Synthesis of Polyenes.

THE SIXTH PEDLER LECTURE, DELIVERED BEFORE THE CHEMICAL SOCIETY ON JANUARY 27TH, 1938.

By RICHARD KUHN.

IT is with great pleasure that I most sincerely thank the Chemical Society for the invitation, with which they have honoured me, to give the sixth lecture in memory of Sir Alexander Pedler. With admiration I have become acquainted with the career of this natural philosopher, whose investigations ranged from Organic Chemistry through Physics to Astronomy. In contrast to this versatility stands the problem with which I, aided by a number of outstanding collaborators, have been engaged for more than ten years. This lies in the artificial preparation of compounds containing the largest possible number of conjugated double bonds. I propose to speak to-night of some of the results obtained so far in this scheme of research. The synthetic methods which have proved most serviceable will be given most prominence. I can only refer briefly in a few places to the connection between chemical constitution and physical properties. In this connection, there are, besides the regularities in melting points (Kuhn and Grundmann, *Ber.*, 1936, **69**, 224), the exhaustive measurements of the absorption and fluorescence spectra carried out by my prematurely deceased colleague, K. W. Hausser (Hausser, Kuhn, Smakula, and Kreuchen, *Z. physikal. Chem.*, 1935, *B*, **29**, 363; Hausser, Kuhn, Smakula, and Hoffer, *ibid.*, p. 371; Hausser, Kuhn, Smakula, and Deutsch, *ibid.*, pp. 378, 384; Hausser, Kuhn, and Seitz, *ibid.*, p. 391; Hausser, R. Kuhn, and E. Kuhn, *ibid.*, p. 417; Hausser and Smakula, *Angew. Chem.*, 1935, **47**, 657; **48**, 152).

A. $C_6H_5\cdot[CH{:}CH]_n\cdot C_6H_5$ ($n = 1, 2, 3, 4, 5, 6, 7, 8, 11, 15$).

For the synthesis of the diphenyl polyenes (Kuhn and Winterstein, *Helv. Chim. Acta*, 1928, **11**, 87), we have to-day the following methods:

1 : 6-Diphenylhexatriene (III) (Smedley, J., 1908, **93**, 372) is best obtained by treating a suspension of hydrocinnamoin in ether with the calculated quantity of phosphorus di-iodide (P_2I_4). The di-iodide, most probably formed as intermediate, spontaneously splits off iodine, and one obtains in a few minutes the yellow hydrocarbon in theoretical yield:

$$\text{(I)}\ \mathrm{Ph{\cdot}CH{:}CH{\cdot}CHO + 2H + OHC{\cdot}CH{:}CHPh}$$
$$\Big\downarrow \mathrm{Zn}$$
$$\text{(II)}\ \mathrm{Ph{\cdot}CH{:}CH{\cdot}CH(OH){\cdot}CH(OH){\cdot}CH{:}CHPh}$$
$$\Big\downarrow \mathrm{P_2I_4}$$
$$\text{(III)}\ \mathrm{Ph{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CHPh}$$

This reaction, discovered with Winterstein (*loc. cit.*) in 1927, can be carried out not only with 1 : 2-glycols, but also, as Kuhn and Wallenfels (unpublished work) have recently shown, with 1 : 4-glycols and with 1 : 6-glycols, and thus has general application in the synthesis of the polyenes. The 1 : 4-glycols (VI) are readily obtainable by condensation of polyene aldehydes with acetylenedimagnesium bromide (IV), and subsequent partial hydrogenation of the acetylenic glycols (V). Diphenyloctatetraene was obtained in very good yield by this method as follows:

$$\mathrm{Ph{\cdot}CH{:}CH{\cdot}CHO + \text{(IV)}Br{\cdot}Mg{\cdot}C{\vdots}C{\cdot}MgBr + OHC{\cdot}CH{:}CHPh}$$
$$\Big\downarrow$$
$$\text{(V)}\ \mathrm{Ph{\cdot}CH{:}CH{\cdot}CH(OH){\cdot}C{\vdots}C{\cdot}CH(OH){\cdot}CH{:}CHPh}$$
$$\Big\downarrow \mathrm{H_2}$$
$$\text{(VI)}\ \mathrm{Ph{\cdot}CH{:}CH{\cdot}CH(OH){\cdot}CH{:}CH{\cdot}CH(OH){\cdot}CH{:}CHPh}$$
$$\Big\downarrow \mathrm{P_2I_4}$$
$$\text{(VII)}\ \mathrm{Ph{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CHPh}$$

The *phosphorus di-iodide method* permits therefore of the preparation not only of compounds with an odd, but also of those with an even, number of conjugated double bonds. The 1 : 6-glycols are obtained according to Straus and Kollek (*Ber.*, 1926, **59**, 1664) in a similar way, diacetylenedimagnesium bromide, $Br{\cdot}Mg{\cdot}C\vdots C{\cdot}C\vdots C{\cdot}MgBr$, being used.

Kuhn and Winterstein (*loc. cit.*) first obtained 1 : 12-diphenyldodecahexaene (IX) by condensation of 5-phenylpentadienal (VIII) with succinic acid in the presence of lead oxide, a mixture of glacial acetic acid and acetic anhydride being used as solvent :

$$\text{(VIII)}\ Ph{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CHO + HO_2C{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2H + OHC{\cdot}CH{:}CH{\cdot}CH{:}CHPh$$
$$\downarrow$$
$$\text{(IX)}\ Ph{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CHPh$$

They obtained the yellow 1 : 8-diphenyloctatetraene by using cinnamaldehyde in place of phenylpentadienal, and the copper-coloured 1 : 16-diphenylhexadecaoctaene from 7-phenylheptatrienal. In general, with succinic acid as the " middle piece," this *lead oxide method* yields hydrocarbons with an *even* number of conjugated double bonds.

The synthesis of diphenyl polyenes with an odd number of double bonds ($n = 5$, $n = 7$), was achieved by substitution of dihydromuconic acid, $HO_2C{\cdot}CH_2{\cdot}CH{:}CH{\cdot}CH_2{\cdot}CO_2H$, for succinic acid.

It would be expected that dihydrohexatriene-1 : 6-dicarboxylic acid, $HO_2C{\cdot}CH_2{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH_2{\cdot}CO_2H$, should give rise to even-number hydrocarbons by the lead oxide method. The recent synthesis of this substance has made it possible to attempt this experiment. Kuhn and Grundmann (*Ber.*, 1936, **69**, 1757) found that butadiene-1 : 4-diacetic acid (X), prepared by them, did indeed yield 1 : 12-diphenyldodecahexaene (IX) by condensation with cinnamaldehyde and lead oxide :

$$Ph{\cdot}CH{:}CH{\cdot}CHO + \text{(X)}HO_2C{\cdot}CH_2{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH_2{\cdot}CO_2H + OHC{\cdot}CH{:}CHPh \longrightarrow \text{(IX)}$$

Another synthesis of the same hydrocarbon was rendered possible, when a year ago Kuhn and Wallenfels (*Ber.*, 1937, **70**, 1331), succeeded in preparing the orange-coloured 11-phenylundecapentaenal $Ph{\cdot}[CH{:}CH]_5{\cdot}CHO$, and the deep red 15-phenylpentadecaheptaenal, $Ph{\cdot}[CH{:}CH]_7{\cdot}CHO$, by condensation of cinnamaldehyde with crotonaldehyde in the presence of piperidine acetate. By the action of benzylmagnesium chloride on the pentaenal (XI) they obtained by the usual *Grignard reaction* the alcohol (XII), which was not isolated. This was converted into 1 : 12-diphenyldodecahexaene (IX) by removal of water and formation of the conjugated double bond system :

$$\text{(XI)}\ Ph{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CHO + ClMg{\cdot}CH_2Ph$$
$$\text{(XII)}\ Ph{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH(OH){\cdot}CH_2Ph$$

The hexaenes prepared by these *three* different methods were shown to be identical by mixed melting point (267°) and by the positions of their very sharp absorption bands.

We had endeavoured for some time to extend the series of diphenyl polyenes still further. But it turned out that the well-proved lead oxide method began to fail at about eight conjugated double bonds. We recognised that any considerable progress would only be made possible by the discovery of a fundamentally new synthetic method. Such a method was recently found with K. Wallenfels (Kuhn, *Angew. Chem.*, 1937, **50**, 703). The oxygen atom of the polyene aldehydes, just like that of the simple aldehydes, can be replaced by an atom of sulphur by the action of hydrogen sulphide under suitable conditions. Similarly, the preparation of selenoaldehydes by the action of hydrogen selenide is also possible. It was known that sulphur may be split off from thiobenzaldehyde, and that the hypothetical bivalent radical benzylidene so formed dimerises to stilbene. This reaction can now also be carried out with polyene thio- and seleno-aldehydes. The removal of the sulphur is best brought about by metals such as copper, metal carbonates, various reducing agents, and also by certain amines such as piperidine

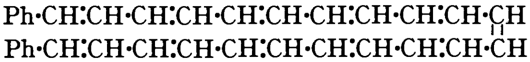
From 11-phenylundecapentaenal (XI), we obtained in this way 1 : 22-diphenyldocosaundecaene (XIV) :

(XI) $\mathrm{Ph{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CHO}$

$$\downarrow \mathrm{H_2S,\ H_2Se}$$

(XIII*a*) $\mathrm{Ph{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CHS}$
(XIII*b*) $\mathrm{Ph{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CHSe}$

$$\downarrow \mathrm{Cu}$$

(XIV) 

$$\begin{array}{l}\mathrm{Ph{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH}\\ \qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad \|\\ \mathrm{Ph{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH}\end{array}$$

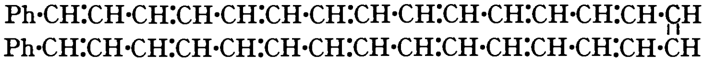
This hydrocarbon was violet-black, and had a marked metallic lustre. It melted at 318°. From 15-phenylpentadecaheptaenal (XV) we succeeded in preparing 1 : 30-diphenyltriacontapentadecaene (XVII) by means of the corresponding thioaldehyde (XVI) :

(XV) $\mathrm{Ph{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CHO}$

$$\downarrow$$

(XVI) $\mathrm{Ph{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CHS}$

$$\downarrow$$

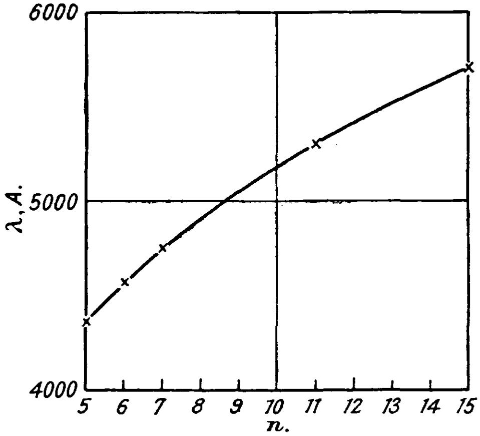
(XVII) 

$$\begin{array}{l}\mathrm{Ph{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH}\\ \qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad \|\\ \mathrm{Ph{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH}\end{array}$$

This hydrocarbon with thirty methene groups in a straight chain is the highest member of the polyene series known at present. The solid is greenish-black, and its solutions are violet-red. The constitution given follows from the position of the absorption bands. These, together with those of the lower homologues, fit into a regular series, as was shown with Hausser :

$n = 5$ $\lambda = 4340$ A. in nitrobenzene
$n = 6$ $\lambda = 4580$ A. in nitrobenzene
$n = 7$ $\lambda = 4740$ A. in nitrobenzene
$n = 11$ $\lambda = 5300, 4930, 4620$ A. in nitrobenzene
$n = 15$ $\lambda = 5700, 5320$ A. in nitrobenzene

FIG. 1.



Wave-lengths of the first absorption bands in nitrobenzene for $\mathrm{C_6H_5{\cdot}[CH{:}CH]_n{\cdot}C_6H_5}$.
n = *number of conjugated double bonds.*

We have not yet succeeded in preparing the pentadecaene in the pure state. The ability to sublime in a high vacuum falls off much lower down the series, and the solubility decreases so rapidly with the increasing number of conjugated double bonds that we were unable to find a solvent from which to recrystallise the pentadecaene.

B. $\mathrm{CH_3{\cdot}[CH{:}CH]_{\mathit{n}}{\cdot}CHO}$ ($n = 1, 2, 3, 4, 5,$ —, 7, —, 9) *and* $\mathrm{CH_3{\cdot}[CH{:}CH]_{\mathit{n}}{\cdot}CO_2H}$ ($n = 1, 2, 3, 4, 5, 6,$ —, 8).

The fundamental method for the synthesis of the purely aliphatic polyenes, to which we now turn, is the aldol-like condensation of acetaldehyde with itself. A convenient preparation of sorbaldehyde was discovered (Kuhn and Hoffer, *Ber.*, 1930, **63**, 2164; 1931, **64**, 1977) in 1930 in the action of piperidine on a mixture of acetaldehyde and crotonaldehyde. The attempt to condense crotonaldehyde with itself under the same conditions was, however, unsuccessful. As was found later (Kuhn, Badstübner, and Grundmann, *Ber.*, 1936, **69**, 98) the crotonaldehyde condensed in the required sense only after exposure to sunlight, or after irradiation with a mercury lamp. This effect was apparently due to the formation of a small quantity of crotonic acid by autoxidation. If the irradiated " active " crotonaldehyde was shaken with alkali, it became " inactive " again. If some crotonic acid was added, the condensation proceeded at once even in the dark. We also found that the crotonic acid could be replaced by other acids. The sole necessary condition is that the amine used as catalyst should be present as a salt, and not as the free base. For preparative work " piperidine acetate," an equimolecular mixture of piperidine and glacial acetic acid, is employed. Since then we have used this catalyst frequently for aldehyde condensations, and Kuhn and Grundmann (*Ber.*, 1937, **70**, 1318) have obtained with it a series of higher vinylene homologues of crotonaldehyde (XVIII) :

(XVIII) $\mathrm{CH_3{\cdot}CH{:}CH{\cdot}CHO}$ (XIX) $\mathrm{CH_3{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CHO}$
(XX) $\mathrm{CH_3{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CHO}$ (XXI) $\mathrm{CH_3{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CHO}$
(XXII) $\mathrm{CH_3{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CHO}$
(XXIII) $\mathrm{CH_3{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CHO}$
(XXIV) $\mathrm{CH_3{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CHO}$

100 G. of the orange-red dodecapentaenal ($n = 5$) can be obtained by the action of piperidine acetate on 1 kg. of crotonaldehyde. The hexadecaheptaenal ($n = 7$) forms deep red needles of melting point 218° (Kuhn, Grundmann, and Trischmann, *Z. physiol. Chem.*, 1937, **248**, IV). Bernhauer (*Biochem. Z.*, 1932, **249**, 199; **251**, 173) showed that the yield of octatrienal from the condensation of crotonaldehyde varied widely with the kind of piperidine used. This is also true of the higher polyene aldehydes. In recent experiments (Kuhn and Grundmann, unpublished work) the catalyst and the reaction conditions have been so much improved that 40% of the cheap crotonaldehyde is converted into a deep red, crystalline mixture of polyene aldehydes.

All these aldehydes condense with malonic acid in pyridine to give the carboxylic acid with one double bond more. In the case of the higher aldehydes, it is essential to use piperidine as catalyst in the Doebner reaction; with the lower aldehydes, addition of piperidine considerably lowers the yields, since here the condensation of the aldehyde with itself becomes too rapid. On the other hand, the higher aldehydes condense but slowly with themselves in the presence of piperidine salts, so that the reaction with the methylene group of the malonic acid predominates (Kuhn and Grundmann, *Ber.*, 1937, **70**, 1318).

A further difference between the " lower " and the " higher " polyene aldehydes lies in the fact that the former with malonic acid and piperidine yield the monocarboxylic acids directly, whereas the higher aldehydes in the presence of piperidine yield only the dicarboxylic acids. These must then be converted into the corresponding polyene carboxylic acids by decarboxylation. This is carried out by boiling with acetic acid and acetic anhydride rather than by dry thermal decomposition (*idem, loc. cit.*).

(XXV) $\mathrm{CH_3{\cdot}CH{:}CH{\cdot}CO_2H}$ (XXVI) $\mathrm{CH_3{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CO_2H}$
(XXVII) $\mathrm{CH_3{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CO_2H}$
(XXVIII) $\mathrm{CH_3{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CO_2H}$
(XXIX) $\mathrm{CH_3{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CO_2H}$
(XXX) $\mathrm{CH_3{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CO_2H}$
(XXXI) $\mathrm{CH_3{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}C(CO_2H)_2}$

The first coloured compound of this series is the decatetraenecarboxylic acid ($n = 4$) (Kuhn and Hoffer, *Ber.*, 1930, **63**, 2164; 1931, **64**, 1977). The hexadecaheptaenalmalonic acid ($n = 8$) (Kuhn, Grundmann, and Trischmann, *Z. physiol. Chem.*, 1937, **248**, IV) crystallises from pyridine in deep violet needles. Eight molecules of hydrogen are taken up during the catalytic hydrogenation. Subsequent distillation yields a colourless oil, which solidifies at once. This crystallises from alcohol in greasy shining platelets of melting point 69°, which are identical in all their properties with natural stearic acid.

The above total direct synthesis of stearic acid is also of interest in connection with the biological synthesis of fatty acids in Nature. This may be founded on a catalytic condensation of eight molecules of acetaldehyde in a straight chain. We are not as yet acquainted with the intermediate stages actually occurring in Nature, but evidently not only acetaldehyde, but also its derivatives or predecessors like pyruvic acid (Smedley-Maclean), may undergo the aldol condensation. During metabolism, reduction certainly occurs at an earlier stage than in our synthesis, since highly unsaturated fatty acids, which could be detected by their colour, have not as yet been observed in either plants or animals. The catalytic hydrogenation of polyene aldehydes proceeded smoothly in all cases, yielding the corresponding saturated alcohols. In this way pure cetyl alcohol of melting point 48·5° was obtained from hexadecaheptaenal ($n = 7$) (Kuhn, *Angew. Chem.*, 1937, **50**, 703).

C. $CH_3{\cdot}[CH{:}CH]_n{\cdot}CH_3$ ($n = 1, 2, 3, 4, —, 6$).

The polyene aldehydes react normally with alkylmagnesium halides, forming the corresponding carbinols. Kuhn and Grundmann (*Ber.*, 1938, **71**, 442), who established this, also found an excellent means for dehydrating the secondary alcohols so obtained, and thus preparing the aliphatic polyene hydrocarbons. This reagent is a 1—2% solution of *p*-toluenesulphonic acid in ether.

We obtained from sorbaldehyde (XXXII) and ethylmagnesium bromide 1 : 6-dimethylhexatriene (XXXIV), previously prepared by other methods (Urion, *Ann. Chim.*, 1934, [ii], **1**, 5).

$$\text{(XXXII)}\ CH_3{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CHO + BrMg{\cdot}CH_2{\cdot}CH_3$$

$$\downarrow$$

$$\text{(XXXIII)}\ CH_3{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH(OH){\cdot}CH_2{\cdot}CH_3$$

$$\downarrow$$

$$\text{(XXXIV)}\ CH_3{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH_3\text{, m. p. 52°}$$

We also obtained the new compounds 1 : 8-dimethyloctatetraene (XXXVI) from octatrienal, and 1 : 12-dimethyldodecahexaene (XXXVIII) from dodecapentaenal :

(XXXV) $CH_3{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH(OH){\cdot}CH_2{\cdot}CH_3$
(XXXVI) $CH_3{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH_3$, m. p. 125°
(XXXVII) $CH_3{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH(OH){\cdot}CH_2{\cdot}CH_3$
(XXXVIII) $CH_3{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH_3$, m. p. 205°

The hexaene can be sublimed undecomposed in a high vacuum as lemon-yellow needles. It is the first synthetic purely aliphatic hydrocarbon with colour. It gives with antimony trichloride in chloroform an indigo-blue solution with an absorption band at 5980 A.

The new hydrocarbons are notable for the extreme sharpness of their absorption bands (Kuhn, *loc. cit.*).

D. $HO_2C{\cdot}[CH{:}CH]_n{\cdot}CO_2H$ ($n = 1, 2, 3, 4, 5, —, 7$) *and* $HO_2C{\cdot}CH_2{\cdot}[CH{:}CH]_n{\cdot}CO_2H$ ($n = 1, 2, 3, 4$).

Until quite recently, muconic acid ($n = 2$) was the highest synthetic member of the polyene ωω′-dicarboxylic acid series. Crocetin and bixin are natural products of the same type with seven and nine conjugated double bonds respectively. They, however, contain four methyl groups as side chains. A procedure, discovered with Grundmann

(Kuhn and Grundmann, *Ber.*, 1936, **69**, 1757, 1979; 1937, **70**, 1318), has made it possible to prepare the symmetrical polyene dicarboxylic acids up to $n = 7$.

(XXXIX) $HO_2C\cdot CH:CH\cdot CO_2H$ (XL) $HO_2C\cdot CH:CH\cdot CH:CH\cdot CO_2H$
(XLI) $HO_2C\cdot CH:CH\cdot CH:CH\cdot CH:CH\cdot CO_2H$
(XLII) $HO_2C\cdot CH:CH\cdot CH:CH\cdot CH:CH\cdot CH:CH\cdot CO_2H$
(XLIII) $HO_2C\cdot CH:CH\cdot CH:CH\cdot CH:CH\cdot CH:CH\cdot CH:CH\cdot CO_2H$
(XLIV) $HO_2C\cdot CH:CH\cdot CH:CH\cdot CH:CH\cdot CH:CH\cdot CH:CH\cdot CH:CH\cdot CH:CH\cdot CO_2H$

One starts from the polyene moncarboxylic esters (XLV), which are condensed with potassium ethoxide and oxalic ester to oxalo-polyene carboxylic esters (XLVI). Lapworth (J., 1900, **77**, 1276) discovered this reaction for crotonic ester ($n = 1$), and Borsche (*Ber.*, 1932, **65**, 868; *Annalen*, 1933, **505**, 177) had already successfully applied it to sorbic ester ($n = 2$). It is noteworthy that, in the case of the higher esters, the condensation only proceeds in the presence of pyridine.

$$\text{(XLV)}\quad RO_2C\cdot CO_2R + CH_3\cdot[CH:CH]_n\cdot CO_2R$$
$$\Big\downarrow \text{KOEt, Py}$$
$$\text{(XLVI)}\quad RO_2C\cdot CO\cdot CH_2\cdot[CH:CH]_n\cdot CO_2R$$
$$\Big\downarrow Ac_2O$$
$$\text{(XLVII)}\quad RO_2C\cdot C(OAc):CH\cdot[CH:CH]_n\cdot CO_2R$$
$$\Big\downarrow \text{Al,Hg}$$
$$\text{(XLVIII)}\quad RO_2C\cdot CH(OAc)\cdot[CH:CH]_n\cdot CH_2\cdot CO_2R$$
$$\Big\downarrow R'OH,\ NaOH$$
$$\text{(XLIX)}\quad R'O_2C\cdot[CH:CH]_{n+1}\cdot CO_2R'$$

The oxalo-esters (XLVI) so obtained were acetylated with acetic anhydride, and the acetyl compounds (XLVII), which are derived from the enol forms, were reduced with aluminium amalgam. In accordance with Thiele's rule, they take up two hydrogen atoms at the ends of the conjugated system (XLVIII). The last stage is the removal of acetic acid (OAc and H from the ends of the chain !) by aqueous or alcoholic alkali. If the acetyldihydro-compound is treated with methyl-alcoholic alkali, the dicarboxylic acid (XLIX) is obtained as the dimethyl ester, and ethyl-alcoholic alkali yields the diethyl ester. Thus interchange of the ester groups occurs during the reaction. In this way one can pass from the monocarboxylic acids with n double bonds to the dicarboxylic acids with $n + 1$ double bonds.

The synthesis of tetradecaheptaene-1 : 14-dicarboxylic acid ($n = 7$) did not follow the above scheme exactly. During the reduction of the acetyloxalo-ester $RO_2C\cdot C(OAc):CH\cdot[CH:CH]_6\cdot CO_2R$ with aluminium amalgam, the expected acetyldihydro-compound $RO_2C\cdot CH(OAc)\cdot[CH:CH]_6\cdot CH_2\cdot CO_2R$ was not formed, but the dodecahexaene-1 : 12-diacetic ester $RO_2C\cdot CH_2\cdot[CH:CH]_6\cdot CH_2\cdot CO_2R$ was formed by replacement of the acetyl group by an atom of hydrogen. However, the polyene diacetic esters $RO_2C\cdot CH_2\cdot[CH:CH]_n\cdot CH_2\cdot CO_2R$ can be dehydrogenated to the polyene dicarboxylic esters by the action of atmospheric oxygen in the presence of alkali, a reaction found (Kuhn and Drumm, *Ber.*, 1932, **65**, 1458) for crocetin and bixin. We have made use of this in the synthesis of tetradecaheptaene-1 : 14-dicarboxylic acid, the formula of which differs from that of crocetin only in the absence of the four methyl side chains.

The oxalic ester method can also be applied to the *synthesis of methylated polyene dicarboxylic acids* (Kuhn and Grundmann, *Ber.*, 1937, **70**, 1894). In this connection it may be observed that not only methyl groups, but also methylene groups at the ends of a conjugated system, will condense with oxalic ester. It is possible, therefore, to obtain one and the same compound in two different ways, accordingly as the "right" or the "left" carboxyl group is introduced as oxalic ester. Thus β-methylmuconic acid (LII) can be prepared either from ββ-dimethylacrylic ester (L) or from β-ethylacrylic ester (LIV) as shown by the following formulæ. We obtained practically the same yields (36%) by both methods :

$$\begin{tikzcd}
\mathrm{RO_2C{\cdot}CO_2R + CH_3{\cdot}CMe{:}CH{\cdot}CO_2R\ (L)} \arrow[r] & \mathrm{RO_2C{\cdot}CO{\cdot}CH_2{\cdot}CMe{:}CH{\cdot}CO_2R\ (LI)} \arrow[d] \\
 & \mathrm{(LII)\ RO_2C{\cdot}CH{:}CH{\cdot}CMe{:}CH{\cdot}CO_2R} \\
\mathrm{(LIV)\ RO_2C{\cdot}CH{:}CH{\cdot}CH_2Me + RO_2C{\cdot}CO_2R} \arrow[r] & \mathrm{RO_2C{\cdot}CH{:}CH{\cdot}CHMe{\cdot}CO{\cdot}CO_2R\ (LIII)} \arrow[u]
\end{tikzcd}$$

β-Methylhexatrienedicarboxylic acid (LVII) affords another example of this kind. Either β-methylsorbic ester (LV) or hexadiene-1 : 3-carboxylic acid ester (LIX) can be used as starting material, but the yields by the second route are very much better than by the first. In general, it appears that the course of the synthesis is rendered more difficult by β-methyl groups.

$$\begin{tikzcd}
\mathrm{(LV)\ RO_2C{\cdot}CO_2R + CH_3{\cdot}CH{:}CH{\cdot}CMe{:}CH{\cdot}CO_2R} \arrow[d] \\
\mathrm{(LVI)\ RO_2C{\cdot}CO{\cdot}CH_2{\cdot}CH{:}CH{\cdot}CMe{:}CH{\cdot}CO_2R} \arrow[d] \\
\mathrm{(LVII)\ RO_2C{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CMe{:}CH{\cdot}CO_2R} \\
\mathrm{(LVIII)\ RO_2C{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CHMe{\cdot}CO{\cdot}CO_2R} \arrow[u] \\
\mathrm{(LIX)\ RO_2C{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH_2Me + RO_2C{\cdot}CO_2R} \arrow[u]
\end{tikzcd}$$

1 : 5-Hexatrienedicarboxylic acid (LXIII) was of especial interest on account of its connection with a metabolic product of geraniol. It was synthesised (Kuhn and Grundmann, *Ber.*, 1937, **70**, 1894) by the following route :

$$\begin{tikzcd}
\mathrm{(LX)\ CH_2Me{\cdot}CH{:}CH{\cdot}CHO + Zn + CHMeBr{\cdot}CO_2R} \arrow[d] \\
\mathrm{(XLI)\ CH_2Me{\cdot}CH{:}CH{\cdot}CH{:}CMe{\cdot}CO_2R} \arrow[d, "\mathrm{RO_2C{\cdot}CO_2R}"] \\
\mathrm{(LXII)\ RO_2C{\cdot}CO{\cdot}CHMe{\cdot}CH{:}CH{\cdot}CH{:}CMe{\cdot}CO_2R} \arrow[d] \\
\mathrm{(LXIII)\ HO_2C{\cdot}CH{:}CMe{\cdot}CH{:}CH{\cdot}CH{:}CMe{\cdot}CO_2H} \arrow[d] \\
\mathrm{(LXIV)\ HO_2C{\cdot}CH{:}CMe{\cdot}CH_2{\cdot}CH_2{\cdot}CH{:}CMe{\cdot}CO_2H} \\
\mathrm{(LXV)\ HO{\cdot}CH_2{\cdot}CH{:}CMe{\cdot}CH_2{\cdot}CH_2{\cdot}CH{:}CMe{\cdot}CH_3} \arrow[u]
\end{tikzcd}$$

By complete reduction, introduction of two bromine atoms, and removal of two molecules of hydrogen bromide, the triene dicarboxylic acid (LXIII) was converted into 1 : 5-dimethylhexadiene-1 : 6-dicarboxylic acid (LXIV). This was identical with a dicarboxylic acid discovered by Hildebrandt (*Arch. exper. Path.*, 1907, **45**, 110) in the urine of dogs and rabbits fed with geraniol (LXV) or geranic acid (Kuhn, F. Köhler, and L. Köhler, *Z. physiol. chem.*, 1936, **242**, 171).

This change in geranic acid in the animal organism appears to be analogous to that discovered by Verkade for fatty acids, and named by him ω-oxidation. These biological methods yield very much better results with the polyene carboxylic acids than with the fatty acids (Kuhn, F. Köhler, and L. Köhler, *ibid.*, 1937, **247**, 197). One cannot indeed feed the free acids, their salts or esters, but must use the amides, methylamides, anilides, etc. Kuhn and (Miss) Löw (unpublished work) have shown that, in the case of the fatty acids, such protection of the carboxyl group is of scarcely any value, since an amidase liberates the carboxyl group. The amides of the polyene carboxylic acids are, however, very stable against this enzyme.

Hexatrienedicarboxylic acid monoamide (LXVII) crystallises in a yield of 42% from the urine of rabbits which have received octatriene acid amide (LXVI). The former could be saponified with aqueous potash to the hexatriene-1 : 6-dicarboxylic acid (LXVIII).

(LXVI) $CH_3{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CO{\cdot}NH_2$
(LXVII) $HO_2C{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CO{\cdot}NH_2$
(LXVIII) $HO_2C{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CO_2H$

The decatetraene acid amide (LXIX) yielded the octatetraenedicarboxylic acid monoamide (LXX) in a yield of 20%. This was saponified to the yellow octatetraene-1 : 8-dicarboxylic acid (LXXI).

(LXIX) $CH_3{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CO{\cdot}NH_2$
(LXX) $HO_2C{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CO{\cdot}NH_2$
(LXXI) $HO_2C{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CO_2H$

Yields up to 83% have been obtained in other cases. It appears from this work that, by using rabbits, preparative oxidations can be carried out, and that these are specific in their nature. Methyl is oxidised to carboxyl, but all double bonds in the molecule remain intact. The polyene dicarboxylic acids isolated from rabbit urine have been shown by mixed melting points to be identical with the corresponding dicarboxylic acids obtained by the oxalic ester synthesis.

The free oxalo-polyene carboxylic acids may readily be obtained by saponification of the oxalo-polyene carboxylic esters. These, like α-keto-acids in general, can be oxidised with hydrogen peroxide to the compounds with one carbon atom less. Grundmann (*Ber.*, 1937, **70**, 1148), who demonstrated this, thus obtained the following vinylene homologues of glutaconic acid :

(LXXII) $HO_2C{\cdot}CH_2{\cdot}CH{:}CH{\cdot}CO_2H$
(LXXIII) $HO_2C{\cdot}CH_2{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CO_2H$
(LXXIV) $HO_2C{\cdot}CH_2{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CO_2H$
(LXXV) $HO_2C{\cdot}CH_2{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CO_2H$

The absorption spectra of these compounds correspond exactly with those of the monocarboxylic acids $CH_3{\cdot}[CH{:}CH]_n{\cdot}CO_2H$ with the same number of conjugated double bonds. The methylene group thus isolates the carboxyl completely from the chromophore. Glutaconic acid ($n = 1$) is very conveniently obtained in this way from crotonic ester, and also the dicarboxylic acid with $n = 2$ from sorbic ester. The latter acid has been shown to be identical with the piperylenedicarboxylic acid obtained by Willstätter (*Ber.*, 1895, **28**, 3271; 1898, **31**, 1535) by degradation of cocaine.

During the oxidation with hydrogen peroxide, removal of two carbon atoms also occurs to a small extent. One obtains from oxalosorbic ester not only piperylenedicarboxylic acid but also muconic acid. Thus it is possible by the indirect route of condensation with oxalic ester and subsequent oxidation with hydrogen peroxide to imitate *in vitro* the animal experiments of Dr. and Mrs. Köhler—the oxidation of methyl to carboxyl without affecting the double bonds present in the molecule.

E. *Polyenes of the Terpene Group.*

Polyenes, whose carbon skeletons may be considered as built up of isoprene residues, occur in the pigments of the carotene group. The question naturally presents itself as to how far the synthetic methods already known can be applied to the synthesis of such substances. The answer is that we are as yet only at the beginning of this field.

The aldol condensation of terpene aldehydes with other aldehydes by means of piperidine acetate and similar amine salts has been successful in several cases. For example, the condensation of citral (LXXVI) with acetaldehyde carried out by Kuhn, Badstübner, and Grundmann (*Ber.*, 1936, **69**, 98) yields citrylideneacetaldehyde (LXXVII) in very good yield.

(LXXVI) $CMe_2{:}CH{\cdot}CH_2{\cdot}CH_2{\cdot}CMe{:}CH{\cdot}CHO + CH_3{\cdot}CHO$

$$\downarrow$$

(LXXVII) $CMe_2{:}CH{\cdot}CH_2{\cdot}CH_2{\cdot}CMe{:}CH{\cdot}CH{:}CH{\cdot}CHO$

We are indebted to Heilbron and his collaborators for other important examples of this kind (J., 1937, 755).

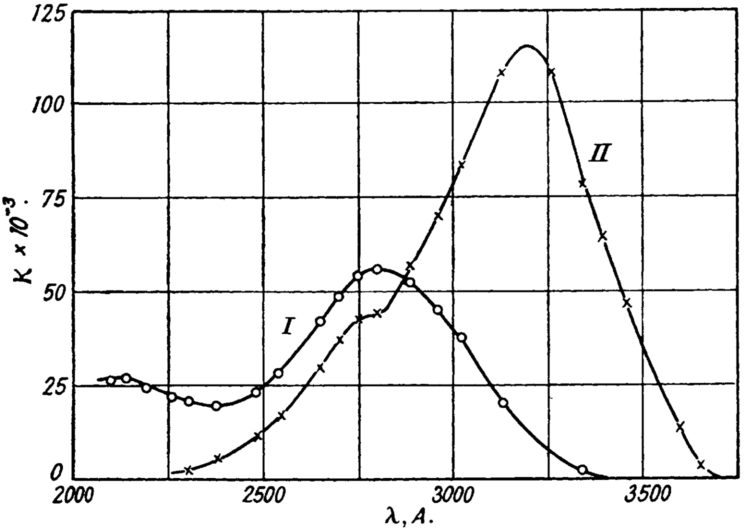
Especially noteworthy is the discovery of Fischer (*Ber.*, 1935, **68**, 1726) that β-methylcrotonaldehyde, first made available by him, condenses with itself under the same conditions as crotonaldehyde, forming the interesting dehydrocitral (LXXVIII) and farnesinal (LXXIX):

(LXXVIII) $2CMe_2{:}CH{\cdot}CHO \longrightarrow CMe_2{:}CH{\cdot}CH{:}CH{\cdot}CMe{:}CH{\cdot}CHO$

(LXXIX) $CMe_2{:}CH{\cdot}CH{:}CH{\cdot}CMe{:}CH{\cdot}CH{:}CH{\cdot}CMe{:}CH{\cdot}CHO$

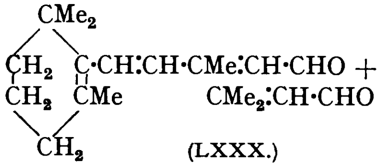
From the formula for vitamin A (LXXXII) suggested by Karrer (*Helv. Chim. Acta*, 1931, **14**, 1431), it might be expected that the synthesis of the corresponding aldehyde (LXXXI) could be carried out by condensation of β-ionylideneacetaldehyde (LXXX) with β-methylcrotonaldehyde:

FIG. 2.

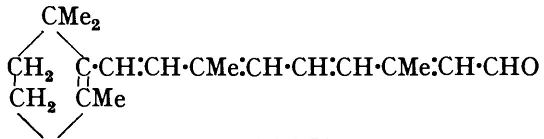


I, β-Iononesemicarbazone.
II, β-Ionylideneacetaldehydesemicarbazone.
Solvent: ethyl alcohol.

$$\kappa = \frac{2{\cdot}30}{c \times d} \log_{10}\frac{I_0}{I} \text{ (d in cm., c in mol./l.).}$$



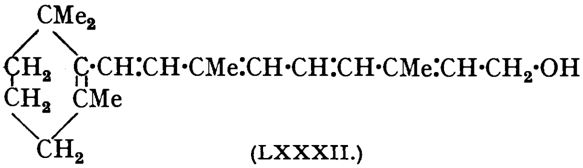
(LXXX.)



(LXXXI.)

We had already undertaken several unsuccessful experiments on the synthesis of the necessary β-ionylideneacetaldehyde. Dr. C. J. O. R. Morris, whom I am very pleased to see again this evening, was successful in solving this problem (Kuhn and Morris, *Ber.*, 1937, **70**, 853). By application of the chromous chloride method of v. Braun (*Ber.*, 1934, **67**, 269, 1735) to the *o*-toluidide of the already known β-ionylideneacetic acid, he was able to reduce the carboxyl group to an aldehyde group. The β-ionylideneacetaldehyde so obtained was characterised by a beautifully crystalline semicarbazone of melting point 194°. The absorption spectrum of this you see in Fig. 2 in comparison with that of β-iononesemicarbazone.

By condensation of the aldehyde with methylbutenal, and subsequent reduction by the Meerwein–Ponndorf method with aluminium *iso*propoxide, Morris obtained an oil, evidently a mixture of different alcohols. Among these was one which gave the blue colour with antimony trichloride in chloroform characteristic of vitamin A. The position of the absorption band was, as with the natural vitamin, at 6100 A., and a mixture of the natural and the synthetic compound could not be differentiated by chromatographic analysis. The synthetic alcohol (LXXXII) caused growth and healing of xerophthalmia with rats reared on a vitamin A-free diet.



(LXXXII.)

Since neither the natural nor the synthetic vitamin was pure, quantities which gave the same blue colour with antimony trichloride in chloroform were compared. In this way it was found that the growth effect of $0{\cdot}8 \times 10^{-6}$ g. of the synthetic alcohol corresponded with that of $0{\cdot}9 \times 10^{-6}$ g. of the natural vitamin A. Thus, not only the optical but also the biological properties show very close agreement.