75**, 4621; (*b*) *Science*, 1955, **121**, 607.

[69] Bu'Lock, Jones, Mansfield, Thompson, and Whiting, *Chem. and Ind.*, 1954, 990.

[70] Jones and Whiting, personal communication.

[71] Birkinshaw and Chaplen, *Biochem. J.*, 1955, **60**, 255.

[72] Bu'Lock, Jones, and Turner, *Chem. and Ind.*, 1955, 686, and unpublished work.

Mixtures of these compounds were separated by chromatography on alumina, and the structures, all of which have been confirmed by comparison with synthetic materials, were assigned largely on the evidence of spectroscopic data and the identification of hydrogenation products. In all the

(XXX) $HO_2C\cdot CH{=}CH\cdot C{\equiv}C\cdot CH{=}CH\cdot CO_2H$
(XXXI) $CH_3\cdot CH{=}CH\cdot C{\equiv}C\cdot C{\equiv}C\cdot CH{=}CH\cdot CH_2\cdot OH$
(XXXII) $HO\cdot CH_2\cdot CH_2\cdot CH_2\cdot C{\equiv}C\cdot C{\equiv}C\cdot CH{=}CH\cdot CO_2R$
(XXXIII) $RO_2C\cdot CH_2\cdot CH_2\cdot C{\equiv}C\cdot C{\equiv}C\cdot CH{=}CH\cdot CO_2R$
(XXXIV) $CH_3\cdot CH{=}CH\cdot C{\equiv}C\cdot C{\equiv}C\cdot CH{=}CH\cdot CO_2R$
(XXXV) $RO_2C\cdot CH{=}CH\cdot C{\equiv}C\cdot C{\equiv}C\cdot CH{=}CH\cdot CO_2R$

compounds, the double bonds have *trans*-configurations ; this, the occurrence of a C_8 compound (XXX), and the presence in several of oxygen functions at both ends of the molecule, all distinguish the *P. anthracophilus* group from the otherwise similar group of C_{10} compounds from Compositæ. The alcohol (XXXI) (*trans-trans*-matricarianol) in fact occurs in both (p. 380). The compounds (XXXI)—(XXXV) are also produced by at least one other fungus, *Polyporus fumosus*.[72]

Allenes. The first acetylenic antibiotics to be described were, as it happened, not simple polyacetylenes but compounds containing a still more remarkable group, the optically active allene unit ; the fulfilment of van't Hoff's predictions by a micro-organism would have pleased Pasteur. Allenic formulæ had been put forward incorrectly for a number of natural products, including Carlina oxide, but the first natural allene to be identified as such was the antibiotic mycomycin, from *Nocardia acidophilus*.[73] For this the structure (IV) was established by Celmer and Solomons,[74] making full use of the newly established spectroscopic data ; elucidation of the structure was assisted by the observation that the very labile mycomycin is transformed by alkali into a more tractable compound *iso*mycomycin, with changes in ultraviolet and infrared spectra and complete loss of optical activity. *iso*Mycomycin forms a maleic anhydride adduct, and its structure

(IV) $H\cdot C{\equiv}C\cdot C{\equiv}C\cdot CH{=}C{=}CH\cdot CH{=}CH\cdot CH{=}CH\cdot CH_2\cdot CO_2H$
(XXXVI) $CH_3\cdot C{\equiv}C\cdot C{\equiv}C\cdot C{\equiv}C\cdot CH{=}CH\cdot CH{=}CH\cdot CH_2\cdot CO_2H$

(XXXVI) has been confirmed by synthesis.[75] Mycomycin itself, with a free ethynyl group, is extremely unstable, and at room temperature undergoes almost complete resinification in a very short time.

Mycomycin is a C_{13} compound ; somewhat similar compounds with shorter carbon chains are produced by three Polyporales, *Poria corticola*, *P. tenuis*, and an un-named fungus B.841.[13] These produce a mixture of acetylenic allenes which when resolved by counter-current distribution methods afforded the C_{11} acid nemotinic acid (XXXVII), its lactone nemotin

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[73] Johnson and Burdon, *J. Bact.*, 1947, **54**, 281.

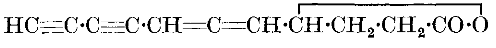
[74] Celmer and Solomons, *J. Amer. Chem. Soc.*, 1952, **74**, 1870, 2245, 3838 ; 1953, **75**, 1372, 3430.

[75] Bohlmann, *Chem. Ber.*, 1954, **87**, 712.

(XXXVIII),[76] and smaller amounts of the homologues odyssic acid (XXXIX) and odyssin (XL).[77] The C_{11} compounds are as labile as mycomycin, but

(XXXVII) $HC\equiv C\cdot C\equiv C\cdot CH=C=CH\cdot CH(OH)\cdot CH_2\cdot CH_2\cdot CO_2H$

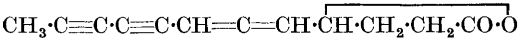
(XXXVIII)



$HC\equiv C\cdot C\equiv C\cdot CH=C=CH\cdot \overline{CH\cdot CH_2\cdot CH_2\cdot CO\cdot O}$

(XXXIX) $CH_3\cdot C\equiv C\cdot C\equiv C\cdot CH=C=CH\cdot CH(OH)\cdot CH_2\cdot CH_2\cdot CO_2H$

(XL)



$CH_3\cdot C\equiv C\cdot C\equiv C\cdot CH=C=CH\cdot \overline{CH\cdot CH_2\cdot CH_2\cdot CO\cdot O}$

the C_{12} compounds are a little more stable and some derivatives were obtained in crystalline form. The alkali-catalysed isomerisations of these allenes differ from that of mycomycin, nemotinic acid being converted rather slowly into the triyne (XLI) (*iso*nemotinic acid), whereas its lactone isomerises very readily to the enetriyne (XLII) (nemotin A).[78] Odyssic acid and odyssin behave similarly, and the structure (XLIII) assigned to odyssin A has been confirmed by synthesis.[79] The allenes (XXXVII)—(XL) combine optically active allene units with a second asymmetric centre, which retains its activity in, for example, *iso*nemotinic acid (XLI).

(XLI) $HC\equiv C\cdot C\equiv C\cdot C\equiv C\cdot CH_2\cdot CH(OH)\cdot CH_2\cdot CH_2\cdot CO_2H$

(XLII) $HC\equiv C\cdot C\equiv C\cdot C\equiv C\cdot CH=CH\cdot CH_2\cdot CH_2\cdot CO_2H$

(XLIII) $CH_3\cdot C\equiv C\cdot C\equiv C\cdot C\equiv C\cdot CH=CH\cdot CH_2\cdot CH_2\cdot CO_2H$

Two compounds which shows changes of ultraviolet absorption spectrum on alkali treatment reminiscent of the nemotin–nemotin A reaction have been detected amongst the metabolites of *Drosophila substrata*,[80] and these too may be allene derivatives. (The partial characterisation [81] of fucoxanthin, a carotenoid from marine algæ, as an allene, though not strictly relevant, may perhaps be noted at this point.)

Other compounds. Several fungi produce polyacetylenes of as yet unknown structure. Besides metabolites of two species of *Coprinus* and one of *Marasmius*,[82] some compounds from *Polyporus biformis* may be especially noted. One of these may be a C_{10} glycol; a second, originally described as a C_9 glycol with a diene-diyne chromophore, is probably nona-4 : 6 : 8-triyne-1 : 2-diol, which would show only weak absorption in most of the ultraviolet region, together with about 5% of a diene-diyne.[83]

In several fungi, including *P. biformis* and *Agrocybe dura*, the amount of solvent-extractable material in the culture medium may be increased by

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[76] Bu'Lock, Jones, and Leeming, *J.*, 1955, 4270.

[77] *Idem*, unpublished work.

[78] Bu'Lock, Jones, Leeming, and Thompson, *J.*, 1956, 3767.

[79] Jones, Skatteböl, and Whiting, personal communication.

[80] Anchel, *Arch. Biochem. Biophys.*, 1953, **43,** 127.

[81] Sörensen, personal communication; *Tids. Kjemi*, 1955, **15,** 129; Torto, and Weedon, *Chem. and Ind.*, 1955, 1219.

[82] Doery, Gardner, Burton, and Abraham, *Antibiotics and Chemotherapy*, 1951, **1,** 409; Anchel, personal communication; Benz, Scandinavian Chem. Meeting VIII, June 14—17th, 1953.

[83] Robbins, Kavanagh, and Hervey, *Proc. Nat. Acad. Sci. U.S.A.*, 1947, **33,** 176; Anchel and Cohen, *J. Biol. Chem.*, 1954, **208,** 319; Anchel, personal communication.

boiling ;[67, 83] since the known polyacetylenes in each case contain hydroxyl groups it would seem likely that boiling liberates some of the material from easily hydrolysed water-soluble conjugates of unknown nature.

Biological Activity

It will have been apparent from preceding sections that many of the natural sources of acetylene derivatives were first studied because of their physiological activity. However, the activity of the source has not always been traced to the acetylenic constituents, and in certain cases where active acetylenes have been isolated other closely related acetylenes have also been found and proved to be inactive. Thus there is no reason to expect any general kind of physiological activity in acetylenic compounds.

For example, the poisonous Umbelliferæ *Œnanthe crocata* and *Cicuta virosa* have very similar pharmacological action, causing violent convulsions ; both plants are important stock-poisons. The toxic effects are due to two different C_{17} glycols, (XXII*a*) and (XXIV*a*) ; these toxins are accompanied in the plants by the corresponding monoalcohols (XXII*b*) and (XXIV*b*), but these closely related compounds are virtually non-toxic.[63]

A similar situation exists in regard to the antibiotic activity of some fungi. Thus that of *Clitocybe diatreta* is due not to the amide (XXVII) but solely to the corresponding nitrile (XXVIII).[68b] The patterns of antibiotic activity of the allenes nemotin (XXXVIII) and mycomycin (IV) are completely changed when these compounds are isomerised to nemotin A (XLII) and *iso*mycomycin (XXXVI).[13, 74] The activities of some polyacetylene antibiotics have been summarised by Anchel ;[15] it is there noted that several are unusually active against mycobacteria, and some also show marked antifungal activity.

None of the antibiotics so far studied has any clinical usefulness ; some are far too unstable and several are highly toxic to animals. However, it is not impossible that some more useful member of the series will be discovered, either as a natural metabolite or as a synthetic material. For most of the polyacetylenes from Compositæ no physiological data have been recorded (cf. ref. 9).

The *N*-*iso*butylamide anacyclin (XXV) belongs to a class of compounds, some of which show strong insecticidal and/or sialogogue activity and others of which are inactive. The factors determining these physiological activities are not yet clear but would appear to be at least partly stereochemical. Anacyclin itself is only slightly toxic to houseflies, but half-hydrogenation of the diyne group gives a product with high activity.[66]

Biosynthetic Aspects

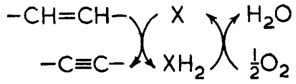
The problem of the biosynthesis of acetylene compounds is twofold, being concerned (*a*) with the biological formation of triple bonds, and (*b*) with the biosynthesis of particular compounds and their relationship to more conventional metabolites. There has as yet been very little in the way of a direct attack upon either problem, but some pointers to probable solutions can be found in the evidence at present available.

Origin of Triple Bonds.—Several lines of evidence suggest that the origin of triple bonds should be considered as part of a wider problem, that of the biological origin of carbon–carbon multiple bonds in general; this problem is unsolved even for the simplest important example, oleic acid. Several of the natural acetylenes belong to well-defined classes of natural products the majority of which possess no triple, but only double, bonds. Thus the acetylenic acids from seed oils are typical in all respects, save in the presence of triple bonds, of the far bigger category of unsaturated C_{18} acids from similar sources. Equally the amide anacyclin is typical of the group of natural *N*-*iso*butylamides. In the same way fucoxanthin appears to differ from more conventional carotenoids only in the presence of an allene group, and it may well be that some of the fungus polyacetylenes are similarly related to members of a growing class of microbiological products with unbranched polyene chains; unfortunately, structures of only a few of these are known.[84]

It is important not to overestimate the thermodynamic instability of acetylenes. Thus, to consider the simplest case, the formation of acetylene from ethylene by oxidation with atmospheric oxygen would be only some 10 kcal. mole^{-1} less exothermic than the corresponding oxidation of ethane:

$$C_2H_6(g) + \tfrac{1}{2}O_2(g) \longrightarrow C_2H_4(g) + H_2O(l) + 32{\cdot}5 \text{ kcal.}$$
$$C_2H_4(g) + \tfrac{1}{2}O_2(g) \longrightarrow C_2H_2(g) + H_2O(l) + 23{\cdot}0 \text{ kcal.}$$

Differences of the same order—modified somewhat by entropy factors and changes in first- and second-order conjugation—would be expected between the heats of various pairs of reactions in which double and triple bonds were formed by oxidation. Thus for enzymic oxidations it might be concluded that the aerobic dehydrogenation of ethylenes to acetylenes would be thermodynamically feasible and sufficiently exothermic to allow the intermediate participation of various redox systems if required, *e.g.*:



Such direct dehydrogenations are known to operate in at least two important biosyntheses of double bonds, the succinoxidase reaction:

$$HO_2C{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2H \rightleftharpoons \textit{trans}\text{-}HO_2C{\cdot}CH{=}CH{\cdot}CO_2H$$

and the various acyl-coenzyme A $\alpha\beta$-dehydrogenations, *e.g.* with butyryl-coenzyme A:

$$CH_3{\cdot}CH_2{\cdot}CH_2{\cdot}CO{\cdot}SA \rightleftharpoons \textit{trans}\text{-}CH_3{\cdot}CH{=}CH{\cdot}CO{\cdot}SA$$
$$(\text{Coenzyme A} = \text{A–SH})$$

Both enzymes play a fundamental part in synthesis and breakdown of fats;[85] they are metalloflavoprotein systems with similar electron-acceptor

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[84] Cf. Oroshnik, Vining, Mebane, and Taber, *Science*, 1955, **121**, 147.

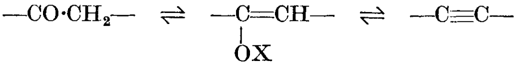
[85] For useful summaries see Lynen, *Nature*, 1954, **174**, 962, and *Ann. Rev. Biochem.*, 1955, **24**, 653.

requirements,[86] and both give *trans*-ethylenes. The intimate mechanism of their action is obscure.

Similar considerations apply equally to what may be called the " dehydrative " routes to unsaturated compounds. Enzymic reactions of this kind leading to double bonds are known, *e.g.*, " crotonase " : [87]

$$trans\text{-}\mathrm{CH_3{\cdot}CH{=}CH{\cdot}CO{\cdot}SA} \rightleftharpoons \mathrm{CH_3{\cdot}CH(OH){\cdot}CH_2{\cdot}CO{\cdot}SA} \rightleftharpoons \mathrm{CH_2{=}CH{\cdot}CH_2{\cdot}CO{\cdot}SA}$$

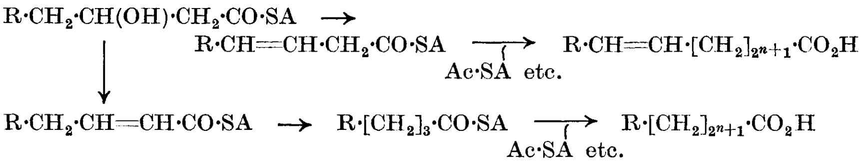
In such dehydrations the heat of reaction is generally rather low ; once more the corresponding reaction, dehydration of an enol by way of a suitable enol derivative to a triple bond, appears to be thermodynamically feasible ; the reverse reaction is of course well known *in vitro* and has been shown to occur biologically (cf. p. 394).



$$\mathrm{{-}CO{\cdot}CH_2{-}} \rightleftharpoons \mathrm{{-}\underset{\displaystyle OX}{\underset{|}{C}}{=}CH{-}} \rightleftharpoons \mathrm{{-}C{\equiv}C{-}}$$

Consideration of the origin of double-bond unsaturation thus constitutes a relevant analogy for the problem of triple-bond biosynthesis. Unfortunately the known enzymic reactions in which double bonds are formed are all rather special and throw little light on the general case, that of multiple bonds more or less insulated from other functional groups. Of this general case oleic or tariric acid may be taken as typical. Three routes to unsaturated fatty acids appear to warrant consideration.

(i) " *Residual* " *unsaturation.* On this hypothesis, unsaturated and saturated fatty acids arise by diverging routes from the same precursors, the unsaturation in the former being " left behind ", as it were, in the process of biosynthesis. The routes branch at a β-hydroxyacylcoenzyme A stage, where alternative modes of dehydration are possible (cf. crotonase, above). Formation of a saturated fatty acid would involve dehydration to an $\alpha\beta$-unsaturated acyl derivative, reduction, and further repeated condensation with coenzyme A. The alternative dehydration product, a $\beta\gamma$-unsaturated compound, by reacting directly with further acetylcoenzyme A, would give rise to an unsaturated fatty acid :



$$\begin{tikzcd}
\mathrm{R{\cdot}CH_2{\cdot}CH(OH){\cdot}CH_2{\cdot}CO{\cdot}SA} \arrow[dr] \arrow[dd] & & \\
& \mathrm{R{\cdot}CH{=}CH{\cdot}CH_2{\cdot}CO{\cdot}SA} \arrow[r, "\mathrm{Ac{\cdot}SA\ etc.}"'] & \mathrm{R{\cdot}CH{=}CH{\cdot}[CH_2]_{2n+1}{\cdot}CO_2H} \\
\mathrm{R{\cdot}CH_2{\cdot}CH{=}CH{\cdot}CO{\cdot}SA} \arrow[r] & \mathrm{R{\cdot}[CH_2]_3{\cdot}CO{\cdot}SA} \arrow[r, "\mathrm{Ac{\cdot}SA\ etc.}"'] & \mathrm{R{\cdot}[CH_2]_{2n+1}{\cdot}CO_2H}
\end{tikzcd}$$

This hypothesis, outlined briefly by Lynen,[85] has the advantage of explaining acceptably the patterns of unsaturation most often found in the natural fatty acids (*e.g.*, $\mathrm{R{\cdot}CH{=}CH{\cdot}[CH_2]_{2n+1}{\cdot}CO_2H}$), and in this respect is superior

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[86] Mahler, *J. Biol. Chem.*, 1954, **206**, 13 ; Kearney and Singer, *Biochim. Biophys. Acta*, 1955, **17**, 596.

[87] Wakil and Mahler, *J. Biol. Chem.*, 1954, **207**, 125 ; Stern, Raw, and Del Campillo, *Fed. Proc.*, 1954, **13**, 304.

to the schemes of Hilditch[88] or Robinson.[89] Variations leading to the less common acids with, *e.g.*, conjugated double bonds, may be formulated readily, and the simpler acetylenic acids might be formed similarly by way of allenic intermediates. The relative amount of unsaturated acids formed would be controlled by the availability of reduced coenzyme rather than by the position of equilibrium of the " crotonase " reaction.

(ii) *Direct dehydrogenation.* Experiments in which abnormal (deuterated[90] or odd-numbered[91]) fatty acids supplied to various organisms were re-isolated as, for example, $\Delta^{9,10}$-derivatives, suggest that dehydrogenation (or hydroxylation followed by dehydration) can occur at specific points on the hydrocarbon chain:

$$CH_3{\cdot}[CH_2]_{m+n+2}{\cdot}CO_2H \rightleftharpoons CH_3{\cdot}[CH_2]_m{\cdot}CH{=}CH{\cdot}[CH_2]_n{\cdot}CO_2H$$

If such reactions in fact occur, there is no *a priori* reason why similar reactions leading to acetylenic acids should not take place.

(iii) *Indirect dehydrogenation.* A third explanation requires the known $\alpha\beta$-dehydrogenation step to be followed by controlled double-bond migration:

$$CH_3{\cdot}[CH_2]_{m+n}{\cdot}CH{=}CH{\cdot}CO_2H \rightleftharpoons CH_3{\cdot}[CH_2]_m{\cdot}CH{=}CH{\cdot}[CH_2]_n{\cdot}CO_2H$$

The fact that all these schemes, suitably amended, and also the hypothesis of enol dehydration (p. 389), could explain the biosynthesis of the acetylenic seed-oil acids, is of wider significance since, as will appear from the following section, other natural acetylenes probably arise in an essentially similar manner, *i.e.*, as offshoots of more normal routes of fat synthesis.

Origin of the Carbon Skeleton.—In the first place it may be observed that all the known natural acetylenes are derived from unbranched chains of carbon atoms. Formally this generalisation applies even to those compounds containing heterocyclic or aromatic rings, and in fact suggests that these may arise from open-chain precursors (cf. p. 393). Such a situation contrasts sharply with the best known group of natural polyenes, the branched-chain carotenoids, but is parallel to that in two groups already mentioned, the natural fatty acids and the unbranched polyenes from micro-organisms. It is only natural to attempt to explain the biosynthesis of all such compounds in similar terms, particularly since the biosynthesis of fatty acids is comparatively well understood.[85]

The role of the two-carbon unit of acetyl coenzyme A in the biosynthesis of saturated fatty acids is of course firmly established, and schemes extending this to the common unsaturated acids have already been outlined, with the observation that, given an acceptable hypothesis for the origin of triple bonds, the schemes can be extended to cover the examples of the C_{18}

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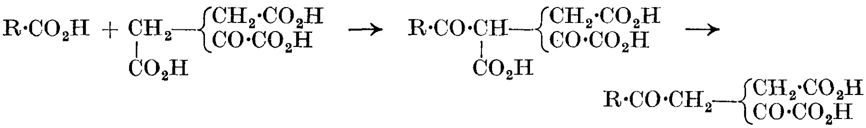
[88] Hilditch, *Oléagineux*, 1955, **10**, 83; " The Chemical Constitution of Natural Fats ", Chapman and Hall, London, 1956, p. 463 *et seq.*

[89] Robinson, " The Structural Relationships of Natural Products ", Oxford Univ. Press, 1955, p. 6.

[90] Schoenheimer and Rittenberg, *J. Biol. Chem.*, 1936, **113**, 505.

[91] Appel, Bohm, Keil, and Schiller, *Z. physiol. Chem.*, 1947, **282**, 220.

acetylenic fatty acids. However, the natural acetylenes do not in general display that marked preference for chains of even numbers of carbon atoms which is characteristic of the fatty acids proper. Chains of 8, 9, 10, 11, 12, 13, 14, 17, and 18 carbon atoms have all been found. In particular cases there may be special explanations for the occurrence of an odd-numbered chain; a carbon atom may have been gained by *C*-methylation or lost by decarboxylation. The latter explanation seems rather likely on *a priori* grounds for compounds lacking a terminal oxygen function. However, even in the series of acids from natural fats the occurrence of odd-numbered carbon chains is not unknown[92] and it is unlikely that their biosynthesis proceeds by routes essentially different from that established for the even-numbered fatty acids. For example, during the building-up of the chain, further condensation of an even-numbered acid might take place with a four-carbon unit (such as succinic or oxaloacetic acid) instead of with acetic acid, and be followed by decarboxylation of the β-keto-acid, giving an acid with an odd-numbered carbon chain:



$$R{\cdot}CO_2H + \underset{\displaystyle CO_2H}{\underset{|}{CH_2}}{-}\left\{\begin{matrix}CH_2{\cdot}CO_2H\\CO{\cdot}CO_2H\end{matrix}\right. \longrightarrow R{\cdot}CO{\cdot}\underset{\displaystyle CO_2H}{\underset{|}{CH}}{-}\left\{\begin{matrix}CH_2{\cdot}CO_2H\\CO{\cdot}CO_2H\end{matrix}\right. \longrightarrow R{\cdot}CO{\cdot}CH_2{-}\left\{\begin{matrix}CH_2{\cdot}CO_2H\\CO{\cdot}CO_2H\end{matrix}\right.$$

In addition to the role of acetylcoenzyme A in primary metabolic processes, biosynthesis from "acetate" units has been demonstrated for a variety of complex metabolites and has been inferred for others from their pattern of oxygenation.[93] The latter approach is not readily applicable to polyacetylenic compounds; moreover, acetate is not the only "building-unit" to merit consideration. The transfer of hydroxyacetaldehyde units is important in plant biosynthesis and succinylcoenzyme A is important as a precursor, *e.g.*, of the pyrrole pigments. Faced with such considerations it seems advisable to limit further speculation to cases where some experimental data are available. At present such evidence has only been obtained for certain fungal acetylenes.

C_{11} and C_{12} Allenes.—A biosynthetic scheme for nemotinic acid must account for the following facts: the precursors must be intermediates in the "normal" glucose metabolism of the fungus;[94] labelled carbon supplied as acetate is efficiently converted into polyacetylenes; the formation of polyacetylenes is stimulated by the addition of acetic, succinic, or malonic acid;[95] in addition to the C_{11} compound nemotinic acid, the fungus also produces a C_{12} compound odyssic acid.[96] The scheme must also account for the formation of the allene groups, which in nemotinic and odyssic acid are unstable. All these requirements can be met by a scheme such as that on page 392, which assumes the biological equivalence of —$CO{\cdot}CH_2$— and

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[92] Cf., *e.g.*, Shorland, Gerson, and Hansen, *Biochem. J.*, 1955, **59**, 350; **61**, 702.

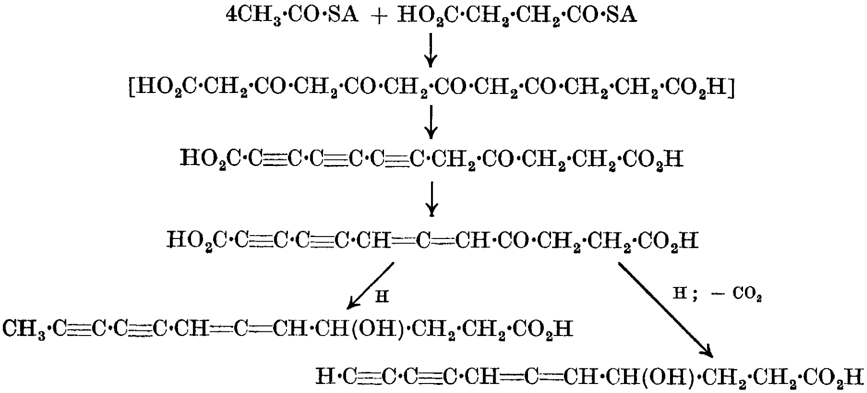
[93] Birch and Donovan, *Austral. J. Chem.*, 1953, **6**, 360, and subsequent papers.

[94] Bu'Lock and Leadbeater, *Biochem. J.*, 1956, **62**, 476.

[95] *Idem*, unpublished results.

[96] Bu'Lock, Jones, and Leeming, *J.*, 1956, 3767.

—C≡C— groups, and which uses acetyl- and succinyl-coenzyme A as precursors.



$$\mathrm{4CH_3{\cdot}CO{\cdot}SA + HO_2C{\cdot}CH_2{\cdot}CH_2{\cdot}CO{\cdot}SA}$$
$$\downarrow$$
$$\mathrm{[HO_2C{\cdot}CH_2{\cdot}CO{\cdot}CH_2{\cdot}CO{\cdot}CH_2{\cdot}CO{\cdot}CH_2{\cdot}CO{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2H]}$$
$$\downarrow$$
$$\mathrm{HO_2C{\cdot}C{\equiv}C{\cdot}C{\equiv}C{\cdot}C{\equiv}C{\cdot}CH_2{\cdot}CO{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2H}$$
$$\downarrow$$
$$\mathrm{HO_2C{\cdot}C{\equiv}C{\cdot}C{\equiv}C{\cdot}CH{=}C{=}CH{\cdot}CO{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2H}$$
$$\swarrow \mathrm{H} \qquad\qquad \searrow \mathrm{H;\ -CO_2}$$
$$\mathrm{CH_3{\cdot}C{\equiv}C{\cdot}C{\equiv}C{\cdot}CH{=}C{=}CH{\cdot}CH(OH){\cdot}CH_2{\cdot}CH_2{\cdot}CO_2H}$$
$$\mathrm{H{\cdot}C{\equiv}C{\cdot}C{\equiv}C{\cdot}CH{=}C{=}CH{\cdot}CH(OH){\cdot}CH_2{\cdot}CH_2{\cdot}CO_2H}$$

Such a synthesis from acetate and succinate would be promoted by the inhibitory action of malonate on normal succinate oxidation ; allene formation at the keto-acid stage would be facilitated by the gain in conjugation (with the carbonyl group). The alternative reactions at the final stage—reduction of the carbonyl group accompanied either by decarboxylation or by reduction of carboxyl to methyl—lead to nemotinic and odyssic acid respectively.

C_8 and C_{10} Compounds.—Evidence of a rather different kind lends some support to a not dissimilar scheme for the biogenesis of acetylenic compounds in *Polyporus anthracophilus* ; [72] the compounds produced by this fungus are apparently interconvertible by way of smaller molecules.[97] All the compounds are readily derivable from the four compounds shown below, and these (the equivalence of —CO·CH_2— and —C≡C— units being again assumed) can be derived in the manner indicated from the common metabolic intermediates acetate, succinate and fumarate :

$\mathrm{CH_3{\cdot}CH{=}\vdots{=}CH{\cdot}C{\equiv}\vdots{\equiv}C{\cdot}C{\equiv}\vdots{\equiv}C{\cdot}CH{=}\vdots{=}CH{\cdot}CO_2H}$	5 acetate
$\mathrm{HO_2C{\cdot}CH{=}CH{\cdot}C{\equiv}\vdots{\equiv}C{\cdot}C{\equiv}\vdots{\equiv}C{\cdot}CH{=}\vdots{=}CH{\cdot}CO_2H}$	fumarate + 3 acetate
$\mathrm{HO_2C{\cdot}CH_2{\cdot}CH_2C{\equiv}\vdots{\equiv}C{\cdot}C{\equiv}\vdots{\equiv}C{\cdot}CH{=}\vdots{=}CH{\cdot}CO_2H}$	succinate + 3 acetate
$\mathrm{HO_2C{\cdot}CH{=}CH{\cdot}C{\equiv}\vdots{\equiv}C{\cdot}CH{=}\vdots{=}CH{\cdot}CO_2H}$	fumarate + 2 acetate

Further transformations

Whilst it is clear that speculation about the ultimate origin of other natural acetylenes must await the results of further experimental work, a comparison of the structures of various polyacetylenes from the same or related sources serves to draw attention to some other points of possible biogenetic interest.

Thus the co-occurrence in *Clitocybe diatreta* of the amide (XXVII) and the nitrile (XXVIII) suggests a possible biogenesis for the somewhat

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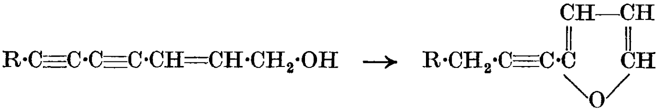
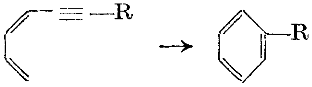
[97] Bu'Lock, Leadbeater, and Turner, unpublished results.

uncommon cyanide group (the production[98] of free hydrocyanic acid by the polyacetylene-producing fungus B.841 may be noted in this connection). In the same way the occurrence in related species of the tridecanol derivative (XIII), the phenylheptanol derivative (XIV) and the (phenylpropyl)furan derivative (II), all isomeric with each other, suggests the possible operation of two interesting transformations. One, the apparent conversion of an acetylenic alcohol into a furan derivative :[55]

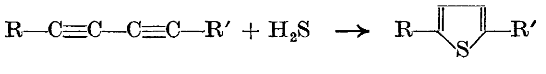


is paralleled by a simpler reaction *in vitro*.[99] The second correlates a hexadienynyl residue and a phenyl group, as seen also in the pair of *Coreopsis* hydrocarbons (XVI) and (XIX), and might suggest a biological variation of the Diels–Alder reaction :



A more cautious interpretation would be to regard it as evidence for a route to aromatic compounds closely related to one leading to straight-chain unsaturated compounds. Such a route would clearly be different from the well-established shikimic acid route. On the other hand, if the previous hypotheses concerning the biosynthesis of acetylenes are generally applicable, such a route to phenyl derivatives would start from the same kind of precursors as are involved in the route from acetate to hydroxybenzene derivatives as postulated by Birch.[93]

In considering the co-occurrence of the thiophen junipal and *p*-anisaldehyde in *Dædalea juniperina*, Birkinshaw and Chaplen[71] suggested that both might arise from a common non-cyclic precursor. The route to the thiophen,* which can be formally written as :



had already been suggested by Challenger and Holmes in connection with the occurrence of αα′-terthienyl, with its unbranched chain of 12 carbon atoms, in certain Compositæ.[100]

In addition to such hypothetical transformations which could involve common precursors rather than acetylenic compounds themselves, there is some direct evidence that the natural acetylenic compounds are not always

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[98] Robbins, Rolnick, and Kavanagh, *Mycologia*, 1950, **42**, 161.

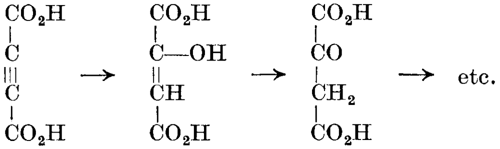
[99] Heilbron, Jones, Smith, and Weedon, *J.*, 1946, 54.

[100] Challenger and Holmes, *J.*, 1953, 1837 ; Zechmeister and Sease, *J. Amer. Chem. Soc.*, 1947, **69**, 273.

* Cf. the isolation from Compositæ of a thiophen corresponding to the addition of hydrogen sulphide to the hydrocarbon (XX) (Sörensen, unpublished work).

mere end-products of metabolism. Thus the polyacetylenes from Basidiomycete B.841 are actively broken down by the fungus mycelium,[94] whilst in *Polyporus anthracophilus* there is a complicated interaction between the breakdown and re-synthesis of the various acetylenic metabolites.[97] In higher plants, seasonal variations in the relative amounts of different acetylenic constituents, as observed in *Œnanthe crocata* and *Cicuta virosa*,[63] may indicate a similar state of affairs.

Recently Eimhjellen [101] has described work with certain strains of Enterobacteriaceæ which will utilise (non-natural) acetylenic compounds such as acetylenedicarboxylic acid as sole carbon source. In these organisms acetylene breakdown follows a pathway similar to that put forward here as a route for their synthesis. Thus acetylenedicarboxylic acid is converted into oxaloacetic acid, apparently by hydration and by way of the enol-form, and not *via* fumaric acid by hydrogenation :



$$HO_2C{-}C{\equiv}C{-}CO_2H \longrightarrow HO_2C{-}C(OH){=}CH{-}CO_2H \longrightarrow HO_2C{-}CO{-}CH_2{-}CO_2H \longrightarrow \text{etc.}$$

The conversion into oxaloacetic acid can be brought about by cell-free extracts, but the reversibility of the reaction has not yet been demonstrated. Other strains will utilise butyne-1 : 4-diol and propynol as sole carbon sources. The oxidation of butyne-1 : 4-diol, hexa-2 : 4-diyne-1 : 6-diol and propynol by soil bacteria has also been described,[102] propynol being stated to afford hexa-2 : 4-diyne-1 : 6-dioic acid. However, under the experimental conditions described (1 month's incubation in air at 22°), this product might perhaps be expected to result from autoxidation and non-enzymic oxidative coupling.

The author is especially grateful to all those who have helped by friendly criticism and by making available results at present unpublished, particularly Professor E. R. H. Jones (Oxford) and Professor N. A. Sörensen (Trondheim).

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[101] Eimhjellen, personal communication ; *Biochem. J.*, 1956, **64,** 4P.

[102] Hanaoka, Harada, and Takizawa, *J. Agric. Chem. Soc. Japan*, 1952, **26,** 151 (*Chem. Abs.*, 1954, **48,** 10,114).