POLYENE SYNTHESES

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Received November 27, 1943

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I. INTRODUCTION

The synthesis of polyenes is of eminent interest not only for the organic chemist but also for the physicochemist, whom it provides with hitherto inaccessible model substances required in the clarification of the laws governing the properties of homologous series, and in the study of conjugated-double-bond systems (9, 30). For the biological chemist, the same polyenes serve as models for comparison with carotenoids and other polyenic substances occurring in nature.

Discussions of the subject of the present review will be found in monographs and textbook chapters on carotenoids; polyene syntheses in particular have been treated by Bogert (6), Jones (24), and Kuhn (58). The interesting problems posed by stereoisomerism in the carotenoids and polyenes have been dealt with by Zechmeister (109).

II. METHODS

A. ALDOL AND ESTER CONDENSATIONS

In condensation reactions leading to higher polyenes at least one of the partners is generally a carbonyl compound in which one or more double bonds are

conjugated with the C=O bond. Thus, crotonaldehyde and its higher polyenic homologs ("vinylogs") are the starting material for straight-chain aliphatic polyenes, whereas methylcrotonaldehyde is used as the building unit of the branched polyene chain characteristic of carotenoids. Compounds like cinnamaldehyde, citral, cyclocitral, and ionone provide cyclic and terpenoid end groups. In addition to these unsaturated carbonyl compounds, acetaldehyde and acetone themselves have been used in polyene syntheses.

1. Acetaldehyde and crotonaldehyde condensations

Acetaldehyde and crotonaldehyde undergo autocondensation in the presence of secondary amines such as piperidine. This type of Knoevenagel reaction has been used successfully for the synthesis of sorbaldehyde (I, hexadienal) (59, 68). The same mixture of acetaldehyde and crotonaldehyde also yields the higher vinylogs octatrienal (II) and decatetraenal (III) (59). Aldehydes with a multiple of four carbon atoms,—namely, octatrienal (II), dodecapentaenal (IV), and hexadecaheptaenal (VI),—have been prepared by the condensation of two, three, and four molecules of crotonaldehyde with one another (5). Difficulties

(I) $CH_3CH{=}CHCH{=}CHCHO$, hexadienal

(II) $CH_3CH{=}CHCH{=}CHCH{=}CHCHO$, octatrienal

(III) $CH_3CH{=}CHCH{=}CHCH{=}CHCH{=}CHCHO$, decatetraenal

(IV) $CH_3CH{=}CHCH{=}CHCH{=}CHCH{=}CHCH{=}CHCHO$, dodecapentaenal

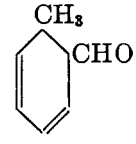
(V) $CH_3CH{=}CHCH{=}CHCH{=}CHCH{=}CHCH{=}CHCH{=}CHCHO$, tetradecahexaenal

(VI) $CH_3CH{=}CHCH{=}CHCH{=}CHCH{=}CHCH{=}CHCH{=}CHCH{=}CHCHO$, hexadecaheptaenal

(VII) $CH_3CH{=}CHCH{=}CHCH{=}CHCH{=}CHCH{=}CHCH{=}CHCH{=}CHCH{=}CHCHO$, octadecaoctaenal

(VIII) $CH_3CH{=}CHCH{=}CHCH{=}CHCH{=}CHCH{=}CHCH{=}CHCH{=}CHCH{=}CHCH{=}CHCHO$, eicosanonaenal

encountered with pure crotonaldehyde led to the discovery that secondary amines themselves are not the catalyst proper in these condensations, but that they must first form salts with the traces of crotonic acid usually present in crotonaldehyde (59). To achieve uniform results the addition of acetic acid has become customary (20, 62, 87). Cyclization occurs as an undesirable side reaction, resulting in the formation of dihydro-*o*-tolualdehyde (IX) (5, 20).



IX

Dihydro-*o*-tolualdehyde

Mixtures of crotonaldehyde with sorbaldehyde yield tetradecahexaenal (V) and even octadecaoctaenal (VII) (91). The polymerization of five to seven molecules of crotonaldehyde was accomplished in solutions of various alcohols; the resulting products were of the general structure $C_{4n-1}H_{4n+2}(OAlk)CHO$. These alkoxy polyene aldehydes are waxy crystalline masses and are converted by complete hydrogenation into monoalkyl ethers of long-chain glycols which, in turn, may be oxidized,—e.g., to methoxylated fatty acids; the position of the methoxyl group is unknown (66). If condensation is carried out in 70 per cent ethanol at room temperature with piperidine acetate, no ethoxyl groups are introduced, but hexadecaheptaenal (VI) and some eicosanonaenal (VIII) are obtained (91). The lowest member of this series in which absorption may be observed within the range of the visible spectrum is the yellow decatetraenal (III); dodecapentaenal (IV) is orange and hexadecaheptaenal (VI) is deep red.

Polyene chains with methyl groups attached to every fourth carbon atom, such as are characteristic for carotenoids and other polyisoprenoid products of nature, may be obtained by condensation reactions with β-methylcrotonaldehyde. This intermediary may be obtained by debromination and hydrolysis of α-bromoisovaleraldehyde acetal (X) (18, 21), or by dehydration of β-hydroxyisovaleraldehyde (XIII), formed from dimethylallylcarbinol (XII) by cleavage

$$\underset{\text{X}}{(CH_3)_2CHCHBrCH(OC_2H_5)_2} \xrightarrow{-HBr} \underset{\text{XI}}{(CH_3)_2C{=}CHCHO}$$

$$\uparrow -H_2O$$

$$\underset{\text{XII}}{(CH_3)_2COHCH_2CH{=}CH_2} \xrightarrow{O_3} \underset{\text{XIII}}{(CH_3)_2COHCH_2CHO}$$

Dimethylallylcarbinol — β-Hydroxyisovaleraldehyde

of the terminal methylene group with ozone (10). Besides cyclic byproducts, the acyclic dimer dehydrocitral (XIV) and the trimer farnesinal (XV) were obtained in analogy to the linear condensation products of crotonaldehyde by catalytic polymerization of β-methylcrotonaldehyde (5, 19, 20).

(XIV) $(CH_3)_2C{=}CHCH{=}CHC(CH_3){=}CHCHO$, dehydrocitral

(XV) $(CH_3)_2C{=}CHCH{=}CHC(CH_3){=}CHCH{=}CHC(CH_3){=}CHCHO$, farnesinal

2. Condensations of terpenoid aldehydes

Citral (XVI, 3,7-dimethyloctadienal) on condensation with acetaldehyde in

(XVI) $(CH_3)_2C{=}CHCH_2CH_2C(CH_3){=}CHCHO$, citral

(XVII) $(CH_3)_2C{=}CHCH_2CH_2C(CH_3){=}CHCH{=}CHCHO$, citrylideneacetaldehyde

the presence of piperidine acetate (3, 59) or sodium amide (1) yields citrylideneacetaldehyde (XVII, 5,9-dimethyldecatrienal). This compound has the aroma

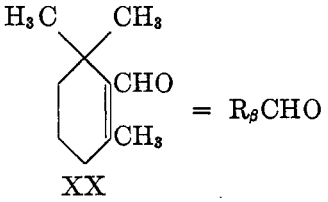
of pears; the reason for its non-identity with the citrylideneacetaldehyde obtained by von Braun and Rudolph (8) from citrylideneacetic acid by reduction with chromous chloride (see section 14) is not yet understood. β-Cyclocitral does not lend itself to the Knoevenagel reaction; therefore β-cyclocitrylideneacetaldehyde had to be prepared by cyclization of the semicarbazone of citrylideneacetaldehyde (39). Correspondingly, citral has been condensed with crotonaldehyde and β-methylcrotonaldehyde, yielding 7,11-dimethyldodecatrienal (XVIII) and 3,7,11-trimethyldodecatrienal (XIX) (1, 3).

(XVIII) $(CH_3)_2C{=}CHCH_2CH_2C(CH_3){=}CHCH{=}CHCH{=}CHCHO$,
7,11-dimethyldodecatrienal

(XIX) $(CH_3)_2C{=}CHCH_2CH_2C(CH_3){=}CHCH{=}CHC(CH_3){=}CHCHO$,
3,7,11-trimethyldodecatrienal

The latter compound is also designated as pseudo-ionylideneacetaldehyde. The original condensation product is not a pure substance, according to Karrer (49); it may, however, be separated through the semicarbazones into two isomeric forms designated "a" and "b". A similar condition is encountered in the case of substance XVIII; the cause of the isomerism in these cases still awaits elucidation. Because of the length of the chain, cyclization cannot be confined to the tail end of the molecule, but bicyclic condensation products are obtained, presumably in the nature of trimethyl- and tetramethyl-hexahydronaphthaldehydes (4).

The condensation of β-cyclocitral (XX) with β-methylcrotonaldehyde (25)



XX

β-Cyclocitral

yielded a material which, upon reduction of the aldehyde group, gave a product resembling vitamin A in ultraviolet absorption spectrum and antimony trichloride reaction. No biological tests have been reported on this product, and it seems plausible that the polyene system present resulted from autocondensation of methylcrotonaldehyde (see Part III), an assumption (44) which reconciles these observations with the reported failure of β-cyclocitral to undergo Knoevenagel reactions. Pseudo-ionylideneacetaldehyde (XXI) and β-methylcrotonaldehyde yield under various conditions a variety of ill-defined products (XXII?) giving a blue reaction with antimony trichloride, probably for the same reason as in the preceding case (49). Likewise, the condensation of β-ionylideneacetaldehyde (XXIII), if available, with β-methylcrotonaldehyde should lead to

axerophthal (XXIV), the C_{20}-aldehyde corresponding to vitamin A (axerophthal) (72) and presumably identical with retinene (80a).

$$(CH_3)_2C{=}CHCH_2CH_2C(CH_3){=}CHCH{=}CHC(CH_3){=}CHCHO + (CH_3)_2C{=}CHCHO \rightarrow$$
XXI

$$(CH_3)_2C{=}CHCH_2CH_2C(CH_3){=}CHCH{=}CHC(CH_3){=}CHCH{=}CHC(CH_3){=}CHCHO$$
XXII

$$R_\beta CH{=}CHC(CH_3){=}CHCHO + (CH_3)_2C{=}CHCHO \rightarrow$$
XXIII

$$R_\beta CH{=}CHC(CH_3){=}CHCH{=}CHC(CH_3){=}CHCHO$$
XXIV

Axerophthal

3. Condensations of aromatic aldehydes

In the aromatic series, cinnamylideneacetaldehyde (5-phenylpentadienal, XXV) has been synthesized from benzaldehyde and crotonaldehyde (59, 77), 11-phenylhendecapentaenal (XXVI) from cinnamaldehyde and two molecules of crotonaldehyde, and 15-phenylpentadecaheptaenal (XXVIII) from cinnamaldehyde and three molecules of crotonaldehyde (74, 90); 13-phenyltridecahexaenal (XXVII) was prepared from XXV and two molecules of crotonaldehyde (90). An analogous series of polyene aldehydes with a terminal α-furyl group has been

(XXV) $C_6H_5CH{=}CHCH{=}CHCHO$, 5-phenylpentadienal

(XXVI) $C_6H_5CH{=}CHCH{=}CHCH{=}CHCH{=}CHCH{=}CHCHO$, 11-phenylhendecapentaenal

(XXVII) $C_6H_5CH{=}CHCH{=}CHCH{=}CHCH{=}CHCH{=}CHCH{=}CHCHO$, 13-phenyltridecahexaenal

(XXVIII) $C_6H_5CH{=}CHCH{=}CHCH{=}CHCH{=}CHCH{=}CHCH{=}CHCH{=}CHCHO$, 15-phenylpentadecaheptaenal

prepared up to 15-(α-furyl)pentadecaheptaenal (XXIX, $n = 7$) by condensation of furfural or α-furylacrylaldehyde with acetaldehyde or crotonaldehyde in the presence of piperidine acetate (56, 90).

$$\underline{OCH{=}CHCH{=}C(CH{=}CH)_n}CHO \qquad (n = 2, 3 \cdots 7)$$
XXIX

4. Condensations with acetone

The condensation of unsaturated aldehydes with acetone leads to polyenic methyl ketones. In analogy to the synthesis of pseudo-ionone (XXX) from citral (XVI) with acetone (84), citrylidenecrotonaldehyde (XVIII) and pseudoionylideneacetaldehyde (XIX) ("a"-forms) condense with acetone in the presence of sodium ethoxide (4) to form 10,14-dimethyl- and 6,10,14-trimethylpentadecapentaenones (XXXI and XXXII). Acetone has also been condensed with the two isomeric γ-[2,2,6-trimethyl-1(and 5)-cyclohexen-1-yl]-α-methyl-

(XXX) $(CH_3)_2C{=}CHCH_2CH_2C(CH_3){=}CHCH{=}CHCOCH_3$, pseudoionone

(XXXI) $(CH_3)_2C{=}CHCH_2CH_2C(CH_3){=}CHCH{=}CHCH{=}CHCOCH_3$, 10,14-dimethylpentadecapentaenone

(XXXII) $(CH_3)_2C{=}CHCH_2CH_2C(CH_3){=}CHCH{=}CHC(CH_3){=}CHCOCH_3$, 6,10,14-trimethylpentadecapentaenone

crotonaldehydes (XXXIII, XXXIV), yielding two isomeric ketones $C_{17}H_{26}O$ (XXXV, XXXVI) (36).

(XXXIII) $R_\beta CH_2CH{=}C(CH_3)CHO$

(XXXIV) $R_\alpha CH_2CH{=}C(CH_3)CHO$

(XXXV) $R_\beta CH_2CH{=}C(CH_3)CH{=}CHCOCH_3$

(XXXVI) $R_\alpha CH_2CH{=}C(CH_3)CH{=}CHCOCH_3$

(XXXVII) $R_\beta CH{=}CHC(CH_3){=}CHCH{=}CHCOCH_3$

(XXXVIII) $R_\beta CH{=}CHC(CH_3){=}CHCH{=}CHC(CH_3){=}CHCH{=}CHCOCH_3$

Similarly, the important ketone $C_{18}H_{26}O$ (XXXVII) could be synthesized from β-ionylideneacetaldehyde, if available (41). Finally, the ketone $C_{23}H_{32}O$ (XXXVIII) was obtained in the Oppenauer oxidation of vitamin A with aluminum isopropoxide instead of the expected axerophthal (XXII), owing to the condensation of the latter with acetone (2).

5. Malonic ester type syntheses

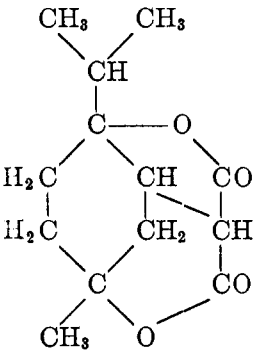
The condensation of acetaldehyde and diethyl malonate to yield diethyl acetylidenemalonate and thence crotonic acid has been extended to the synthesis of sorbic acid (15) and of higher polyenecarboxylic acids up to hexadecaheptaenylidenemalonic acid (XXXIX, $n = 7$) (63). The higher members of this

$$CH_3(CH{=}CH)_nCH(COOH)_2 \qquad (n = 1, 2 \ldots 7)$$

XXXIX

series display increasing depth of color, the ethyl ester of the last member being deep violet. On catalytic hydrogenation of the ethyl ester of XXXIX ($n = 7$), hexadecylmalonic ester is formed, from which stearic acid is obtained by saponification and decarboxylation (67).

A peculiar reaction was observed in the attempted synthesis of citrylidenemalonic acid from citral and malonic ester with pyridine (104) and saponification of the citrylidenemalonic ester (28) with baryta. A substance was obtained which was insoluble in sodium carbonate solution and even in cold dilute sodium hydroxide, and tasted bitter rather than acidic. These properties were accounted for by the formation of a dilactone with two of the three double bonds eliminated. On reëxamination, however, the substance proved to be fully saturated; Kuhn and Hoffer (69) were able to demonstrate the disappearance of the third double bond and to prove that "citrylidenemalonic acid" is identical with (menthyl-3)malonic acid dilactone-1,4 (XL).



XL

(Menthyl-3)malonic acid dilactone-1,4

The condensation of citral with ethyl cyanoacetate leads to citrylidenecyanoacetic ester; saponification of this ester with 20 per cent potassium hydroxide is accompanied by cyclization and degradation to cyclocitral (101).

Whereas diethyl malonate reacts with aldehydes only, ethyl cyanoacetate combines with ketones in the presence of acetamide in acetic acid under continuous removal of water by distillation (12). Wittig and Hartmann (105) prepared isopropylidenecyanoacetic ester (XLI) as the starting material for further condensations of isoprenoid chains. Attempts in model experiments to condense this ester with benzaldehyde or cinnamaldehyde by Cope's method (12) led to replacement of the isopropylidene group by the benzylidene or cinnamylidene group (yielding XLII or XLIII), rather than to condensation. However,

(XLI) $(CH_3)_2C{=}C(CN)COOC_2H_5$, isopropylidenecyanoacetic ester
(XLII) $C_6H_5CH{=}C(CN)COOC_2H_5$, benzylidenecyanoacetic ester
(XLIII) $C_6H_5CH{=}CHCH{=}C(CN)COOC_2H_5$, cinnamylidenecyanoacetic ester

with piperidine acetate as catalyst, condensation occurred at one of the terminal methyl groups. By similar reactions, the methyl ester of α-cyanosorbic acid (XLIV) was prepared and, in turn, condensed with cinnamaldehyde leading to the nitrile of 9-phenylnonatetraenic acid (XLV).

$$CH_3CH{=}CHCH{=}C(CN)COOCH_3 + C_6H_5CH{=}CHCHO \rightarrow$$

XLIV

Methyl α-cyanosorbate

$$C_6H_5CH{=}CHCH{=}CHCH{=}CHCH{=}CHCN$$

XLV

9-Phenylnonatetraenonitrile

The same authors (105) condensed β-ionone with ethyl cyanoacetate, using a solution of acetamide and ammonium acetate in acetic acid as catalyst. The

resulting ethyl β-ionylidene-α-cyanoacetate (XLVI) was saponified in three stages, yielding an ionylideneacetic acid (XLVII) identical with material prepared by Karrer (52).

(XLVI) $R_\beta CH{=}CHC(CH_3){=}C(CN)COOC_2H_5$
(XLVII) $R_\beta(?)CH{=}CHC(CH_3){=}CHCOOH$

Polyenic α-keto acids may be prepared by the condensation of polyene aldehydes with pyruvic acid in strongly alkaline solution (23).

6. Oxalic ester condensations

The condensation of polyenemonocarboxylic acids with diethyl oxalate leads to several series of polyenedicarboxylic acids. The reaction of diethyl oxalate and ethyl crotonate in the presence of potassium ethylate, leading to the keto acid XLVIII (n = 1), was discovered by Lapworth (78).

$$HOOCCOCH_2(CH{=}CH)_nCOOH$$
XLVIII

The next homolog of this series was prepared with ethyl sorbate (7). Rubidium ethylate has been recommended for these condensations, but the condensation of the higher members of the series requires the presence of pyridine (29, 62, 63, 64). The resulting oxalopolyenic esters, when treated with acetic anhydride, yield the acetyl derivatives of their enol forms (XLIX). These, in turn, upon reduction with aluminum amalgam, add one molecule of hydrogen at the ends of the conjugated-double-bond system. The resulting acetyl dihydro compounds (L), on treatment with potassium hydroxide in methanol, split off acetic acid, and the dimethyl esters of the polyenedicarboxylic acids (LI) are thus obtained.

(XLIX) $C_2H_5OOCC(OCOCH_3){=}CH(CH{=}CH)_nCOOR$
(L) $C_2H_5OOCCH(OCOCH_3)(CH{=}CH)_nCH_2COOR$
(LI) $CH_3OOC(CH{=}CH)_{n+1}COOCH_3$
(LII) $HOOCCH_2(CH{=}CH)_nCOOH$

This reaction was carried as far as tetradecaheptaene-1,14-dicarboxylic acid (n = 6). With the higher members, the aluminum amalgam reduction tends to replace the acetoxyl group by hydrogen, an undesirable side reaction. However, the resulting esters of polyenediacetic acids can be dehydrogenated by atmospheric oxygen in the presence of alkali (60). Oxidation of the oxalopolyenic esters with hydrogen peroxide leads to the dicarboxylic acids of the glutaconic acid series which have an odd number of carbon atoms (29) (LII).

$$HOOCCH_2(CH{=}CH)_nCOOH$$
LII

The oxalic ester method may also be utilized for the synthesis of methylated dicarboxylic acids such as β-methylmuconic acid (LIII) and 1,5-dimethylhexatrienedicarboxylic acid (LIV), from which 1,5-dimethylhexadiene-1,5-

dicarboxylic acid (LV) is obtained by partial hydrogenation with sodium amalgam (64). This acid is identical with the acid found by Hildebrandt (42) in the

(LIII) $HOOCCH{=}CHC(CH_3){=}CHCOOH$, β-methylmuconic acid
(LIV) $HOOCCH{=}C(CH_3)CH{=}CHCH{=}C(CH_3)COOH$, 1,5-dimethyl-1,3,5-hexatriene-1,5-dicarboxylic acid
(LV) $HOOCCH{=}C(CH_3)CH_2CH_2CH{=}C(CH_3)COOH$, 1,5-dimethyl-1,5-hexadiene-1,5-dicarboxylic acid
(LVI) $CH_3CH{=}C(CH_3)CH_2CH_2CH{=}C(CH_3)_2$, geraniol

urine of dogs and rabbits as a catabolic product of geraniol (LVI).

7. Perkin type condensations

A double Perkin reaction of succinic acid in the presence of lead oxide with two molecules of cinnamaldehyde (LVII) resulted in the formation of 1,8-diphenyl-octatetraene (LX) (76). Higher homologs with two and four more vinyl groups

$$C_6H_5(CH{=}CH)_mCHO + H_2C(COOH)_2 + CHO(CH{=}CH)_mC_6H_5 \longrightarrow C_6H_5(CH{=}CH)_nC_6H_5 + 2CO_2$$

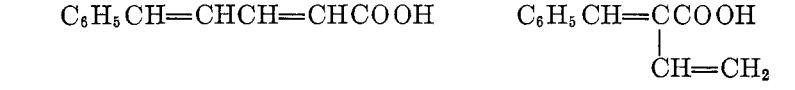
(LVII, $m = 1$; LVIII, $m = 2$; LIX, $m = 3$)
(LX, $n = 4$; LXI, $n = 6$; LXII, $n = 8$)

(LXI, LXII) were correspondingly obtained with 5-phenylpentadienal (LVIII = XXV) and 7-phenylheptatrienal (LIX). The synthesis of diphenylpolyenes with an odd number of double bonds was achieved by the substitution of dihydromuconic acid (LXIII) for succinic acid. Even butadiene-1,4-diacetic acid (LXIV) may be used as center piece in this reaction (62).

$$HOOCCH_2(CH{=}CH)_nCH_2COOH$$

(LXIII, $n = 1$; LXIV, $n = 2$)

In order to obtain crystalline products in the condensation of benzaldehyde with crotonic acid, the latter has to be used in the form of its anhydride and triethylamine is employed as catalyst. The resulting product differs from the known stereomeric forms of cinnamylideneacetic acid (LXV) and was identified as α-vinylcinnamic acid (LXVI); the mechanism of its formation presupposes a shift of the double bond from crotonic acid to vinylacetic acid (71).



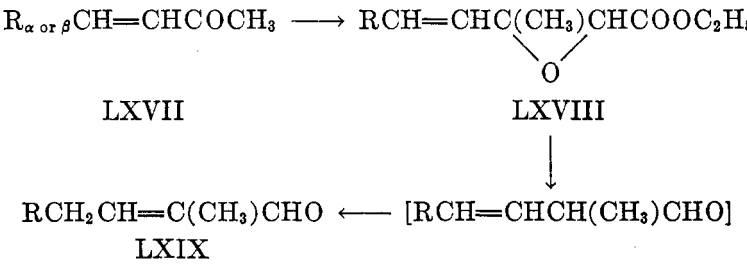
LXV — Cinnamylideneacetic acid

LXVI — α-Vinylcinnamic acid

8. Glycidic ester synthesis

The glycidic ester synthesis of aldehydes, when applied to the ionones (LXVII), leads to aldehydes $C_{14}H_{22}O$ (43). A careful comparison of the products

obtained both from α- and from β-ionone showed that they retained the respective position of the cyclic double bond, but that the double bond of the ionone side chain had moved in both compounds one carbon atom forward and fallen into conjugation with the aldehydic carbonyl group (LXVIII→LXIX) (34).



Although this reaction increases the length of the chain by one carbon only, it appears to be of significance for further syntheses.

9. Ethyl acetoacetate synthesis

This synthesis has proved of minor significance in the polyene field. It may be mentioned here, for example, that Ruzicka and Fischer (83) condensed the chloride $C_{15}H_{25}Cl$ (LXX) with ethyl acetoacetate in the course of the synthesis of tetrahydrovitamin A. Gould and Thompson (27) describe the reaction of the

(LXX) $R_\beta CH_2CH_2C(CH_3)=CHCH_2Cl$
(LXXI) $R_\beta CH=CHC(CH_3)=CHCH_2CH_2COCH_3$

corresponding triply unsaturated bromide, formulated $C_{15}H_{23}Br$, with ethyl acetoacetate and the formation of a ketone $C_{18}H_{28}O$ (LXXI). Geranylacetone has been prepared from geranyl bromide by an acetoacetic ester synthesis (88). Geranylacetone may also be obtained by rearrangement of the geranyl ester of acetoacetic acid; such esters are prepared from the sodium compound of the unsaturated alcohol plus diketene (54a) (LXXII, LXXIII).

(LXXII) $(CH_3)_2C=CHCH_2CH_2CH=C(CH_3)CH_2OCOCH_2COCH_3$
(LXXIII) $(CH_3)_2C=CHCH_2CH_2CH=C(CH_3)CH_2CH_2COCH_3 + CO_2$

B. SYNTHESES WITH METALLOÖRGANIC COMPOUNDS

10. Reformatsky syntheses

The Reformatsky reaction of carbonyl compounds with ethyl bromoacetate and zinc has been applied to a number of polyenic methyl ketones such as crotonylideneacetone, cinnamalacetone, and 6-methyl-3,5-heptadiene-2-one (21, 70). The resulting β-hydroxy esters yield, depending on the conditions of dehydration, *cis*- or *trans*-isomers of β-substituted crotonic acids. *Cis–trans* pairs of 3-methyloctatrienic acid (LXXIV), 3-methyl-7-phenylheptatrienic acid (LXXV), and 3,7-dimethyloctatrienic acid (LXXVI) were thus obtained from the three ketones mentioned above. The higher melting form of LXXVI was identical with natural dehydrogeranic acid (11). It was found (22) that unsaturated β-hydroxy esters are simultaneously decarboxylated and dehydrated

upon saponification; thus polyenes are formed besides the expected acids. Decarboxylation occurred more readily when a number of conjugated double bonds were present. The hydrocarbons phenylpentadiene, 2-methylheptatriene (from LXXIV), and 2,6-dimethylheptatriene (from LXXVI) were prepared in this manner (21).

(LXXIV) $CH_3CH{=}CHCH{=}CHC(CH_3){=}CHCOOH$, 3-methyloctatrienic acid

(LXXV) $C_6H_5CH{=}CHCH{=}CHC(CH_3){=}CHCOOH$, 3-methyl-7-phenylheptatrienic acid

(LXXVI) $(CH_3)_2C{=}CHCH{=}CHC(CH_3){=}CHCOOH$, 3,7-dimethyloctatrienic acid

A Reformatsky reaction of 2-penten-1-al with ethyl α-bromopropionate was used in the synthesis of Hildebrandt's acid (LV) (64). The condensation of 6-methyl-3,5-heptadiene-2-one (LXXVII) with α-bromopropionic ester followed by simultaneous decarboxylation and dehydration, led to alloöcimene (LXXVIII $\rightarrow$ LXXIX) (21).

$$(CH_3)_2C{=}CHCH{=}CHCOCH_3 + BrCH(COOC_2H_5)CH_3 \longrightarrow$$

LXXVII

6-Methyl-3,5-heptadiene-2-one

$$(CH_3)_2C{=}CHCH{=}CHC(OH)(CH_3)CH(COOH)CH_3$$

LXXVIII

$\downarrow -H_2O, -CO_2$

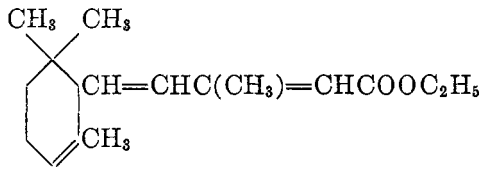
$$(CH_3)_2C{=}CHCH{=}CHC(CH_3){=}CHCH_3$$

LXXIX

Alloöcimene

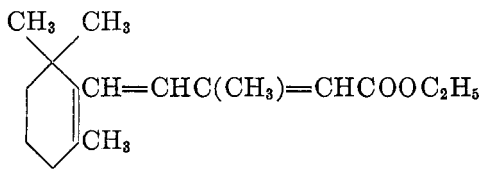
The condensation of ethyl bromoacetate with β-ionone results in a mixture of isomeric ethyl ionylideneacetates (13, 40, 52, 72). Upon saponification a crystalline acid of m.p. 125°C. was obtained in poor yield (52; *cf.* 105). Ethyl α-ionylideneacetate was prepared by the same method (93); the ultraviolet absorption spectrum (95) does not contradict the formulation LXXX with two ethylene bonds in conjugation with the carbethoxyl group. However, the Reformatsky condensation of pure β-ionone under the same conditions yielded a product closely resembling the α-ester in boiling point, refractive index, and ultraviolet absorption; the spectrum definitely excluded the formulation LXXXI with a total of four conjugated double bonds. The slight differences in ultraviolet absorption between the two esters and also two other isomers, prepared

by the use of magnesium instead of zinc, may be due to *cis–trans* isomerism (95; *cf.* 109).



LXXX

Ethyl α-ionylidene-acetate



LXXXI

Ethyl β-ionylidene-acetate

An extension of the Reformatsky reaction to ethyl γ-halogenocrotonate was described with benzaldehyde and cyclohexanone as model substances, yielding, upon dehydration of the primary reaction product, cinnamylideneacetic acid (LXXXII) and cyclohexylidenecrotonic acid (LXXXIII). Similarly, ethyl γ-bromo-β-methylcrotonate was observed to undergo a Reformatsky reaction with benzophenone (92) and with β-cyclocitral (95), but dehydration of the resulting δ-hydroxy acids (such as LXXXIV from cyclocitral) met with difficulties (*cf.* 25a).

(LXXXII) $C_6H_5CH{=}CHCH{=}CHCOOH$, cinnamylideneacetic acid
(LXXXIII) $C_6H_{10}{=}CHCH{=}CHCOOH$, cyclohexylidenecrotonic acid
(LXXXIV) $R_\beta CHOHCH_2C(CH_3){=}CHCOOH$

11. Zinc and cadmium alkyls

Methylzinc iodide was used to extend the side chain of "β"-ionylideneacetyl chloride to ionylideneacetone ("eu-ionone", LXXXV) (51). The application of cadmium alkyls according to the method of Gilman (26) and deBenneville (14) for this and similar purposes seems promising in view of the authors' experiments with the condensation of crotonyl chloride and dimethylcadmium resulting in the formation of 3-penten-2-one (LXXXVI).

$RCH{=}CHC(CH_3){=}CHCOCH_3$ — LXXXV

$CH_3CH{=}CHCOCH_3$ — LXXXVI

12. Grignard reactions

The polyene aldehydes react as expected with alkylmagnesium halides and yield the respective secondary alcohols (LXXXVII); these are dehydrated preferably by a 1 or 2 per cent solution of toluenesulfonic acid in ether (65). Octatriene, decatetraene, and tetradecahexaene were obtained by this procedure

(LXXXVIII). By the use of benzylmagnesium chloride one can extend this reaction to the preparation of polyenes with terminal phenyl groups: e.g., 1,12-diphenyldodecahexaene (74). Another method for the preparation of diphenyl-

$$\underset{\text{LXXXVII}}{CH_3(CH{=}CH)_nCHOHCH_2CH_3} \xrightarrow{-H_2O} \underset{\text{LXXXVIII}}{CH_3(CH{=}CH)_{n+1}CH_3}$$

polyenes has been mentioned previously (section 7); a third alternative utilizes a di-Grignard compound as a symmetrical middle link. The dimagnesium bromides of acetylene, and especially of diacetylene, have been found superior in this respect to the corresponding ethylenic derivatives. The Grignard condensation of acetylene with unsaturated aldehydes has been used by Dupont to obtain 2,8-decadiene-5-yne-4,7-diol (LXXXIX) (16, 38; *cf.* 79, 96).

$$2CH_3CH{=}CHCHO + BrMgC{\equiv}CMgBr \rightarrow \underset{\text{LXXXIX}}{CH_3CH{=}CHCHOHC{\equiv}CCHOHCH{=}CHCH_3}$$

The application of these reactions to aromatic carbonyl compounds constitutes the third method for the synthesis of diphenylpolyenes mentioned above. Two molecules of cinnamaldehyde with dibromoacetylene yield the acetylene

(XC) $C_6H_5CH{=}CHCHOHC{\equiv}CCHOHCH{=}CHC_6H_5$

(XCI) $C_6H_5CH_2CHOHC{\equiv}CCHOHCH_2C_6H_5$, 1,6-diphenyl-3-hexyne-2,5-diol

glycol (XC) (16). Two molecules of phenylacetaldehyde with dibromoacetylene give 1,6-diphenyl-3-hexyne-2,5-diol (XCI); the diphenylhexatriene obtainable from this glycol by hydrogenation and dehydration may also be obtained from the reaction of two molecules of benzaldehyde with dibromodiacetylene (74). By analogous reactions, diphenylpolyenes with branched side chains were obtained: e.g., 1,8-diphenyl-2,7-dimethyloctatetraene (XCIII) from α-methylcinnamaldehyde (XCII) and acetylene, and 1,10-diphenyl-3,8-dimethyldecapentaene (XCV) from benzalacetone (XCIV) and diacetylene by partial hydrogenation of the intermediate glycols and subsequent dehydration.

$$\underset{\text{XCII}}{2C_6H_3CH{=}C(CH_3)CHO} + BrMgC{\equiv}CMgBr \rightarrow$$

α-Methylcinnamaldehyde

$$\underset{\text{XCIII}}{C_6H_5CH{=}C(CH_3)CH{=}CHCH{=}CHC(CH_3){=}CHC_6H_5}$$

1,8-Diphenyl-2,7-dimethyloctatetraene

$$\underset{\text{XCIV}}{2C_6H_5CH{=}CHCOCH_3} + BrMgC{\equiv}CC{\equiv}CMgBr \rightarrow$$

Benzalacetone

$$\underset{\text{XCV}}{C_6H_5CH{=}CHC(CH_3){=}CHCH{=}CHCH{=}C(CH_3)CH{=}CHC_6H_5}$$

1,10-Diphenyl-3,8-dimethyldecapentaene

Two molecules of benzophenone (XCVI) or fluorenone lead, through a Grignard reaction with diacetylene, to the respective glycols (XCVII) and eventually to tetraphenylhexatriene (XCVIII) and di(biphenylene)hexatriene (75).

$$2(C_6H_5)_2CO + BrMgC{\equiv}CC{\equiv}CMgBr \rightarrow$$

XCVI

Benzophenone

$$(C_6H_5)_2(OH)CC{\equiv}CC{\equiv}CC(OH)(C_6H_5)_2$$

XCVII

$$(C_6H_5)_2C{=}CHCH{=}CHCH{=}C(C_6H_5)_2$$

XCVIII

Tetraphenylhexatriene

The practical significance of one-sided Grignard reactions in the acetylene group is confined to substituted acetylenes (85, 86). Thus, the Grignard compound of 1-hexyne (butylacetylene) has been condensed with crotonaldehyde (XCIX) (37). The Grignard compound of (1,2-dimethylvinyl)acetylene (C) was condensed with butyraldehyde, crotonaldehyde, and citral (33). In the

(XCIX) $CH_3CH{=}CHCHOHC{\equiv}CCH_2CH_2CH_2CH_3$

(C) $CH_3CH{=}C(CH_3)C{\equiv}CMgBr$

case of all the α,β-unsaturated aldehydes mentioned, the configuration $-CR_1{=}CR_2CHOHC{\equiv}C-$ forms the center of the condensation product. Treatment with acids favors an anionotropic rearrangement to $-CR_1(OH)CR_2{=}CHC{\equiv}C-$ (33, 37, 46, 79).

Various Grignard reactions have been performed with α-ionone, leading to the expected carbinols. The alcohol $C_{14}H_{23}OH$ was obtained with methylmagnesium bromide and converted into the corresponding hydrocarbon β-cyclocitrylideneisobutene $C_{14}H_{22}$ (CI) (55). Similarly, allylmagnesium bromide (52) and 4-methyl-2,4-hexadienylmagnesium bromide (80) have been shown to give tertiary carbinols (CII, CIII) with α-ionone. These reactions cannot be dupli-

(CI) $R_\alpha CH{=}CHC(CH_3){=}CH_2$

(CII) $R_\alpha CH{=}CHC(CH_3)(OH)CH_2CH{=}CH_2$

(CIII) $R_\alpha CH{=}CHC(CH_3)(OH)CH_2CH{=}CHC(CH_3){=}CHCH_3$

cated in the case of β-ionone, presumably owing to the presence of a second conjugated ethylene bond. Kipping and Wild (55) successfully condensed β-ionone with methyl iodide and also with bromobenzene by substituting lithium for magnesium. The unaltered presence of the β-configuration in the reaction products was confirmed by the formation of geronic acid through ozonolysis and by spectroscopic evidence.

Phenyllithium was also applied to the introduction of four phenyl groups into the dimethyl ester of dihydromuconic acid, leading after dehydration of the glycol (CIV) to tetraphenylhexatriene (107) (XCVIII), identical with that obtained from benzophenone and diacetylene (74).

$$(C_6H_5)_2(OH)CCH{=}CHCH{=}CHC(OH)(C_6H_5)_2$$

CIV

The attractive idea of combining two citral groups by a polyene chain, albeit a shorter one than in carotenoids, has been realized in the combination of two molecules of geranylacetone (CV) with the Grignard compound from 1,4-dibromobutane; dehydration of the resulting glycol with iodine yielded squalene (CVI). Using pseudo-ionone (CVII) instead of geranylacetone, one obtains dehydrosqualene (CVIII) (88).

$$2(CH_3)_2C{=}CHCH_2CH_2C(CH_3){=}CHCH_2CH_2COCH_3 + BrCH_2CH_2CH_2CH_2Br$$

CV

Geranylacetone

$$\rightarrow [(CH_3)_2C{=}CHCH_2CH_2C(CH_3){=}CHCH_2CH_2C(CH_3){=}CHCH_2{-}]_2$$

CVI

Squalene

$$2(CH_3)_2C{=}CHCH_2CH_2C(CH_3){=}CHCH{=}CHCOCH_3 + BrCH_2CH_2CH_2CH_2Br$$

CVII

Pseudoionone

$$\rightarrow [(CH_3)_2C{=}CHCH_2CH_2C(CH_3){=}CHCH{=}CHC(CH_3){=}CHCH_2{-}]_2$$

CVIII

Dehydrosqualene

Again, in the case of β-ionone abnormal reactions occur; in attempts to condense β-ionone with ethylene dibromide or 1,4-dibromobutane in the presence of magnesium, the pinacol of β-ionone, $C_{26}H_{42}O_2$ (CIX), was formed by reduction

$$R_\beta CH{=}CHC(CH_3)(OH)C(CH_3)(OH)CH{=}CHR_\beta$$

CIX

(96). The reaction of β-ionone with the magnesium compounds of vinylethinyl bromide (CX) and of butadienylethinyl bromide (CXIII) leads to carbinols which can be partly hydrogenated, yielding products to which the formulas CXI and CXIV were assigned.

$$R_\beta CH{=}CHCOCH_3 + BrMgC{\equiv}CCH{=}CH_2 \rightarrow$$

β-Ionone CX

$$R_\beta CH{=}CHC(CH_3)(OH)CH{=}CHCH{=}CH_2$$

CXI

$$C_{13}H_{20}O + BrMgC{\equiv}CCH{=}CHCH{=}CH_2 \rightarrow$$

CXIII

$$R_\beta CH{=}CHC(CH_3)(OH)CH{=}CHCH{=}CHCH{=}CH_2$$

CXIV

Attempts to rearrange them into primary alcohols (CXII, CXV) failed (98).

(CXII) $R_\beta CH{=}CHC(CH_3){=}CHCH{=}CHCH_2OH$

(CXV) $R_\beta CH{=}CHC(CH_3){=}CHCH{=}CHCH{=}CHCH_2OH$

The ketone $C_{17}H_{26}O$ (CXVI), which differs in the position of the linear conjugated system from the natural carotenoids, has been converted by ethylmagnesium bromide to the carbinol CXVII (34).

(CXVI) $R_\beta CH_2CH{=}C(CH_3)CH{=}CHCOCH_3$ (= XXXV)
(CXVII) $R_\beta CH_2CH{=}C(CH_3)CH{=}CHC(CH_3)(OH)CH_2CH_3$

13. Acetylene condensations

Another group of condensations with acetylene is based on Nef's reaction of ketones with acetylene in the presence of sodium. The application of this procedure to β-ionone yielded amongst other products the carbinol CXVIII, which was converted by partial hydrogenation to the corresponding allyl alcohol.

$$R_\beta CH{=}CHC(CH_3)(OH)C{\equiv}CH$$
CXVIII

Whereas no Rupe rearrangement of the ethinylcarbinol to the α,β-unsaturated aldehyde could be achieved (13, 40), the allyl rearrangement of the vinylcarbinol was described (27).

Better yields are obtained in the condensation of one molecule of aldehyde with unsubstituted acetylene by this method or with sodium amide or tertiary potassium butoxide than with the Grignard method discussed above. Sodium acetylide in liquid ammonia yields satisfactory amounts of the ethinylcarbinols derived from acrolein, crotonaldehyde, 2-methylcrotonaldehyde, tiglic aldehyde, and 2-ethyl-2-hexenal (45). Ethinylgeraniol (CXIX) was prepared by this method from citral (34). Finally, an ethinylcarbinol was obtained from the aldehyde

(CXIX) $(CH_3)_2C{=}CHCH_2CH_2CH{=}C(CH_3)CH(OH)C{\equiv}CH$
(CXX) $R_\beta CH_2CH{=}C(CH_3)CHOHC{\equiv}CH$

$C_{14}H_{22}O$ (LXIX). The constitution CXX is doubtful and some rearrangement seems to take place (34). These ethinylcarbinols contain the same grouping as the substances obtained by Grignard synthesis and are subject to the same anionotropic rearrangement.

C. REDUCTIONS AND OXIDATIONS

14. Reduction and hydrogenation

Many syntheses in the polyene field involve procedures of hydrogenation, both in the chain and in the functional groups. Acetylene bonds frequently have to be reduced to ethylene bonds. This end may be achieved by a variety of methods with differing degrees of specificity. Metallic sodium in alcohol, Raney nickel, palladium on various carriers, and platinum have all been used for this purpose. The uptake of hydrogen must be controlled in order to interrupt hydrogenation at the ethylene level. An unusually specific catalyst for the partial hydrogenation of triple bonds is an iron catalyst, prepared from an iron-aluminum alloy in analogy to the method used for Raney nickel (81, 100). Vinylacetylenes are thus easily converted into the corresponding dienes. In the

case of symmetrical divinylacetylenes, the resulting hexatrienes seem to undergo a rearrangement whereby one of the original double bonds is moved one step closer to the partly hydrogenated acetylene bond, resulting in a vinyl-allene configuration (99) (CXXI, CXXII).

$$\underset{\text{CXXI}}{RCH{=}CRC{\equiv}CCH{=}CHR} + H_2 \rightarrow \underset{\text{CXXII}}{RCH_2CR{=}C{=}CHCH{=}CHR}$$

The removal of the elements of two molecules of water from a polyenic glycol leads to a polyene with two more double bonds. Frequently, however, 1,2-, 1,4-, or 1,6-glycols are available as intermediates. These require the removal of two hydroxyls only and the introduction of a single additional ethylene bond. Obviously, such a reaction is in the nature of a reduction (*cf.* CXXIII and CXXIV) (102). A reagent specific for this reduction has been found in phosphorus diiodide, P_2I_4 (76), by means of which dihydrocinnamoin (CXXV) has

(CXXIII) $CH_3CH{=}CHCHOHCHOHCH{=}CHCH_3$
(CXXIV) $CH_3CH{=}CHCH{=}CHCH{=}CHCH_3$
(CXXV) $C_6H_5CH{=}CHCHOHCHOHCH{=}CHC_6H_5$
(CXXVI) $C_6H_5(CH{=}CH)_nC_6H_5$
(CXXVII) $C_6H_5CH{=}CHCHOHCH{=}CHCHOHCH{=}CHC_6H_5$

been converted into diphenylhexatriene (CXXVI, $n = 3$) and 1,8-diphenyl-1,4,7-octatriene-3,6-diol (CXXVII) into diphenyloctatetraene (CXXVI, $n = 4$). The former instance illustrates the synthesis of a symmetrical polyene with an odd number of double bonds.

Phosphorus diiodide in pyridine solution produces an unusual effect when reacting on a substance such as 1,1,6,6-tetraphenyl-2,4-hexadiyn-1,6-diol (CXXVIII), in which no hydrogen atoms are available for the removal of two molecules of water. Tetraphenylhexapentaene is formed by this reducing agent, and also by chromous chloride or by hydriodic acid; this substance (CXXIX) is a representative of the cumulenes, interesting substances with a chain of contiguous double bonds (75).

(CXXVIII) $(C_6H_5)_2(OH)CC{\equiv}CC{\equiv}CC(OH)(C_6H_5)_2$
(CXXIX) $(C_6H_5)_2C{=}C{=}C{=}C{=}C{=}C(C_6H_5)_2$

The synthesis of longer polyene chains from two equal fragments without a middle piece can be afforded by certain reductive procedures. Dihydrocinnamoin (CXXV) is obtainable from cinnamaldehyde by reduction with zinc. In analogy to the reductive condensation of thiobenzaldehyde through the free benzylidene radical to stilbene, thio- and seleno-polyene aldehydes may be dimerized by various reducing agents; thus, 1,22-diphenyldocosahendecaene (CXXXI), a hydrocarbon of purple-black color with metallic lustre and having a melting point of 318° C., was prepared from 11-phenylhendecapentaenal

$$\underset{\text{CXXX}}{2C_6H_5(CH{=}CH)_5CHO} \ (H_2S,H_2Se) \rightarrow \underset{\text{CXXXI}}{C_6H_5(CH{=}CH)_{11}C_6H_5}$$

11-Phenylhendecapentaenal 1,22-Diphenyldocosahendecaene

(CXXX) (58). An unusual condensation of two molecules of allyl chloride to hexatriene and of two molecules of methallyl chloride to 2,5-dimethylhexatriene by means of sodium amide in liquid ammonia with comparatively good yields has been described (54).

The particular suitability of aldehydes for polyene syntheses frequently requires the reduction of carboxyl groups to aldehyde groups in the presence of double bonds. The reduction method of von Braun and Rudolph (8) has been tried for the conversion of ethyl ionylideneacetate to ionylideneacetaldehyde with indifferent results (72). The ester is treated with the Grignard compound of *o*-toluidine, and the resulting *o*-toluidide is converted by phosphorus pentachloride into the imide chloride, which in turn is reduced by chromous chloride to the aldehyde (see, however, 53, 34). Another attempt to prepare ionylideneacetaldehyde,—namely, by dry distillation of the mixed barium salts of ionylideneacetic acid and formic acid,—led to a carbonyl compound, which was not identical with the expected ionylideneacetaldehyde (9), but which was recently shown to be α-ionone (93). Analogous scissions of ethenoid linkages in the α,β-position to carbonyl groups have been described: e.g., in the breakdown of citral into methylheptenone and acetaldehyde (103).

15. Oxidation and dehydrogenation

In those instances where an aldehyde has to be derived from the corresponding primary alcohol, the use of ketones and aluminum alcoholate is indicated. Since acetone is prone to condense with the unchanged aldehyde, the use of diisopropyl ketone has been recommended (31, 32). In the case of natural vitamin A, this reaction leads to the formation of axerophthal (XXII) or, when using acetone, to the formation of the ketone $C_{23}H_{32}O$ (XXXVIII) (2). Conversely, aluminum isopropoxide in isopropyl alcohol is the reagent of choice for the reduction of polyenic aldehydes to the respective alcohols (1, 19, 20, 72, 82). Polyenecarboxylic acids have been prepared from the corresponding aldehydes by oxidation with silver oxide (5, 82). The preparation of acids of the glutaconic series (LII) by the oxidation of oxalopolyenic esters (XLVIII) with hydrogen peroxide has been mentioned in section 6 (29). In the same section, reference has been made to the dehydrogenation of polyenediacetic acids to polyenedicarboxylic acids with one more double bond by atmospheric oxygen in the presence of alkali (60). Finally, 1,1,6,6-tetraphenyl-1,5-hexadiene (CXXXII) has been dehydrogenated to the corresponding triene (XCVIII) by selenium dioxide (87).

$$(C_6H_5)_2C{=}CHCH_2CH_2CH{=}C(C_6H_5)_2$$

CXXXII

1,1,6,6-Tetraphenyl-1,5-hexadiene

III. Attempts at Synthesis of Vitamin A

One of the most interesting practical applications of polyene syntheses would be a successful synthesis of vitamin A. The two main obstacles in this task, as well as in the synthesis of other natural carotenoids, are the conjugated-double-

bond system and the lateral methyl groups, which necessitate the use of ketones instead of the more reactive aldehydes. The former difficulty,—namely, that offered by the conjugated-double-bond system,—is circumvented in syntheses of perhydrogenated or at least partly hydrogenated products, which have played an important part in the confirmation of the structural formulas proposed for vitamin A and other carotenoids.

The perhydro derivatives of the acyclic carotenoid dicarboxylic acids crocetin and norbixin (bixin is the monomethyl ester of norbixin),—namely, perhydrocrocetin and perhydronorbixin,—have been synthesized by sequences of classical reactions (6, 47, 48). For the synthesis of squalene see section 12 (CVI, CVIII). The mono-unsaturated natural alcohol phytol, the alcoholic component of chlorophyll, has been synthesized by F. G. Fischer and Loewenberg (17). A Wurtz synthesis of dihydrophytyl bromide yielded perhydrolycopene (50). Des-crocetin, tetradecaheptaene-1,14-dicarboxylic acid, has been prepared by Kuhn and Grundmann (63).

Perhydrovitamin A was synthesized by Karrer, Morf, and Schoepp (51). In this case, as in all cases mentioned above, the identity of the synthetic perhydro derivative with the hydrogenation product of the corresponding natural substance was established. Ruzicka and Fischer (83), starting from dihydro-β-ionone, synthesized tetrahydrovitamin A according to formulas CXXXIII to CXXXVIII. Neither the tetrahydrovitamin, which may also be designated

$$\underset{\text{CXXXIII}}{R_\beta CH_2CH_2COCH_3} \xrightarrow{CH{\equiv}CH\ +\ H_2} \underset{\text{CXXXIV}}{R_\beta CH_2CH_2C(OH)(CH_3)CH{=}CH_2} \xrightarrow{PCl_5}$$

$$\underset{\text{CXXXV}}{R_\beta CH_2CH_2C(CH_3){=}CHCH_2Cl} \xrightarrow{CH_3COCH_2COOC_2H_5}$$

$$\underset{\text{CXXXVI}}{R_\beta CH_2CH_2C(CH_3){=}CHCH_2CH_2COCH_3} \xrightarrow{CH{\equiv}CH\ +\ H_2}$$

$$\underset{\text{CXXXVII}}{R_\beta CH_2CH_2C(CH_3){=}CHCH_2CH_2C(OH)(CH_3)CH{=}CH_2} \xrightarrow{(CH_3CO)_2O}$$

$$\underset{\text{CXXXVIII}}{R_\beta CH_2CH_2C(CH_3){=}CHCH_2CH_2C(CH_3){=}CHCH_2OH}$$

as 1-β-cyclogeranylgeraniol, nor the dihydrovitamin A (CXXXIX) of Gould and Thompson (27), showed any vitamin A activity. The latter authors used

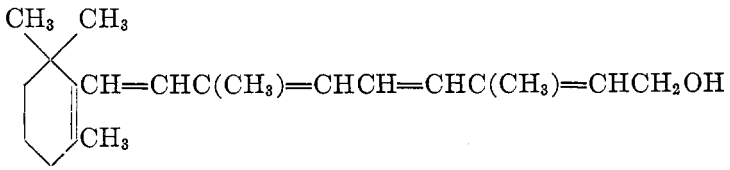
$$\underset{\text{CXXXIX}}{R_\beta CH{=}CHC(CH_3){=}CHCH_2CH_2C(CH_3){=}CHCH_2OH}$$

Tetrahydrovitamin A

essentially the same sequence of reactions as Ruzicka, but started from ionone instead of dihydroionone.

The numerous attempts to prepare a biologically active alcohol with twenty carbon atoms and five conjugated double bonds according to the specifications

of formula CXL have not yet met with success. Kuhn and Morris (72) claim the synthesis of a mixture containing 7 per cent of biologically active material by the following steps:



CXL

Vitamin A

$$R_\beta CH{=}CHC(CH_3){=}CHCOOC_2H_5 \xrightarrow{CrCl_2\ etc.}$$

CXLI (= LXXXI)

$$R_\beta CH{=}CHC(CH_3){=}CHCHO \xrightarrow{(CH_3)_2CH{=}CHCHO}$$

CXLII

$$R_\beta CH{=}CHC(CH_3){=}CHCH{=}CHC(CH_3)CH{=}CHCHO \xrightarrow{H_2} CXL$$

CXLIII (= XXII)

Except for their own scantily reported biological tests, all evidence gathered in the attempted repetition of the work of Kuhn and Morris speaks against their claims. First, the β-configuration of the ethyl ionylideneacetate (CXLI), obtained by the Reformatsky condensation of β-ionone with ethyl bromoacetate, is highly questionable (93, 95; *cf.* 108). Second, the reduction of this ester by the chromous chloride method, as described by Kuhn and Morris could not be reproduced by Karrer (53), Heilbron (34, 35), Krauze (57), or the authors. Finally, the formation of a chromogen for the Carr–Price reaction in a condensation involving the use of β-methylcrotonaldehyde is ambiguous, since here, as in the case of the attempted synthesis of Fuson and Christ (25), autopolymerization of methylcrotonaldehyde offers a sufficient explanation for a blue color reaction with antimony trichloride (see section 2).

Obviously, the preparation of authentic β-ionylideneacetaldehyde (CXLII) would present one of the most important stepping stones in the synthesis of vitamin A. Neither the above synthesis by Kuhn and Morris, nor the method of Davies, Heilbron, and coworkers with barium formate (13), nor the insufficiently supported Grignard reaction of β-ionone with diethyl bromoacetal (57) have led to success in this direction. The acetylene method of Ruzicka and Fischer (83), which works well in the dihydroionone series, gave very poor yields in the case of β-ionone itself (27). The alcohol $R_\beta CH{=}CHC(CH_3){=}CHCH_2OH$ (CXLIV) formed as an intermediate in the latter synthesis, is a potential source of ionylideneacetaldehyde by Oppenauer dehydrogenation.

In view of the objections against the condensation of β-ionylideneacetaldehyde with methylcrotonaldehyde, an alternative synthesis has been considered (40): Condensation of ionylideneacetaldehyde with acetone would lead to the isoprenolog of ionone, the ketone $C_{18}H_{26}O$ (XXXVII) (section 4). An authentic synthesis of this ketone depends on the preparation of β-ionylideneacetaldehyde. It would form an appropriate starting material for another acetylene synthesis and allylic rearrangement leading to vitamin A, analogous to the reactions CXXXVI → CXXXVIII. The extended Reformatsky condensation of ethyl γ-iodocrotonate with β-ionone has been suggested by Jones as an alternative (44). This would lead to the acid $C_{17}H_{24}O_2$ (CXLV), the chloride of which may be combined with methylcadmium to yield the ketone $C_{18}H_{26}O$ (XXXVII) mentioned above.

$$R_\beta CH{=}CHC(CH_3){=}CHCH{=}CHCOOH$$

CXLV

The unexpected tendency of the conjugated-double-bond system of β-ionone and its derivatives to undergo rearrangement into α-ionone and its respective derivatives under a variety of experimental conditions complicates most of the proposed synthetic schemes and necessitates the checking of the steric configuration by time-consuming physical and chemical tests at every step. The resolution of α-ionone into its enantiomers (94) offers the possibility to use optically active α-ionone as an indicator for the occurrence or otherwise of such rearrangements. The only authenticated β-ionone derivative with more than thirteen carbon atoms is β-cyclocitrylideneisobutene (*cf.* CI), obtained by the reaction of methyllithium upon β-ionone. Hence Kipping and Wild, in a preliminary communication (55), allude to a synthesis of vitamin A by condensation of β-ionone with the methyl ether of 6-bromo-3-methyl-2,4-hexadien-1-ol, $BrCH_2CH{=}CHC(CH_3){=}CHCH_2OCH_3$(CXLV), yielding the methyl ether of vitamin A.

Another possible scheme for the synthesis of vitamin A has been envisaged by Heilbron, Johnson, Jones, and Spinks (34) as illustrated by the following formulas: The ethinylcarbinol CXLVIII(= CXX, section 13) may be obtainable from the aldehyde CXLVII (= LXIX, section 8), and could then be condensed with a derivative of butanolone (CXLIX), with a protected hydroxyl group. As an alternative, the aldehyde CXLVII may be condensed with a correspondingly protected derivative of the ethyl carbinol CL.

(CXLVII) $R_\beta CH_2CH{=}C(CH_3)CHO$
(CXLVIII) $R_\beta CH_2CH{=}C(CH_3)CHOHC{\equiv}CH$
(CXLIX) $CH_3COCH_2CH_2OR$
(CL) $CH{\equiv}CC(OH)(CH_3)CH_2CH_2OR$

In either alternative one may anticipate difficulties in the dehydration and in the anionotropic rearrangement of the primary condensation products.

IV. Synopsis of Synthetic Polyenes

Classification	Method	References
Aliphatic hydrocarbons ...	(a) Dehydration of secondary or tertiary carbinols obtained by Grignard reaction from carbonyl compounds	(21, 65)
	(b) Thermal dehydration of glycols	(88, 102)
	(c) Simultaneous dehydration and decarboxylation of hydroxy acids	(21)
	(d) Wurtz reaction	(54)
Terpenoid polyenes.....	(a) Dehydration as above (a)	(22, 55)
	(b) Simultaneous dehydration and decarboxylation as above (c)	(21, 22)
Aromatic hydrocarbons with even number of double bonds.....	(a) Dehydration of carbinols	(65)
	(b) Geminal Perkin reaction of aromatic aldehydes with succinic acid or its vinylogs	(5, 76)
	(c) Grignard reaction of unsaturated aromatic aldehydes with benzyl halogenide	(74)
	(d) Geminal Grignard reaction of aromatic aldehydes with an aliphatic middle piece	(16, 74)
	(e) "Dehydroxylation" of 1,2- or 1,6-glycols with phosphorus diiodide	(76)
Aromatic hydrocarbons with odd number of double bonds.....	(a) Geminal Perkin reaction of aromatic aldehydes with dihydromuconic acid	(62)
	(b) "Dehydroxylation" of 1,4-glycols	(76)
	(c) Dehydrogenation of less unsaturated hydrocarbons with selenium dioxide	(87)
	(d) Reductive condensation of polyenic aldehydes	(58)
	(e) Aryl lithium condensation of dihydro muconic ester and dehydration of resulting ditertiary glycol	(107)
Cumulenes.....	Dehydration of acetylenic glycols by various reagents	(75)
Primary alcohols.....	(a) Ponndorf hydrogenation of aldehydes	(1, 19, 20, 72, 82)
	(b) Allylic rearrangement	(27, 33, 37, 46, 79, 98)

Classification	Method	References
Secondary and tertiary alcohols	(a) Grignard condensation of aldehydes and ketones	(37, 52, 55, 65, 80)
	(b) Acetylene condensation of aldehydes and ketones	(34, 45)
Glycols	(a) Reductive condensation of two molecules of aldehyde	(58)
	(b) Geminal Grignard condensation with dibromoacetylene and partial hydrogenation	(16, 38, 79, 96)
	(c) Geminal double Grignard condensation with dicarboxylic esters	(74)
Aldehydes	(a) Oppenauer dehydrogenation	(3)
	(b) von Braun reduction of ester *via* imide chloride	(8, 34, 53, 72)
	(c) Thermal reaction of barium salt with barium formate	(9, 34, 93)
	(d) Aldol condensations	(1, 3, 5, 19, 20, 39, 56, 59, 62, 68, 77, 87, 90, 91)
Ketones	(a) Condensation with acetone	(2, 4, 36, 84)
	(b) Condensation with ethyl acetoacetate	(27, 83, 88)
	(c) Condensation of acyl chlorides with methylzinc or methylcadmium	(14, 26, 51)
Monocarboxylic acids	(a) Oxidation of aldehydes	(5, 82)
	(b) Malonic ester synthesis with aldehydes and decarboxylation	(15, 63)
	(c) Cyanoacetic ester condensation, followed by saponification and decarboxylation	(12, 105)
	(d) Reformatsky synthesis	(13, 21, 40, 52, 64, 70, 72, 93, 95, 105)
	(e) Elimination of CO from α-keto acids	(23)
Dicarboxylic acids; substituted malonic acids	Malonic ester synthesis	(15, 63)
Dicarboxylic acids; fumaric acid series	Oxaloacetic ester synthesis	(7, 29, 60, 62, 63, 64, 78)
Dicarboxylic acids; glutaconic acid series	Oxidation of oxalo acids with hydrogen peroxide	(29)

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