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Natural and Synthetic Acetylenic Antimycotics

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The available information about natural and synthetic acetylenic compounds exhibiting antifungal activity is surveyed and it is shown that the class of acetylenic compounds with functional groups is extremely promising as regards the search for new drugs, particularly in view of the increase of the number of strains which have acquired immunity to the preparations used at the present time.
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I. INTRODUCTION

Fungal diseases (mycoses) affect man, various animals, and plants. Agents responsible for mycoses are numerous and the clinical symptoms are various[1-6]. Fungal diseases of the skin, caused by parasitic fungi or dermatomycetes, are encountered in all regions of the world. Humanity has suffered from mycoses since ancient times. They are highly contagious and give rise to chronic conditions. Clinical observations have shown that dermatophytes, which have become adapted by evolution to the skin and its derivatives, can sometimes affect also internal organs, bone tissue, and the central nervous system[5-7]. Although skin mycoses affect mainly the surface layers of the skin, they constitute a serious problem for the health service since the incidence of certain skin mycoses is comparable to that of the common cold or dental caries and the treatment of patients with skin mycoses is enormously expensive[4-5]. The problem of the chemotherapy of patients with fungal inflections has attracted the attention of a wide range of specialists-dermatologists, pharmacologists, biochemists, and chemists[6-10].

Antifungal antibiotics (griseofulvin, nystatin, and others) have occupied a leading place among the drugs and in connection with methods for the modern treatment of mycoses. However, it would be incorrect to assume that the problem of the treatment of dermatomycoses has been fully solved. Numerous communications devoted to the description of complications and failures in the employment of recognised antimycotics have been published[6,7]. The spectrum of their activity frequently limited: fungal strains resistant to these antibiotics have appeared. Hitherto, preparations with adequate activities and lacking side effects have been missing from the arsenal of antifungal agents. The acute nature of the problem of the chemotherapy of fungal diseases requires the improvement of the existing medicinal preparations and has stimulated a persistent search for new antimycotics.

The search for active antifungal preparations is based on various classes of compounds[6,11]. Natural antibiotics of the acetylenic series, containing carbofunctional groups in their structure, are extremely promising[8,11-16].

II. NATURAL ACETYLENIC ANTIMYCOTICS

Acetylenic compounds are fairly common in nature as metabolites of many plants and as antibiotics generated by fungi and actinomycetes[8,11-17]. It has been established that acetylenic and polyacetylenic fragments can enter into the composition of the molecules of a wide variety of natural organic substances, but the functions of these highly unsaturated compounds in the metabolism of plants and microorganisms remain not altogether clear[12].

The majority of the acetylenic compounds have been isolated from plant essential oils and fats and from fungal culture liquids[11,13-15]. The classical studies[15-23] provide an idea about the systematic research on natural poly-ynes and the enormous effort by several schools of investigators—those of Sörensen in Norway, Bu'Lock and Jones in England, and Bohlmann in Germany. The experimental data on all natural polyacetylenes known at the beginning of 1971 have been successfully surveyed in a monograph describing many aspects of the problem[12].

Comprehensive studies on the poly-ynes encountered in nature have shown that, apart from their theoretical interest, associated with the elucidation of their role in the biosynthetic processes involving the living cell, they are of considerable practical interest in view of their high biological activity. Many natural polyacetylenes retard the growth of various bacterial and fungal species even at high dilutions. According to Shemyakin's data[8], antifungal activity has been noted among 353 antibiotics (this number has now increased). The pronounced antifungal activity of natural poly-ynes investigated in this respect has attracted particular attention. The best known of these are capillin (I), wyerone (IV), agrocybin (VI), biformene (VII), nemotin (IX), and others.

Capillin has attracted the steady attention of investigators by virtue of its high antifungal activity and comparatively simple structure. Capillin has in fact led to the publication of numerous studies devoted to the synthesis and investigation of the biological properties of analogous and related compounds[24-36]. This diacetylene was isolated in 1957 from the essential oil of *Artemisia capillaris* and the formula of 1-phenylhexa-2,4-diyn-1-one (I) proposed for it was confirmed by synthesis[28,31]:

$$CH_3{-}C{\equiv}C{-}C{\equiv}CH \xrightarrow{NaNH_2} CH_3{-}C{\equiv}C{-}C{\equiv}C{-}CHOH{-}C_6H_5 \rightarrow$$
$$\xrightarrow[AcOH]{CrO_3} C_6H_5{-}CO{-}C{\equiv}C{-}C{\equiv}C{-}CH_3 \quad .$$
(I)

The acetylenic compound (II), called capillene, had been isolated previously[32] from the essential oil of plants of the same genus. It transpired later that it is identical with agropyrene[33] and "dehydroagropyrene"[37].

$$C_6H_5{-}CH_2{-}C{\equiv}C{-}C{\equiv}C{-}CH_3$$
(II)

The demonstration of the identity of agropyrene from *Agropyrum repens* and capillene from *Artemisia campestris* and determination of the structure were preceded by research prosecuted by several investigators over a period of almost three decades. Thus Harada[29,30] determined more accurately the formula of capillene and confirmed it by synthesis in accordance with the following scheme:

$$C_6H_5-CH_2-C\equiv CH \xrightarrow[CH_3C\equiv Cl]{MgBrC_2H_5} C_6H_5-CH_2-C\equiv C-C\equiv C-CH_3 \quad .$$
(II)

It was shown later that capillene is oxidised to capillin on prolonged storage in air. Both capillene and capillin exhibit an exceptionally strong antimicrobial activity and also high activity against various phytopathogenic fungi. Capillin arrests the growth of dermatophytes in a nutrient medium at very low concentrations (0.25 $\mu g\ ml^{-1}$).[24,28] In tests of its antifungal activity in experiments on animals, capillin proved to be active against *Trychophyton asteroides*[25,38]. Several representatives of aromatic acetylenic compounds closely related to capillin have been isolated from plants of the *Compositae* family: capillon, capillarin, and desmethylcapillin[39-41]. It is noteworthy that an unsaturated hydrocarbon (III) with four conjugated triple bonds, whose antifungal activity surpasses that of capillin, has been detected in extracts from higher plants[42].

$$CH_3-CH=CH-(C\equiv C)_4-CH=CH_2$$
(III)

Natural thienyl- and furyl-poly-ynes with a wide variety of structures exhibit a high antibiotic activity[8,11,12,15,43-57]. Among poly-yne metabolites of higher plants, an extremely effective antimycotic has been detected[43,58,59]—a disubstituted furan derivative. The crystalline compound was isolated from a *Vicia faba* extract. Oxidation of the natural product with potassium permanganate yielded furan-2,5-dicarboxylic acid. According to ^1H NMR and mass-spectrometric data, it was possible to postulate two structures, (IV) and (V), for this compound[12,43,58,59]:

$$CH_3-CH_2-CH=CHC\equiv C-CO-\langle O \rangle -CH=CHCO_2CH_3 \ ;$$
cis *trans*
(IV)

$$CH_3-CH_2-CH=CH-CO-C\equiv C-\langle O \rangle -CH=CHCO_2CH_3 \ .$$
cis *trans*
(V)

The validity of formula (IV) was demonstrated by synthesis from 5-hydroxymethylfurfural[58,59]:

$$HO-CH_2-\langle O \rangle -CHO \xrightarrow[2.\ MnO_2]{1.\ (C_6H_5)_3P=CH-CO_2-CH_3}$$
$$\rightarrow OHC-\langle O \rangle -CH=CH-CO_2-CH_3 \xrightarrow{C_2H_5CH=CH-C\equiv C-MgBr}$$
$$\rightarrow C_2H_5-CH=CH-C\equiv C-CH(OH)-\langle O \rangle -CH=CH-CO_2-CH_3 \xrightarrow{MnO_2}$$
$$\rightarrow C_2H_5-CH=CH-C\equiv C-C(=O)-\langle O \rangle -CH=CH-CO_2-CH_3 \ .$$
cis *trans*
(IV)

The ketoester (IV), called wyerone, can suppress the growth of many pathogenic fungi—*Alternaria brassicicola*, *Aspergillus niger*, *Uromyces fabae*, and *Glomerella cingaluta*—at a concentration of approximately 10 $\mu g\ ml^{-1}$.

Polyunsaturated products from fungal microorganisms are highly polar substances with functional groups. Powerful acetylenic antimycotics—agrocybin (VI)[60,61] and biformene (VII)[62-64]—have been isolated from the culture liquids of basidiomycetes.

An unstable crystalline triyne (VI) has been isolated by extraction from the culture liquid of the fungus *Agrocybe dura*.[60,61] Analysis of spectroscopic data and specific synthesis showed that agrocybin has the structure of the amide of 8-hydroxyocta-2,4,8-triynoic acid (VI)[65,66]:

$$HO-CH_2-C\equiv C-C\equiv CH + HC\equiv C-COOMe \xrightarrow[CuCl]{O_2}$$
$$\rightarrow HOCH_2C\equiv C-C\equiv C-COOMe \xrightarrow{NH_3} HOCH_2-(C\equiv C)_3CONH_2 \ .$$
(VI)

A high antifungal activity is characteristic of agrocybin, but its toxicity is also high: LD_{50} for mice is 60 mg kg^{-1}.[61]

Biformene is an interesting polyacetylenic antibiotic[62-64]. In the study of the antibiotic activity of this poly-yne it was noted that it is active *in vitro* against various representatives of gram-positive and gram-negative microbes and the mycobacteria responsible for tuberculosis. It exhibits a fairly high activity as an antimycotic (0.5–4 $\mu g\ ml^{-1}$), but it did not show a therapeutic effect in tests on animals. After a series of studies, structure (VII) was established for biformene. According to ultraviolet and infrared spectra, its molecule contains a triyne system and an unsubstituted ethynyl group. Since hydrogenation of the natural product led to nonane-1,2-diol, the structure of the triynediol (VII) was proposed for biformene[63,67,68]:

$$HC\equiv C-C\equiv C-C\equiv C-CH_2-CH(OH)-CH_2OH \ .$$
(VII)

The synthetic nona-4,6,8-triyne-1,2-diol (VII), obtained by Bohlmann[69], did not correspond to natural biformene as regards its properties. The epoxide (VIII) proved to be identical with the natural poly-yne[70]:

$$HC\equiv C-C\equiv C-C\equiv C-CH(O)-CH-CH_2OH \ .$$
(VIII)

A whole series of similar epoxides were later isolated from plants of the *Compositae* family[71,72].

A fairly large class of compounds, incorporating the allene-diacetylene group as a structural element, has been discovered among natural poly-ynes. Many compounds of this type exhibit a broad-spectrum antimicrobal activity[73-77].

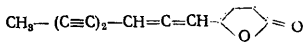
A mixture of antibiotics (IX)–(XII), present in the culture liquids of *Poria tenium*, *Poria corticola*, and the basidiomycete B-841, has been described[73-75]. The pronounced antifungal effect of nemotin (IX) against many strains of various fungi (0.06–16 $\mu g\ ml^{-1}$)[74] has been noted. Its activity does not decrease in the presence of blood serum. Nemotin is the lactone of nemotinic acid (X); the biological activity of compound (X) is close to that of (IX) in terms of its bactericidal spectrum, but its fungicidal activity is different.

$$HC\equiv C-C\equiv C-CH=C=CH-CH=C=CH-\langle O \rangle =O$$
(IX)

$$HC\equiv C-C\equiv C-CH=C=CHCH(OH)(CH_2)_2-COOH$$
(X)

The reliability of structures (IX) and (X) was confirmed by the study of their infrared spectra and isomerisation products. Comparison of the entire set of chemical and spectroscopic characteristics made it possible to identify in the mixture of metabolites of the B-841 fungus the antibiotics odyssin (XI) and odyssic acid (XII)—the

methyl homologues of compounds (IX) and (X) [73-75]:



(XI)

$CH_3-(C\equiv C)_3-CH=C=CHCH(OH)(CH_2)_2-COOH$.

(XII)

The study of the biologically active products of the metabolism of microorganisms stimulated the development of a new field of organic synthesis—research on new compounds with antifungal properties.

III. SYNTHETIC ACETYLENIC ANTIMYCOTICS

The literature data show that acetylenic compounds have recently aroused interest ss drugs [11,35,43,76-87]. The spectrum of the biological activity of acetylenic compounds is unusually broad: they behave as convulsants, anticonvulsants, local anaesthetics, analgesics, hypotensive agents, ganglion-blocking agents, and antibacterial agents [76], and many acetylenic preparations are frequently more active, less toxic, and more readily assimilated by the organism than their olefinic or saturated analogues. The presence of the triple bond in the molecule apparently lowers the toxicity and improves the degree of absorption and metabolism of certain drugs.

Interest in the analogues of natural acetylenic antibiotics has been shown particularly in the last 10–15 years. During this period, mono-, di-, and vinylacetylenic ketones [11,26,27,35,43,77,83,85,88-93], acetylenic ketoacids [94,95], esters [35,76,77,85,87,96-100], and other acetylenic compounds [11,76-81] were synthesised in order to investigate their biological properties.

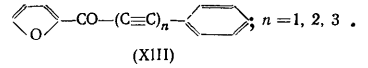
The successful synthesis of complex unsaturated compounds with functional groups has a sound methodological basis in the chemistry of acetylene [11,12,76,100-106]. Many poly-ynes have been obtained by oxidative dimerisation[101,102] and asymmetric condensation[102-104]. They are frequently synthesised in connection with the systematic investigation of acetylenic compounds with properties prediced beforehand[35,36,43,78-80,83-87,90,107-118]. Unfortunately a rigorous scientific theory, which would be able to eliminate empiricism from the synthesis and modification of the molecules of known antibiotics and would enable a purposeful search for new drugs with specific therapeutic activity, is still lacking[119].

The fungicidal activity of natural polyacetylenes depends to a large extent on their structure [12,34,77] and in most cases the activity is rigorously selective, which gives rise to the hope that new synthetic analogues with selective antifungal activity will be obtained [35,43,83-87,110-122].

1. Acetylenic Carbonyl Compounds

The antifungal activity of acetylenic carbonyl compounds is attributed to the presence in their molecules of the conjugated ketoethynyl group [25,26,35,77,123]. The hypothesis of the biological specificity of the ketoethynyl group $-CO-C\equiv C-$ in the capillin molecule and the assumption that this fragment is responsible for the antifungal effect was formulated in two investigations [25,26]. It was confirmed and justified by extensive experimental data on the synthesis of acetylenes with carbofunctional groups and results amplifying the available information about the influence of various structural elements on fungicidal properties [35,43,83,85-87,90,124-135]. Joint investigations by chemists and microbiologists have shown that any structural changes in the ketoethynyl group (the breakdown of conjugation, the introduction of double bonds) cause an appreciable decrease of activity or a sharp change in the nature of the activity of the preparation [35,43,77,81,83,85-87,90,128,132]. It was found that the nature of the substituents at the CO group and the triple bond has little influence on the antibiotic activity, but determines the irritant action and the pharmocological properties of acetylenes with carbofunctional groups [35,36,81,86,135]. The replacement of the phenyl group in capillin itself by chlorophenyl, methoxy-, and thienyl groups leads to a decrease of the antifungal activity and an increase of the irritant action[27,37]. There are data [86,130,136] showing that the irritant action may be greatly reduced by introducing a hydroxy-group into the α-ethynylketone molecule or by the replacement of the alkyl group by the phenyl group. The increase of the length of the carbon chain of the alkyl substituent to C_4 increases the activity of capillin and capillene analogues, but a further increase in chain length lowers the activity[81].

Many investigators attempted to elucidate the relation between antifungal activity and the degree of unsaturation (the number of triple bonds in the antimycotic molecule)[26,35,83-87,121,133,135]. It was shown [83,86,129] that the second acetylenic fragment introduced into the conjugation chain of furylphenylacetylenic ketones (XIII) enhances the antifugal properties somewhat, but the triynones (XIII, $n = 3$) already show a sharp decrease of both fungistatic and bacteriostatic activities:

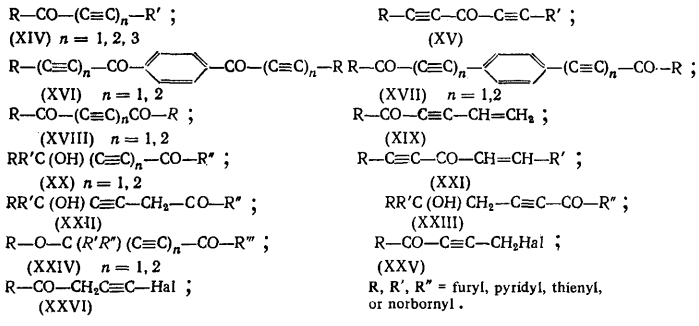


(XIII)

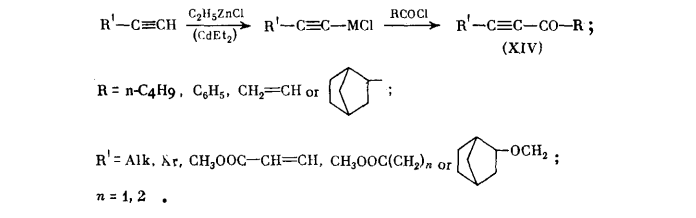
The small biological effect of the triynone (XIII) has been explained [129] by its low solubility in water and its decomposition after the incubation of cultures in a thermostat for many hours. Cases are known where the introduction of a second acetylenic bond into the molecule lowers the antimycotic effect [84,133,134].

Since the use of the known natural antimycotics of the propynone series is precluded by their high toxicity, new methods have been proposed and applied in the search for analogues with low toxicity [35,43,83,137-139] and the known methods have been improved. Fairly extensive data have now been accumulated on the synthesis of α-acetylenic ketones. Surveys of the chemical properties and the methods of synthesis of α-ethynylketones have been published [35,140,141]. The generally accepted methods are not always suitable for the preparation of ketones with other functional groups, owing to the exceptional reactivity of the α-ethynylcarbonyl group. The triple bond in α-ethynylketones is highly activated by the adjacent carbonyl group and readily undergoes various nucleophilic addition reactions. The most rational method for the preparation of ethynylketones is the oxidation of secondary acetylenic alcohols. The use of active manganese dioxide [142] as well as chromium trioxide in sulphuric or acetic acid made it possible to obtain a wide range of acetylenic ketones (XIV)–(XXVI) with various structures by the

oxidation of the corresponding alcohols and glycols [35,43,83,85,87,90,99,137,143]:

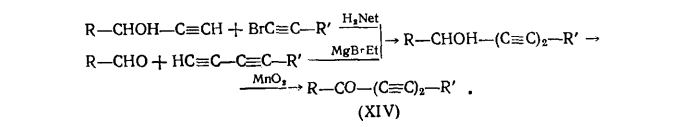


High yields of monoacetylenic and vinylacetylenic ketones, acetylenic diketones, and ketoacid esters have been obtained by the reaction of ethynylzinc or ethynylcadmium reagents, resembling the Iotsich complex in terms of their reactivity, with the chlorides and anhydrides of aliphatic and aromatic acids [85,113-116]:



Ethynylketones (XIV) are active against *Trichophyton gypseum* and a ketone with the norbornene substituent at the carbonyl group showed a distinct therapeutic effect on an experimental model of dermatomycosis [85,86].

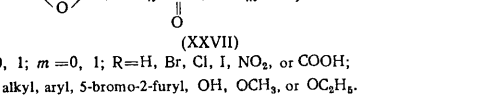
The pentadiynone group, analogous to capillin, is retained in the diacetylenic ketones (XIV, $n = 2$), obtained by the oxidation of secondary diacetylenic alcohols with manganese dioxide [35,83,85,126,127]:



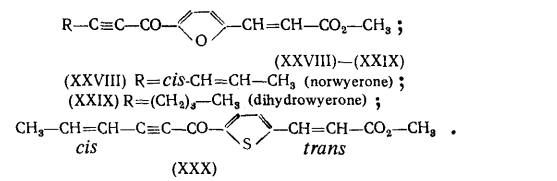
Triacetylenic and tetra-acetylenic ketones have been obtained in accordance with the same scheme [35].

In order to improve the stability of polyunsaturated capillin-like compounds, use was made of silylacetylenic derivates with a high fungicidal activity in relation to *Trichophyton gypseum* and *rubrum*. [117]

In contrast to benzoylacetylenes, furoylacetylenes (XXVII) exhibit a strong antifungal activity combined with a lower toxicity. This observation initiated systematic research into furylalkynes [35,43,83,86]. The monoacetylenic ketone 1-(2-furyl)-5-phenylpent-4-yn-3-one is known [92] to be active not only against *Trichophyton* but also against *Candida* and many other fungi.



A fairly high activity against pathogenic fungi, resembling that of the natural precursor wyerone (IV), is shown by its synthetic analogues (XXVIII)-(XXX) [44,58,59]:



The high antifungal activity of the ketones (XIV) has been noted in a number of patents [89,92,144-148]: data obtained in recent years [35,36,83,85,86,118,144-156] are evidence showing that studies on the practical applications of these substances have been carried out, for example, in the fight against the fungal diseases of plants [150]. A pronounced antifungal activity is characteristic of all the ketones tested. Dermatophytes are particularly sensitive to acetylenic ketones. A common property of ethynylketones is their weak activity against strains of yeast-like fungi and actinomycetes [35,43,83,85,86]. Mention should be made of data [81,82,85,86,122,135] concerning the activity of ethynylketones against the tuberculosis mycobacterium. The high tuberculostatic activity of α-ethynylketones is shown not only *in vitro* but also *in vivo* [35,85,86,135].

Presumably the likely mechanism of the antibiotic activity [157-160] of α-acetylenic ketones is analogous or similar to the mechanism proposed for the activity of $\alpha\beta$-diunsaturated ketones. The antibiotic effect of $\alpha\beta$-diunsaturated ketones has been explained in well known studies [161,162] by their tendency to interact with the sulphhydryl groups of enzymes, which are important for the vital activity of microorganisms. Reactions of this kind with nucleophiles of the SH type are in fact characteristic of ethynylketones to an even greater extent than of vinylketones. The mechanisms of the action of various antifungal substances are not the same. There are data showing [160] that acetylenic derivatives exhibit a more restricted activity on the cytoplasmic membrane than polyenes. It may be that the selective antifungal activity of the acetylenic preparation is associated with the breakdown of the functions of the cell wall, although it need not be of the same type as in polyenes [160]. The tendency to explain the mechanism of the action of antibiotics at a molecular level has been dominant in recent years [9,158,163,164]. The quantum-mechanical treatment of pharmacological problems—the correlation of activity with parameters of the electronic structures of active compounds—appears to be extremely promising [165]. In future we may expect a sharp increase of attention devoted to this problem, without the solution of which the specific synthesis of therapeutically valuable derivatives of natural antibiotics appears to be impossible.

2. Acetylenecarboxylic Acids and Their Derivatives With Antifungal Activity

Amongst natural poly-yne acids and their derivatives, a number of powerful antimycotics have been discovered [8,12,65,73-75], which led to a vigorous search for new antifungal agents based on unsaturated carboxylic acids. Even the structurally simplest propiolic acid and its esters are active against many fungi, while methylpropiolic acid also possesses antibacterial properties. A further increase in the number of methylene groups reduces the bacteriostatic activity and enhances the fungistatic activity. Judging from patent data [166-168], ω-iodoalkynoic acids (XXXI) and their esters (XXXII) are also active against mycoses [169,170]:

In experiments on the mycelia of *Trichophyton* and a yeast-like fungus a study was made of acetylenic acids derived from furan [171-173]. It was shown that the presence of the ketoethynyl group combined with the furan ring in the molecule promotes fungistatic activity, but the introduction of substituents (a bromo- or nitro-group) in the 5-position in the furan ring reduces the fungistatic activity and sharply enhances the bacteriostatic activity.

The esters (XXXIII) of acetylenecarboxylic acids and polyhydric alcohols suppress the growth of bacteria and fungi even at a very low concentration [174]:

$$HO-(CH_2)_n-OH + R-C\equiv C-CO_2H \xrightarrow[H^+]{C_2H_5} R-C\equiv C-COO(CH_2)_nOCO-C\equiv C-R \ .$$

(XXXIII)

The fungistatic activity of dicarboxylic acid esters is somewhat greater than that of the acids themselves, the second carboxy-group having little effect on the activity [77,175,176]. It has been suggested that different esters of acetylene-dicarboxylic acid as well as its salts be used to control the fungal diseases of rice [177].

In the series of dimethyl dicarboxylate esters of the type $(CH_3OC_2-(CH_2)_2-(C\equiv C)_n-(CH_2)_2-CO_2CH_3$ (XXXIV) the fungicidal activity increases sharply on passing from diacetylenic to tetra-acetylenic derivatives [121]. A similar behaviour has also been observed for monocarboxylic acids of type (XXXV) [121]:

$$C_4H_9-(C\equiv C)_n-R \ ;$$

(XXXV)

$R=(CH_2)_m-CO_2H$, CO_2H, or $CH=CHCO_2H$; $m=0-2$.

Kucherov and coworkers [121,178] investigated systematically the pathways leading to the formation of many polyunsaturated mono- and di-carboxylic acids. In order to elucidate the dependence of biological activity on structure, the nature of the functional groups, and the number of triple bonds, acids of two types, (XXXVI) and (XXXVII), were examined [178]:

$$\underset{\text{(XXXVI)}}{R-(C\equiv C)_m-(CH_2)_n-COOH} \qquad \underset{\text{(XXXVII)}}{R-(C\equiv C)_m-(CH=CH)_n-CH_2CH_2-COOH} \ .$$

The Chodkiewicz condensation [102-104] served as a basis for the syntheses, which required the development of easy methods for the formation of fragments with a terminal acetylenic bond, as in compound (XXXVIII):

$$CH_3O_2C-(CH_2)_2-C\equiv CH \xrightarrow{BrC\equiv C-CO_2H} CH_3O_2C(CH_2)_2C\equiv C-C\equiv C-CO_2H$$
$$\downarrow$$
$$CH_3O_2C(CH_2)_2-C\equiv C-C\equiv CH \ .$$

(XXXVIII)

A series of polyunsaturated acids (XXXVII) have been obtained (in yields up to 50%) by the oxidative condensation of the vinylacetylenic acid (XXXIX) and its bromide with different acetylenic acids, alcohols, and hydrocarbons [178]. Carboxylic acids (XXXVII) containing the vinylacetylene group are related to the natural antimycotics—nemotin (IX), odyssin (XI), and Drosophilin.

$$HC\equiv C-CH=CH-CH_2Cl \xrightarrow{NaCH(CO_2C_2H_5)_2} HC\equiv C-CH=CH-CH_2-CH(CO_2C_2H_5)_2$$
$$\downarrow \quad trans,\ cis$$
$$HC\equiv C-CH=CH-CH_2CH_2CO_2H \ .$$
$$trans$$

(XXXIX)

Many vinylacetylenic acids exhibit a powerful selective activity in relation to certain types of pathogenic fungi at concentrations (*in vitro*) comparable to those of the strongest antimycotics (capillene, odyssin).

The method for the preparation of unsaturated ketoacids developed by Bergel'son et al. [95] was extended by Bergel'son and Grigoryan to the synthesis of ketoacids with terminal double and triple bonds [179]. Ketoacids of the type $R-C\equiv C-CO-(CH_2)_n-COOH$ (XL) have been obtained by condensing lithium acetylides with cyclic dicarboxylic acid anhydrides:

$$R-C\equiv CLi + O=C\begin{cases}(CH_2)_n\\ O\end{cases}C=O \rightarrow R-C\equiv C-CO-(CH_2)_n-COOH$$

(XL)

Acetylenic ketoesters with low toxicity, which suppress *in vitro* the pathogenic dermatophytes *Microsporon lanosum* and *Achorion schönleini* at concentrations of 1-2 μg ml^{-1} and *Trichophyton gypseum* at a concentration of 6 μg ml^{-1}, have been obtained by this method. It is noteworthy that the high antifungal activity of the unsaturated ketoester (XL, $R=C_4H_9$, $n=3$) depends on the presence of its molecule of the conjugated ethynylketone group, since its ethylene analogue is less active and the corresponding saturated ketoester altogether fails to suppress the growth of the above fungi [95].

Fungicidal agents have been found recently not only among the esters [160,169,170,174,180-184], but also among the amides of acetylenic acids [185-189]. The propiolamides (XLI)-(XLIII) are particularly active [135,186]:

$$HC\equiv C-COCl + H_2N-(CH_2)_6-H_2N \rightarrow HC\equiv C-CONH-(CH_2)_6-HNCO-C\equiv CH \ ;$$
(XLI)

$$HC\equiv C-CONH-C_6H_4-NHCO-C\equiv CH \qquad MeC\equiv C-CONH-C_6H_4-NHCO-C\equiv CH \ .$$
(XLII) m.p. 228° (XLIII) m.p. > 300°

In order to obtain compounds inhibiting the growth of microbes, studies have been made [190-193] of the synthesis and microbiological properties of acetylenic aminoacids. L-3-(2-propynylthio)alanine (XLIV) may be used as a fungicide active against certain parasitic fungi [191]:

$$HC\equiv CCH_2Br + HSCH_2CH(NH_2)COONa \xrightarrow{NH_3} HC\equiv C-CH_2S-CH_2-CH(NH_2)-COOH \ .$$
(XLIV)

3. Propargyl Ethers

A series of studies have been made and a number of patents have been taken out concerning the synthesis and biological properties of aryl propargyl ethers (XLV), many of which are powerful fungicides [85,87,97-99,131,143,194-210]:

$$Ar-Y-CH_2-C\equiv C-R \qquad Y=O \text{ or } S; \quad R=Hal \text{ or } H.$$

(XLV)

Direct and indirect methods are known for the preparation of ethers from acetylenic alcohols. Terminal propargyl ethers (XLVI) are usually obtained by the interaction of propargyl halides with alkoxides, derived from saturated alcohols, and phenoxides or by the interaction of alkoxides derived from acetylenic carbinols with alkyl halides. The ethers (XLVI) can serve as key substances in the synthesis of a wide variety of bifunctional acetylenes and aminopropargyl ethers exhibiting antifungal activity:

$$\left.\begin{array}{l} R\\ R'\end{array}\right\}C(Hal)-C\equiv CH + R''OM \rightarrow \left.\begin{array}{l} R\\ R'\end{array}\right\}C(OR'')-C\equiv CH + MHal \ ;$$
$$\left.\begin{array}{l} R\\ R''\end{array}\right\}C(OM)-C\equiv CH + R''Hal$$

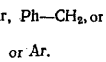
(XLVI) M=K or Na.

A convenient method [203,204] involves the hydroxypropargylation of norbornenes at the strained double bond in the presence of boron trifluoride etherate, which leads to *exo*-propargyloxynorbornanes in satisfactory yields (40 to 97%).

A specific synthesis of new antimycotics made it possible to develop an optimum version of the synthesis of propargyloxyketones (XLVII)[35,87,99]:

$$R{-}OH + BrCH_2C{\equiv}CH \xrightarrow[K_2CO_3]{NaOH} R{-}O{-}CH_2{-}C{\equiv}CH \xrightarrow[2.\ R'CHO]{1.\ MgBrEt} \rightarrow ROCH_2{-}C{\equiv}C{-}CHOH{-}R' \xrightarrow{MnO_2} ROCH_2C{\equiv}C{-}CO{-}R' ;$$

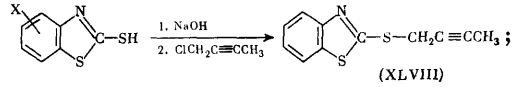
(XLVII)

R=Alk, Ar, Ph—CH_2, or —CH_2;

R'=Alk or Ar.

The introduction of the carbonyl group into ethers derived from acetylenic alcohols made it possible to increase their antifungal activity[82,87,99,130,131]. The study of the antibiotic properties of ketoethers in relation to a large series of strains *in vitro* showed that they exhibit a high antifungal activity, suppressing the growth of dermatophytes at concentrations of 1.2–1.56 $\mu g\ ml^{-1}$. The nature of the substituents at the ether and carbonyl groups plays a certain role, but it was not possible to establish a correlation between the structure of the compounds and their activity[87,99].

Fungistatic and germicidal agents have been discovered among benzthiazolyl propynyl sulphides[211,212]:



(XLVIII)

X = 5-Cl, 4-Me, 6-EtO, etc.

Unsubstituted alkyl ethynylvinyl sulphides HC≡C–CH=CHSAlk (XLIX) proved to be active against certain species of mould developing in PVC coatings in tropical climates[111].

4. Acetylenic Alcohols

The antimycotic activity of monoacetylenic alcohols is low compared with the corresponding carbonyl compounds[77,81,85,86,123], but the inhibiting activity of vinylacetylenic and diacetylenic alcohols is higher. Interesting reports have been published[213-216] about acetylenic carbinols as fungicides. Compounds having the general formula R–C≡CCXCH=CH–R' (L), where R = phenyl or naphthyl and X = H or OH, are active against moulds on plants[213].

Fungistatic activity is also shown by alcohols with a short chain having a phenyl substituent adjacent to a triple bond[77,123]. The introduction of a double bond into short-chain primary alcohols in a position which results in conjugation with the triple bond enhances the fungistatic activity, particularly if the phenyl substituent and the triple bond are at the end of the molecule. The vinylacetylenic carbinol (LI) exhibits fungistatic activity; the same properties are also shown distinctly by the secondary alcohol (LII), in which the double bond is not conjugated with the triple bond, occupying the $\alpha\beta$-position relative to the carbinol carbon:

$$C_6H_5{-}C{\equiv}C{-}HC{=}CH{-}CH_2OH ;$$

(LI)

$$C_6H_5{-}C{\equiv}C{-}CH(OH){-}CH{=}CH{-}C_6H_5 .$$

(LII)

Symmetrical acetylenic and diacetylenic glycols show a very insignificant fungistatic activity, while the asymmetric compounds are more active fungicides. The biological activity apparently depends on the effect of the functional groups on the polarisation of the triple bond[11,77,123]. By varying the structural fragments in the molecule (in order to find highly active water-soluble antimycotics), it was shown that the hydroxy-group in acetylenic ketones removes the irritant effect, increases somewhat the solubility of the compounds in aqueous media, and hardly alters the antifungal activity[35,80,86,131,136]. The antifungal activity of acetylenic ketoacid esters (XL)

$$n\text{-}C_4H_9C{\equiv}C{-}CO(CH_2)_3COOMe$$

disappears when hydroxy-groups are introduced into their molecules[95].

5. Nitrogen-containing Acetylenes

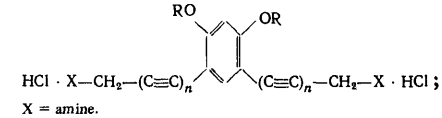
The presence of the amino-group as a rule increases the biological activity of acetylenic compounds[11,76,107,123,217,218]. The spectrum of the pharmacological activity of acetylenic amines is broad, but there have been no comprehensive and specific studies of the biological properties of acetylenic amines.

Data have been published recently on the antifungal activity of aminomethyl derivatives of aryl- and heteryl-acetylenes (LIII) with regularly varying structures[219-220]:

$$Ar(C{\equiv}C)_nH + HCHO + HNRR' \xrightarrow{CuCl} Ar(C{\equiv}C)_nCH_2NRR' .$$

(LIII)

Kotlyarevskii and coworkers[219-223] investigated systematically the spectrum of the biological activity of amino-derivatives of arylpoly-ynes (LIV):

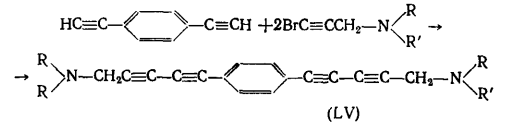


(LIV)

HCl · X—CH_2—$(C{\equiv}C)_n$ ... $(C{\equiv}C)_n$—CH_2—X · HCl ;

X = amine.

Conditions were found for the aminomethylation of diacetylenic compounds in which the main products are either monoamines or diamines. A monoamine may be used to obtain mixed diacetylenic diamines for oxidative dimerisation to tetra-acetylenic diamines or for the formation of triacetylenic diamines (LV)[223]:



(LV)

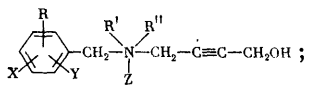
The majority of the compounds tested exhibit a pronounced bacteriostatic activity in relation to acid-resistant bacteria. The structures of the aromatic, acetylenic, and amine fragments influence appreciably the efficiency of their action. The introduction of an electron-donating substituent (CH_3O, CH_3) into the benzene ring and the increase of the degree of unsaturation of compounds (LIII, $n = 2$) result in an increase of biological activity. A further increase of the number of acetylenic groups ($n > 2$) results in a sharp decrease of activity. As the structure of the amine component of the molecule is varied, the antibacterial activity diminishes in the sequence

apparently in parallel with the decrease of the basicity of the amines[219]. It is of interest[84,134] that, among aryl-substituted aminoacetylenic compounds (LIV), amines with a single triple bond in each aliphatic chain are active against fungi. The introduction of the second triple bond into any aliphatic chain leads to the disappearance of activity.

The amino-group can form salts and, like the carboxy-group, may increase the solubility of the preparations in water [35,83-87,118]. In many cases this ionogenic fragment is introduced into the molecule by the Mannich reaction in accordance with the general mechanism

$$RC{\equiv}CH + CH_2O + HNR_2 \rightarrow RC{\equiv}C{-}CH_2NR_2 \quad .$$

In order to synthesise water-soluble antifungal preparations, certain derivatives of furan with functional groups[83], propargyl ethers derived from phenol and β-naphthol[118], a series of terminal acetylenic derivatives of bicycloheptane [85,203,204], and aryl- and heteryl-acetylenes [84,222] were aminomethylated. A series of quaternary ammonium compounds (LVI) exhibiting antifungal activity have been obtained by the quaternisation of tertiary amines [217]:



(LVI)

R', R'' = Alk; R = Alk (8-16 C atoms);

X, Y = CH_3, C_2H_5;

Z = salt-forming anion.

By employing a fungicidal solution (0.001%) of the hydrochloride of [1,4-bis-(2,4,6-trichlorophenoxy)-2-butynyl]dimethylamine and decahydroquinoline in the treatment of the *Verticillium* wilt of the cotton plant, an appreciable improvement of the crop was achieved [118].

Certain acetylenes whose structure incorporates a nitrogen-containing heterocycle are powerful antimycotics [208,209,224]. Thus 5-(3-iodopropargyloxy)-2-methylthiopyrimidine [209] is active (0.1-20 mg litre^{-1}) even against yeast-like fungi. It is noteworthy that the structures of these antimycotics frequently include the hydroxypropargyl fragment [208,209].

6. Acetylenic Hydrocarbons

Only a few poly-ynes with conjugated triple bonds have been investigated hitherto as antimicrobial preparations [77,123,225]. Apparently there is a relation between the number of conjugated triple bonds and antibiotic activity, but its nature is insufficiently clear [77].

Aliphatic hydrocarbons in which the triple bonds occupy the 1-ω-position exhibit a very weak antimicrobial activity [123]. In certain cases [226,227] halogeno-derivatives of hydrocarbons are highly active fungistatic agents. Halogenoalkynes are used to protect fruit from rotting. It may be that the biological effect of the most active iodoalkynes is to some extent due to the action of iodine [77,227].

In conclusion one should note that quantitative data on the antibiotic activities quoted by various authors do not always agree. This can probably be accounted for in the first place by the lack of standard strains (owing to the wide occurrence of cultures of microorganisms adapted to antibiotics) and in the second place by the lack of a sensitive method for the determination of the minimum inhibiting concentrations. Despite its approximate and fragmentary nature, the available information about biological activity make possible not only a qualitative but also a quantitative assessment of many compounds and assists in discovering specific relations. Although screening has not as yet become obligatory for all acetylenes with functional groups, interest in these compounds and the development of methods of synthesising them are to a large extent related to the prospect of investigating their biological properties [35,36,43,76-80,83,85,87]. However, biological tests are frequently episodic in character or are replaced by *a priori* guesswork.

Despite the considerable interest in the class of acetylenic antimycotics, the problem of their activity is largely considered at the level of *in vitro* tests. The decisive factor in the solution of the problem of the possible employment of this class of antimycotics as therapeutic agents is *in vivo* tests. Such studies are a problem for the future, although individual reports on this topic have already been published [25,35,85-87,99,135]. Since material costs are not the dominant factor in the study of drugs, the employment of acetylenes in this field is likely to be still greater in the future.

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