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Biological Activity of Quinolinium Salts

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The review deals with problems in the study and applications of quinolinium salts as biologically active preparations; the relation between the structure of quinolinium salts and their activity is discussed.
The bibliography includes 393 references.

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I. INTRODUCTION

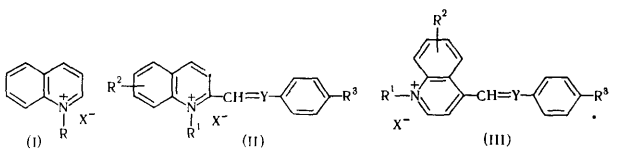
Quinolinium salts (I) have a number of very valuable physiological properties, among which the antimicrobial and antihelminthic properties have been investigated comparatively most thoroughly (although by no means completely). In the middle 1940's the antitumour properties of certain quinolinium compounds were discovered. There are data concerning the hypotensive, ganglion-blocking, carcinogenic, and mutagenic activity of various quinolinium salts. Certain quinolinium derivatives function as plant growth regulators.

During recent years, considerable advances have been achieved in the study of the physiological activity of quinolinium salts; at the present times, many such compounds have found practical application.

The methods of synthesis and chemical properties of quinolinium salts have already been reviewed[1].

II. ANTIMICROBIAL ACTIVITY OF QUINOLINIUM SALTS

In the 1920's Browning and coworkers[2] discovered the antimicrobial properties of certain quinolinium salts. The antiseptic and trypanocidal properties of styryl derivatives [(II), Y = CH] and anils [(II), Y = N], of quinaldinium were investigated in comparative detail[3-8]:



(I) (II) (III)

The analogous lepidinium (III) derivatives exhibited a very low antimicrobial activity at the beginning of the investigations, as a result of which they were not subsequently studied by this particular group of workers.

Examination of the relation between the structure and antiseptic activity revealed that even the simplest styrylquinolinium compounds [for example, II, Y = CH, R^1 = CH_3, R^2 = 6-CH_3, and R^3 = H] are active against *Staphylococcus aureus*. The presence of an amino- and particularly of a dimethylamino-group in the *para*-position of the benzene ring of the styryl substituent in compounds (IV) [II, Y = CH and R^3 = NH_2 or $N(CH_3)_2$] enhances the antiseptic activity. The displacement of these groups to the *meta*- or *ortho*-position is accompanied by a shortening of the conjugation chain involving the amino-group with a positively charged nitrogen atom and leads to a weakening of the antiseptic properties. Acylation of the aminogroup has a similar effect. When the aminogroup is shifted from the 6-position to the 4-position of the quinolinium ring, the activity against *E. coli* diminishes. However, the 4-dimethyl- or 4-diethyl-aminostyrylquinolinium salts have a very marked antiseptic activity in relation to staphylococci[9]. It is interesting that the pyridinium analogue has a lower antiseptic activity while benzoquinolinium derivatives are somewhat more active than the quinolinium salts[10].

Styrylquinolinium salts and anil derivatives of quinolinium salts are in most cases comparatively weak trypanocidal agents (against *T. brucei*)[11-14]. However, 1-methyl-2-(*p*-acetamidostyryl)-6-(aminobenzamido)-quinolinium acetate ("styryl 245") exhibits both therapeutic[15,16] and prophylactic[17] activity in relation to *T. brucei* (in mice). In addition, this compound has a synergistic effect when employed together with tryparsamide[15]. The activity of 2-(*p*-acetamidostyryl)-1-methyl-6-dimethylaminoquinolinium sulphate ("styryl 314")[18] against *T. brucei* was also investigated experimentally in mice.

It is noteworthy that the investigators were unable to discover a direct relation between the antiseptic and trypanocidal activities of the styryl and anil derivatives of the quinolinium salts investigated.

It was also established that certain styryl and anil derivatives of quinolinium salts are active against *Spirillum minus* which causes ratbite fever. 1-Methyl-2-(*p*-dimethylaminophenyliminomethyl)-6-acetamidoquinolinium chloride and sulphate show the most pronounced activity[19]. The corresponding 2-styrylquinolinium salts proved to be inactive in this respect. "Styryl 314" chloride has a very weak activity in relation to spirilla.

The work of Browning and coworkers on the above antimicrobial properties of the styryl and anil derivatives of quinolinium salts attracted the attention of scientists from many countries to these compounds. Österlin[20], who studied the relation between the trypanocidal activity of styrylquinolinium salts and their fluorescence in concentrated sulphuric acid, found that all active preparations exhibit green fluorescence. The absorption and fluorescence spectra were described in detail by Bandow[21]. Curd

and Ellingworth[22] suggested 2-styrylquinolinium compounds with amino-groups in the quinoline ring and in the styryl substituent are trypanocidal agents. Indian workers[23] investigated the effects of certain styryl and anil derivatives of quinolinium salts on paramecia. Petroff and Gump[24] studied the bacteriostatic activity of these compounds on gram-positive and gram-negative bacteria. The anils of 5,6-benzoquinolinium showed a more pronounced bacteriostatic activity: they are more active in relation to cocci but have no effect whatever on *E. coli*.

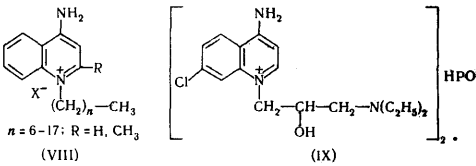
In 1941–1945 extensive studies were carried out in the U. S. A. on the antimalarial properties of many inorganic and organic substances. Various quaternary quinolinium salts were investigated among other organic compounds[25]. The activity of the compounds investigated was compared to that of quinine.

Among styrylquinolinium salts, the most active (when introduced intra-abdominally) proved to be compounds (IV) [II, $R^1 = CH_3$, $R^2 = 6\text{-}CH_3$, $R^3 = N(C_3H_7)_2$] (6 times more active than quinine), (V) [II, $R^1 = CH_3$, $R^2 = 6\text{-}CH_3$, $R^3 = N(\text{iso-}C_3H_7)_2$], and (VI) [II, $R^1 = CH_3$, $R^2 = 7\text{-}CH_3$, $R^3 = N(C_2H_5)_2$] (3 times more active than quinine). The antimalarial activity of the remaining styryl and anil derivatives of quinolinium salts did not exceed 30% of the activity of quinine. Some of them were quite inactive. It is interesting that the quinolinium salt with a phenyl group at the nitrogen atom of the quinolinium ring—compound (VII) [II, $R^1 = C_6H_5$, $R^2 = H$, $R^3 = N(CH_3)_2$, X = Cl] were described for the first time in connection with these studies. It proved to be twice as active as its *N*-methyl analogue.

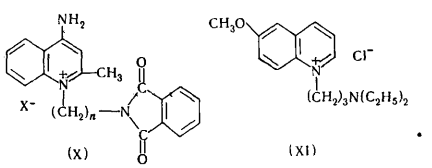
In connection with the study of chemotherapeutic properties, Rubtsov and Bunina synthesised[26] in 1943 quinolinium salts with sulphonamido-groups. The antitubercular activity of some of its compounds was tested[27].

In 1957 Japanese investigators[28] described the antibiotic activity of the "NK-458" preparation [II, $R^1 = C_2H_5$, $R^2 = 6\text{-}N(CH_3)_2$, $R^3 = N(CH_3)_2$, X = I] against trichomonads and pathogenic fungi. Taylor and coworkers[29] showed that 2-(*p*-acetamidostyryl)-1-methyl-6-methylaminoquinolinium methosulphate, an analogue of the preceding preparation, suppressed the development of pyroplasmosis in experiments on white mice. Berg[30] published a study on the synthesis and the trypanocidal properties of styrylquinolinium salts with a *m*-amidinophenyldiazoamino-group in the *para*-position of the styryl substituent. The above compounds proved to be active against *Trypanosoma rhodesiense*, *Trypanosoma congolense*, and also *Babesia rodhaini*. It was also found[31] that 1-ethyl-2-(*p*-dimethylaminostyryl)quinolinium sulphate has some fungistatic activity in relation to *Trychophyton gypseum*, *Trychothecium roseum*, *Achorion quinqueanum*, and *Epidermophyton* Kaufmann-Wolf, but is inactive against *Penicillium simplicissimum*, *Aspergillus niger*, and *Candida albicans*.

Among quaternary quinolinium salts without styryl groups in the 2- and 4-positions of the quinolinium ring, compounds containing amido- and sulphonamido-groups in the 6-position exhibit antimicrobial properties. These salts are recommended as preparations against blood parasites[32]. At the beginning of the 1930's Domagk[33] found that quaternary ammonium salts, including quinolinium salts with long-chain aliphatic substituents, have a high germicidal activity. This discovery promoted a successful search for a new antibacterial preparations. Similar compounds were suggested as disinfectants for surgical instruments, since their high antimicrobial activity is combined with a low toxicity. Shelton and coworkers[34,35] investigated the relation between the structure and germicidal activity of these salts. Some of them are produced commercially. For example, 1-laurylquinolinium bromide is used in practice as a disinfectant[36] under the name "Isotan Q-14". Tetrahydroquinolinium salts containing a long-chain hydrocarbon substituent at the nitrogen atom have antiseptic properties and their toxicity is low[37]. The fungistatic properties of certain quinolinium salts with a long chain hydrocarbon substituent at the nitrogen atom (n-hexyl, n-octyl, n-decyl, and n-dodecyl) were investigated by Zsolnai[31]. All the compounds studied proved to be inactive against *Aspergillus niger*. The last two compounds proved to be active against *Penicillium simplicissimum* and *Candida albicans*. 4-Aminoquinolinium and quinaldinium (VIII) salts with long-chain aliphatic substituents containing between 7 and 18 carbon atoms at the nitrogen heteroatom[38–41] have marked bacteriostatic and bactericidal activity:



The most effective compound in this series is 4-amino-1-dodecylquinaldinium acetate (laurolinium acetate)[42,43], which exhibits antibiotic activity *in vitro* against 32 species of gram-positive and gram-negative bacteria, pathogenic fungi, and certain protozoa. In relation to plasmodia, such salts are apparently relatively ineffective. Thus the activity of preparation (IX) amounts to 40% of that of quinine[25]:



Taylor and Austin[44] developed a method of synthesis of 4-aminoquinaldinium salts of type (X), which are intermediates in the synthesis of medicinal preparations. When the amino- or alkylamino-group is in the 2- rather than the 4-position of the quinolinium ring, the preparation loses its activity. Thus 2-alkylaminoquinolinium and 2-arylaminoquinolinium salts do not exhibit appreciable antiseptic, trypanocidal, and antimalarial activities[45].

Since 8-hydroxyquinoline has a fairly pronounced bactericidal and bacteriostatic activity, numerous quaternary derivatives of hydroxyquinolines were investigated. Müller[46] studied the toxicity and bacteriostatic activity of 8-hydroxy-1-methylquinolinium salts against cocci, *E. coli*, and brucellae. The salts containing high-molecular-weight anions (benzoates and stearates) showed a more pronounced specific bacteriostatic activity, while the corresponding sulphate does not exhibit an appreciable antibacterial activity[47]. However, it was found that salts of 1-alkyl- and 1-arylalkyl-8-hydroxyquinolinium, containing an acyl or nitro-group in the 5-position and an alkyl group in the 7-position, show an appreciable antifungal and bactericidal activity[48]. Various hydroxyquinolinium esters have been suggested as disinfectants[49–51]. Vogt[52] made a detailed study of esters of 8-hydroxyquinolinium and showed that, with increase of the chain in the aliphatic acid group (forming part of the ester group) up to 16 carbon atoms, the activity of the compound rises. The introduction of a thiocyanato-group into the quinoline ring of these compounds leads to a considerable enhancement

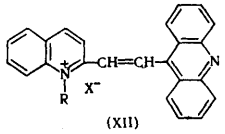
of their bactericidal activity [53,54]. One of the most active compounds of this group is 8-n-butoxy-1-methyl-5-thiocyanatoquinolinium sulphate. Its bactericidal activity against *E. coli* is still apparent at a dilution of 1 : 100 000. Buchmann [55,56] studied the activity of the methyl and ethyl ethers of 4-hydroxy-1,6-dimethyl quinolinium iodide against *Aspergillus niger*, *E. coli*, and *Staphyllococcus aureus*. Although the activity of the preparations was low, it is interesting to note that the ethyl ether proved to be 20 times more active than the methyl ether in relation to *E. coli* and almost twice as active against *Staphyllococcus aureus*. In a study of the antimalarial activity of hydroxyquinolinium derivatives, it was established[25] that, whereas 6-methoxy-1-methylquinolinium iodide exhibits 15% of the activity of quinine, its 1-benzyl analogue is twice as active and preparation (XI) is 10 times as active as quinine. It is also interesting to note that the betaine of 2-hydroxy-1-methylquinolinium has a considerable prophylactic activity against *P. gallinaceum* in chicks (it is almost 8 times as active as sulphadiazine). The antibacterial properties of certain 8-alkoxyquinolinium salts, among which the most active proved to be the 1-methyl-8-octyloxyquinolinium salt, were investigated recently [57].

Among other quinolinium salts with antimicrobial activity, mention should be made of the 1-aryloxymethyl [58], 1-alkylnaphthyl [59], and 1-β-halogenophenoxymethyl derivatives [60]. The latter also exhibit antifungal activity and are more active than the analogous pyridinium salts.

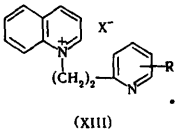
Quinolinium salts containing as the anion a sulphonic acid residue with a long aliphatic chain were also synthesised. They proved to be highly effective bactericidal and fungicidal agents [61]. Sparingly soluble quinolinium salts containing anions of heavy-metal complex acids have been recommended as antifungal and antibacterial preparations (including preparations effective against plant pests) [62].

As a rule quaternary quinolinium salts are more active than the tertiary quinoline bases. However, 4-(2′-nitrovinyl)quinolinium salts proved to be inactive against *Trichomonas vaginalis* and *Candida albicans*, while the corresponding tertiary bases are very effective in this respect [63].

The antimicrobial properties of quinolinium salts with a further heterocyclic ring have also been investigated:



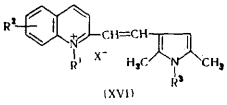
(XII)



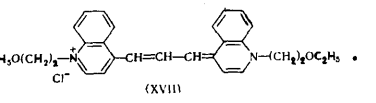
(XIII)

Compounds of type (XII) appreciably suppress the growth of staphylococci at a dilution of 1 : 40 000 in water, but are inactive against trypanosomas [64,65]. 7-Chloro-4-[1′-methyl-4′-1(1″-pyrrolidinyl)butylamino]quinolinium salts have been recommended as antimalarial preparations [66]. However, it is interesting to note that quinine ethiodide shows only 8% of the activity of the tertiary base [25]. 1-[2′-(2″-Pyridyl)ethyl]quinolinium salts (XIII) show fungicidal activity [67].

Quinocyanine dyes, the molecules of which consist of two and more heterocyclic rings (not less than one of which is a quinoline ring) joined by a polymethine chain, are interesting derivatives of quinolinium salts. The first studies on the antimicrobial activity of cyanine dyes with quinolinium rings were carried out by Browning et al. [68] Sensitol red (Pinacyanol), violet, and green were tested against *E. coli* and *Staphylococcus aureus*. Among these sensitol green [Ethyl Red, (XIV)] proved to be the most effective suppressing the growth of *Staphylococcus aureus* at a dilution of 1 : 100 000 in serum and of *E. coli* at a dilution of 1 : 10 000.



(XVI)



(XVII)

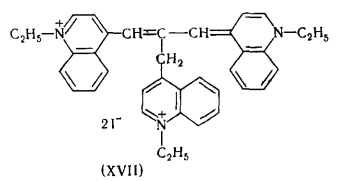
Somewhat later the same investigators[69] published the results of studies on the antiseptic properties of apocyanines, isocyanines, and carbocyanines of the quinolinium series. They did not find among these cyanine dyes compounds meriting attention. At almost the same time Karwacki and Biernacki [70] discovered that a cyanine dye has a slight effect on the micro-organisms responsible for tuberculosis. Petroff and Gump [24] studied the effect of quinolinium dyes (XIV), ethylcyanine T, orthochrome T, and Pinacyanol on gram-positive and gram-negative micro-organisms. The study of the antimalarial activity of cyanine dyes during the second World War [25] showed that the simplest cyanine dyes with two quinoline rings in the molecule exhibit as a rule a low antimalarial activity (15–30% of that of quinine). Carbocyanine (XV) proved to be more active, showing 80% of the activity of quinine. It is interesting that its isomer, 2,2′-trimethinecyanine, is almost 3 times less active (30% of the activity of quinine). Certain quinocyanine dyes—pseudocyanine, isocyanine, and dicyanine in the form of methochlorides—exhibited less than 20% of the activity of quinine in the treatment of chicks infected with *P. gallinaceum*; the activity of Pinacyanol and cryptocyanine was less than 15% than that of quinine. The data from the Rockefeller Institute of Medical Research [25] also indicate that the methochlorides of cyanine, isocyanine, Pinacyanol, dicyanine, 6,6′-dimethylcyanine, and carbocyanine are inactive in relation to these parasites. The activity of Quinolinium Blue is less than 3% of that of quinine against *P. lophurae* in ducks. Among asymmetric quinocyanine dyes, the dimethines with the general formula (XVI) were investigated in greater details. The effect of the substituents R^1, R^2, and R^3 on the antimalarial activity of the compounds was studied.

In 1947 Brooker and Sweet [71] published a short report on the results of chemotherapeutic studies on cyanine dyes. They note that preparation (XVI) ($R^1 = CH_3$, $R^2 =$ 6-CH_2, and $R^3 =$ n-C_5H_{11}) completely suppresses the growth of *L. casei*, *L. arabinosus*, *Streptococcus faecalis*, and *E. coli* at concentrations of the order of $(2–4) \times 10^{-6}$ M. Individual representatives of various classes of cyanine dyes were tested *in vivo* against *Streptococcus haemolyticus*, *Streptococcus viridans*, *Staphylococcus aureus*, *Diplococcus pneumoniae*, *Trypanosoma equiperdum*, and *Treponema pallidum*, which are responsible for encephalitis, influenza, typhus, and a group of interstinal parasites, and also *in vitro* against *Entamoeba histolytica*. Although individual compounds showed a distinct activity against the above micro-organisms, the authors believe that the activity is not high enough to be of therapeutic value. However, Silverman [72,73] reported that 1,1′-dimethyl-2,2′-cyanine iodide suppresses the growth of *E. coli*, although the Ca^{2+} cation behaves as an antagonist. It was also found [74,75] that Quinolinium Blue (1,1′-dipentyl-4,4′-cyanine iodide) is extremely active *in vitro* against the organism responsible for diphtheria and against gram-positive cocci, including *Staphylococcus aureus*. In view of its low toxicity, the preparation was recommended as a therapeutic agent. However, the compound is inactive in relation to pathogenic fungi [31]. Ryzhikov et al. [76] reported that Quinolinium Blue is a moderately strong inactivator of the

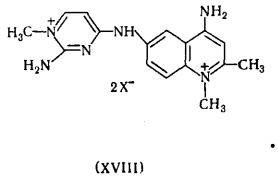
tobacco mosaic virus, suppressing its activity to the extent of 63%. However, later studies by Bobir [77] showed that the preparation is completely indifferent in relation to the above virus.

In 1951, almost 30 years after the studies of Browning [68], it was found that Pinacyanol shows a high bactericidal and bacteriostatic activity against cocci and the organism responsible for diphtheria, whilst its toxicity is very low [78].

A study was also made of the physiological properties of quinocyanine dyes with 3 ring systems. The interaction of 1-ethyl-lepidinium iodide with triethyl orthoformate in acetic anhydride or in dry pyridine are known to give a mixture of polymethine dye, called Lumin (or the Cryptocyanine OA complex). Somewhat later this mixture was separated into components, which were called cryptocyanines 1, 2, 3, 4, and 5 respectively. Cryptocyanine 1 proved to be identical with the so called neocyanine or Koha No. 1 (XVII):



(XVII)



(XVIII)

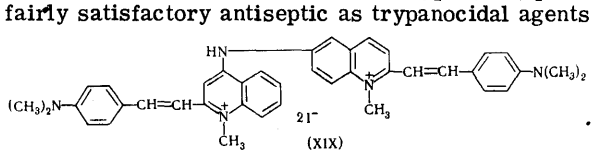
The physiological activity of both the non-purified dye (Lumin), with about 92% of Koha No. 1, as well as that of the individual components, mainly pure Koha No. 1, were investigated by Japanese workers. A detailed study was made of the optimum conditions for the formation of compound (XVII). [79] Hatano [80] found that compound (XVII) exhibits antitubercular activity. Miyazaki [81] reported that Lumin has an appreciable effect in the treatment of human leprosy, 81.9% of 371 patients showing some improvement and only 1.6% deteriorating after a 10 month course of treatment by this preparation. At the same time pure Koha No. 1 has undesirable side effects. However, investigations by other workers showed that this preparation is not quite so effective in the treatment of both experimental and human leprosy [83,84]. Sato and Chida [85] made a more detailed study of the effect of the non-purified product and pure Koha No. 1 on organisms responsible for tuberculosis and for human and experimental rat leprosy. The preparations showed tuberculostatic activity against the Aoyama strain in a dilution of 1 : 100 000–1 : 50 000. However, in relation to the natural organism responsible for tuberculosis, the activity of these compounds was shown only at a dilution of 1 : 10 000. The preparations had no effect on experimental leprosy and did not exhibit a promising therapeutic activity on human leprosy. A study was also made of the antiviral activity of Koha No. 1 in relation to coliphage [86] and of its bactericidal activity against certain pathogenic bacteria [87]. The compound has an appreciable bactericidal activity against *Staphylococcus albus*. Partial suppression is also observed in the case of *E. coli*, *Salmonella typhosa*, and *Shigella dysenteriae*. In all cases the activity increases with the alkalinity of the medium (up to pH 10).

The effect of cyanine dyes on the respiration of *Staphylococcus aureus* and *S. typhi* was investigated [88].

Diquaternary salts with one or two quinolinium rings have very interesting antibiotic properties.

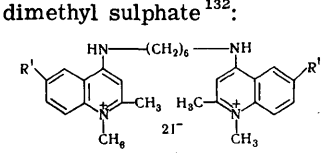
In 1949 a new very effective trypanocidal agent was described [89]; it is a diquaternary quinolinium salt called antrycide (XVIII) (synonyms: quinapyramine, pyraldine). It is active against various trypanosoma species [*T. congolense*, *T. brucei*, *T. evansi* (India and the Sudan), *T. equiperdum*, *T. equinum*, and *T. vivax*]. Veterinary field tests in Africa showed that antrycide salts are effective in both prophylactic and therapeutic treatment [90–93]. Antrycide has been used as the dichloride, the dimethosulphate, or in the form of a mixture of these two salts, the so called "pro-salt". This discovery stimulated the study of similar compounds and in recent years a number of publications dealing with the methods of synthesis of the isomers and analogues of antrycide have appeared [94–107]. New methods have also been developed for the determination of antrycide [108] in biological objects. The chemotherapeutic properties of antrycide were investigated in greater detail by workers in various countries [109–116]. Moreover, studies were performed both with a view to finding more effective therapeutic forms of antrycide in the treatment of trypanosomiases and in order to investigate the effects of antrycide on micro-organisms responsible for other diseases. Tests on mixtures of antrycide with other trypanocidal preparations led to the discovery that a complex of antrycide with suramin is less toxic than antrycide itself [117,118]. The complex also exhibits prophylactic and therapeutic effects in diseases of swine caused by *T. simiae* [119–121]. In tests of antrycide against other pathogenic agents, it was found that the preparation is active against the European trypanosomiasis of horses [122–124], su-auru [125], and the trichomoniasis of cattle [126]. The compound also effects a complete cure in mice infected with *Babesia rodhaini* [29]. Among the reviews in which antrycide is discussed, mention should be made of Williamson's review [127] dealing with the chemotherapy and chemoprophylaxis of African trypanosomiasis and also the review on the mechanism of the action of trypanocidal agents [128]. Babesicidal properties of an analogue of antrycide with a phenyl group in the 2-position of the quinoline ring have also been described [129].

Bisquinolinium salts are effective antimicrobial preparations. Jensch [130] suggested that azo-compounds in which the azo-group is joined to two quinolinium rings be employed as therapeutic preparations against blood parasites. Bis-styrylquinolinium salts of type (XIX) proved to be fairly satisfactory antiseptic as trypanocidal agents [13]:

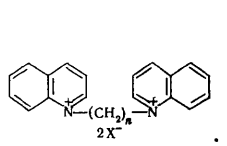


(XIX)

When two moles of 4-methoxy-1-methyl- or 6-amino-(dimethylamino- or methoxy)-4-chloro-quinaldinium iodide react with one mole of hexamethylenediamine, bisquinaldinium salts (XX), which exhibits trypanocidal properties, particularly against *T. rhodesiense*, are formed [132]. These preparations can also be obtained by the methylation of the corresponding tertiary base at the nitrogen heteroatom with dimethyl sulphate [132]:



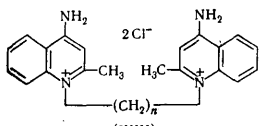
(XX)



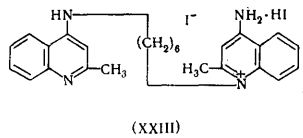
(XXI)

Collier et al. [133] tested the antifungal activity of bisquinolinium salts (XXI) in which both nitrogen atoms are joined by a polymethylene chain. The activity of these compounds, containing between 10 and 20 CH_2 groups, increases with increase of the number of methylene groups to 14–16, after which it falls again. The most active of these (XXI, $n = 14$, 16) inhibits the growth of many pathogenic fungi at a concentration of 0.3–10 μ g ml^{-1}. At the same time the preparations are relatively non-toxic for

warm-blooded animals. Subsequently, in a study of analogues of these compounds, Babs, Collier, and coworkers[134] described in 1956 a new highly effective antibacterial and antifungal agent, which they called Dequadin-1,1′-decamethylenebis-(4-aminoquinaldinium chloride) (XXII, $n = 10$). The preparation is also known as Dequalinium, Decatylene, and Decamine.



(XXII)



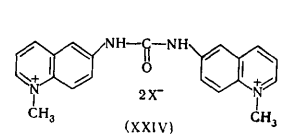
(XXIII)

The preparation is very effective *in vitro* against various gram-positive (cocci, corynebacteria) and gram-negative (intestinal bacteria, salmonellae, proteus, and cholera vibrio) micro-organisms and also against pathogenic fungi[134-136]. In addition Dequadin exhibits a synergistic activity when employed together with antibiotics. However, cases are known of an allergic response in Dequadin therapy after prolonged administration of antibiotics[137]. It is also active against certain pathogenic protozoa, in particular *Trypanosoma congolense*[138], but it is only slightly effective *iv vivo* against *Entamoeba histolytica*[139]. It is noteworthy that the isoquinolinium analogue of Dequadin showed a low trypanocidal activity. Dequadin has also been used as a disinfectant in dental practice[140] and in the surgery of the oral cavity[141], for the local treatment of wounds in humans and animals[142], for the treatment of vaginites caused by *Trychomonas* and *Candida*[143-146], trichophytosis of cattle[147], fungal affections of the skin[148-150], diseases of the throat and respiratory organs[151-153], including those of young children[154,155], and also other diseases[156-158]. Under the name Decamine, this preparation was adopted by the Soviet Pharmacopoeia as a therapeutic agent; various therapeutic forms of the substance have been developed[159-161].

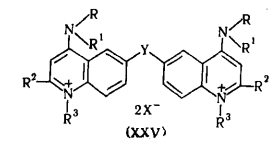
In connection with the very high antibiotic activity of Dequadin, a detailed study was made of its homologues, isomers, and analogues[134,162,163]. A number of patents have been taken out, both for the methods of preparation of Dequadin and analogues and also for its various therapeutic forms[164-170]. In many reviews dealing with new chemical preparations, a fair amount of attention has been devoted to this compound[139,148,171-173].

Homologues of Dequadin containing a smaller number of methylene groups ($n = 6$ and 8) show a considerable activity against *Trypanosoma rhodesiense*[162,174]. Buchmann[56] found that 1,1′-hexamethylenebis(7-methylquinolinium iodide), a Dequadin analogue, is active against *Staphylococcus aureus* and *E. coli*. A report was published in 1967 that certain analogues of Dequadin in the form of acetates with a secondary amino-group in the 4-position of the quinaldinium ring exhibit a higher antimicrobial activity than the unsubstituted preparation. The maximum activity is shown by substances with C_3–C_6 alkyl substituents. However, the toxicity of the preparations is also enhanced. When 4-aminoquinaldine reacts with 1,6-di-iodohexane, 6-(4-quinaldinyl)aminohexyl-4-aminoquinaldinium hydriodide iodide, called tozocide (XXIII), is formed together with the symmetrical compound (XXII, $n = 6$). The preparation is highly active against *Trypanosoma congolense* and *Trypanosoma vivax*, and is more active than both symmetrical isomers[174,176].

Among other bisquinolinium salts with antibacterial properties, mention should be made of bis-1-(6-methylquinolinium)urea salts [Babesan, Pyroplasmin, Acaprin (XXIV)][177,178] which have been recommended for the treatment of pyroplasmosis and taylorosis of domestic animals[179-182]. In addition, Babesan also exhibits an antimalarial activity[25]. The disadvantages of Babesan include the short duration of its action[181] and toxicity[183,184].



(XXIV)



(XXV)

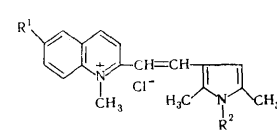
where Y = NH, O, S, or CH_2, R, R^1 = H or alkyl, and R^2, R^3 = alkyl.

Babesan analogues of type (XXV) have also been recommended as preparations for the treatment of piroplasmosis and taylorosis of animals[129,185].

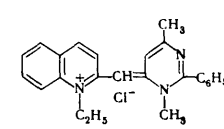
III. ANTIHELMINTHIC ACTIVITY OF QUINOLINIUM COMPOUNDS

Helminthic diseases in man, animals, and birds are very common. About 40% of the earth's population and a large number of animals are infected by pathogenic worms[186]. According to Stoll's data[187], more than 800 million people are affected by helminthiases. The losses in animal husbandry in the USSR due to helminthiases in 1960 amounted to approximately 58 million roubles per annum[188]. Therefore much attention has been devoted to the development of means of combating helminthic infestations. Thus at an SEV [significance of Russian abbreviations obscure (Ed. of Translation)] session in May, 1963 it was resolved that particular attention should be paid to the manufacture of antihelminthic preparations[188].

Among antihelminthic agents, quinolinium derivatives occupy a major place. The study of quinoline derivatives as antihelminthic agents was begun by the work of Brooker and Sweet[71], who synthesised in 1947 a number of quinocyanine dyes with pronounced antihelminthic properties[189]. Studies on a large number of similar compounds showed that two nitrogen atoms separated by an even number of conjugated bonds constitute an essential group for antihelminthic activity. Among all the compounds investigated, compounds (XXV), (XXVII), and (XXVIII) proved to be the most effective.



(XXVI, $R^1 = CH_3$; $R^2 = C_6H_{11}$)
(XXVII, $R^1 = N(CH_3)_2$; $R^2 = C_6H_5$)



(XXVIII)

The first of these, compound (XXVI), has been recommended as a therapeutic agent against *Litomosoides carinii*. Clinical tests on compound (XVIII) against *Wuchereria bancrofti* showed that the preparation is effective against microfilaria but not against the adult parasites[190]. However, when organisms responsible for onchocerciasis are acted upon, the compound kills adult filaria but does not affect the microfilaria[191]. The investigators note an undesirable[191] albeit non-systematic[189] side effect of this preparation. The mechanism of the action of compound (XXVII) on helminthes[192] and on the development of the embryos of *Litomosoides carinii* has been investigated[193]. Pyrimidoquinocyanine dyes of

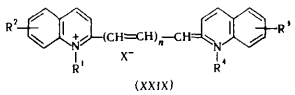
type (XXVIII) have been patented as antihelmintic preparations [194].

Compound (XVIII) has a very satisfactory therapeutic activity. It has been patented under the names Poquil, Vanquin, Povan, Moleac, Pyrvinium, and Pyrroviniquinium [195,196]. Poquil chloride has a high antihelminthic activity in the chemotherapy of enterobiasis and strongylidosis [197-203]. Apart from the chloride, the products of the interaction of phenolphthalein with Poquil is also recommended [204]. Recently reports have been published about the successful application of Poquil pamoate. This preparation is less toxic, since it is sparingly soluble in water and is not absorbed from the gastrointestinal tract in appreciable amounts [205,206] and it does not have a bitter taste [207].

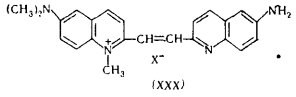
Poquil pamoate has been successfully employed in the treatment of animals and children both as an individual preparation [208-223] and in combination with piperazine [224,225] (preparation Cl-578). The antihelminthic activity of Poquil embonate in enterobiasis has also been investigated [226-228]. However, this preparation is less effective than the pamoate [sic!, embonate and pamoate are trivial names of the same anion (Ed. of Translation)].

The effect of pyrimido- and pyrrolo-quinocyanines of type (XXVI)-(XXVIII) on the metabolic processes in parasites [229-232] and also their side effects and toxicity [189-191,198,205,208,209,233-236] have been investigated.

At the beginning of the 1960's a number of patents for the application of trimethine (XXIX, $n = 1$) and pentamethine (XXIX, $n = 2$) quinocyanine dyes with symmetrical and asymmetric structures, dyes of type (XVII) with three ring systems [237], and also 2-styrylquinolinium salts (II) [238,239] were published.



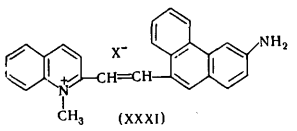
(XXIX)



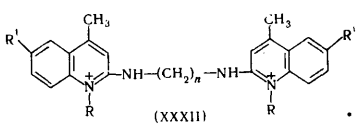
(XXX)

Pentamethine quinocyanines (XXIX, $n = 2$) are very effective antihelminthic agents with a wide spectrum of activity and are recommended for the treatment of helminthiases in man, animals, and birds. Together with a high therapeutic index, they are characterised by a low toxicity, which distinguishes them favourably from their extremely toxic benzothiazole analogue (Dithiazanine). *p*-Dimethylaminostyrylquinolinium salts show a high activity against the larvae of *Ascaris suum*, the larvae and adult forms of tapeworms and also in certain sheep helminthiases caused by *Trichostrongylus colubriformis* [238,239].

In addition the antihelminthic properties of compounds of type (XXX) and (XXXI) [240] and also of bisquinolinium, bis-4-aminoquinaldinium [241], and bis-2-aminolepidinium salts (XXXII) [242] have been investigated.



(XXXI)



(XXXII)

The latter are recommended for the treatment of animals infected with *Syphacia obvelata*, *Hymenolepis nana*, *Dypilidium caninum* and *Taenia pisiformis*.

In conclusion it should be noted that in many reviews dealing with antihelminthic agents considerable attention has been recently devoted to quinolinium derivatives [139,187,188,243-250].

IV. RADIOMIMETIC ACTIVITY OF QUINOLINIUM SALTS

The action of chemical agents on living organisms resembling the effect of radioactive ionising radiation is called radiomimetic [251]. For example, it is known that small doses of radioactive emission have an antiblastic activity, which is used in the treatment of malignant tumours. However, more prolonged action of such radiation causes the appearance of malignant neoplasms (oncogenic activity). In addition, they all have a mutagenic activity.

Certain quinolinium salts have a complete set of the above properties, but some of these have been investigated quite inadequately.

a. Oncogenic Activity of Quinolinium Salts

The oncogenic properties of certain styrylquinolinium salts were first reported by Browning [252,253], who observed that a single subcutaneous administration of 6-acetamido-2-(*p*-aminostyryl)-1-methylquinolinium acetate [Styryl 430, (XXXIII)] results in the appearance of a sarcoma at the site of administration after a certain period. This property has been used for the induction in white mice of an experimental sarcoma [254], the cell chromosomes of which were investigated by Arroyo and Murcia [255]. Another dye [(II, $R^1 = CH_3$, $R^2 = H$, $R^3 = N(CH_3)_2$, Y = CH, and X = SO_4CH_3)] causes malignant affections of the intestinal tract after systematic administration to rats in food over a period of one year (at a dose of 800 mg kg^{-1}) [256]. In connection with the oncogenic activity of compound (XXIII), its effects on the respiration of live cells [257] and on the ability of rats to swim [258] were investigated. Like other carcinogenic agents, the preparation suppresses cell respiration and reduces the capacity of rats for work.

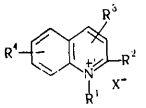
b. The Antitumour Activity of Quinolinium Salts

In recent years the search for effective antitumour agents has been considerably intensified. Among other compounds, numerous quinolinium derivatives were investigated. Shear et al. [259] noted that certain quaternary pyridinium and quinolinium salts decompose sarcoma cells, which attracted much attention to them. However, in a more systematic study it was found that *N*-alkylquinolinium salts unsubstituted in the 2- and 4-positions do not show any activity against sarcoma 180, adenocarcinoma 755, and leukaemia L1210 [260-266] (see Table).

Compounds (XXXIV) and (XXXV) (see Table) are an exception, showing a weak activity against carcinoma and the latter also against sarcoma. At the same time many quinolinium salts containing phenylethyl [(XXXVI) and (XXXVII)], phenylacyl [(XXXVIII)-(XLVI)], and β-naphthoylmethyl [(XLVII) and (XLVIII)] groups at the nitrogen heteroatom are active against sarcoma and some also against adenocarcinoma.

It is interesting to note that, while the simplest quinolinium salts are inactive against sarcoma and carcinoma, the analogous quinaldinium salts containing a methyl group in the 2-position of the quinoline ring exhibit a distinct albeit slight activity in relation to sarcoma [(XLIX)-(LI)]. A similar activity is shown by 2-phenyl-substituted [(LIV)-(LVI)] and 2-styryl-substituted [(LVII)-(LXVI)] quinolinium salts. Some of these are active also in relation to adenocarcinoma (see Table). Quinolinium salts (LVII) with an azomethine group in the 3-position also show

Quinolinium salts active against sarcoma 180 (Sa) and adenocarsinoma 755 (Ca).



Quinolinium salt	R^1	R^2	R^3	R^4	X	Inhibition, %		References
						Sa	Ca	
XXXIV	CH_2COOH	H	H	H	Cl	—	26	266
XXXV	CH_3	H	4-$NH(CH_2)_5CN$	6-OCH_3	I	29	23	267
XXXVI	$CH_2CH_2C_6H_5$	H	H	H	Br	—	55; 32	268
XXXVII	$CH_2CH_2C_6H_5$	H	H	6-Cl	Br	50; 38	56; 45	265
XXXVIII	$CH_2COC_6H_5$	H	H	6-OCH_3	Br	45	21	263
XXXIX	$CH_2COC_6H_4OCH_3$-*p*	3-Br	H	H	Br	46		263
XL	$CH_2COC_6H_4Br$-*p*	H	H	H	I	28	27	263
XLI	$CH_2COC_6H_4Cl$-*p*	H	H	6-Cl	Br	43	—	263
XLII	$CH_2COC_6H_4Br$-*p*	H	H	6-Cl	Br	27	—	269
XLIII	$CH_2COC_6H_4C(CH_3)_2$-*p*	H	H	6-Cl	Br	27		269
XLIV	$CH_2COC_6H_4Br$-*p*	H	3-Br	H	Br	49; 38	35	263
XLV	$CH_2COC_6H_4Cl$-*p*	H	3-Br	H	Br	19	19	263
XLVI	$CH_2COC_6H_4SCH_3$-*p*	H	H	6-OCH_3	I	49; 27	—	265
XLVII	CH_2CO-β-naphthyl	H	H	6-Cl	Br	29	—	265
XLVIII	CH_2CO-β-naphthyl	H	H	8-OH	Br	—	31	265
XLIX	C_2H_5	CH_3	H	6-CH_3	I	32	38	270
L	C_2H_5	CH_3	4-CH_3	H	I	27	—	269
LI	C_2H_5	CH_3	H	H	I	44	—	262
LII	CH_3	CH_3	H	H	I	—	23	271
LIII	$COOC_2H_5$	CH_3	H	H	Cl	37	—	266
LIV	CH_3	C_6H_4Cl-*o*	3-OCH_3	H	I	25	57; 25	264
LV	CH_3	C_6H_4F-*o*	H	H	I	25	22	264
LVI	CH_3	C_6H_4F-*o*	3-CH_3	H	I	33	62; 33	264
LVII	CH_3	CH=CH—C_6H_4OH-*o*	H	8-OH	SO_4CH_3	33	22	272
LVIII	CH_3	CH=CH—C_6H_3OH-*p*-(OCH_3)-*m*	H	8-OH	SO_4CH_3	24	—	272
LIX	CH_3	CH=CH=(1)-naphthyl-2-OH	H	8-OH	SO_4CH_3	38	—	272
LX	CH_3	CH=CH—C_6H_4Cl-*o*	H	H	I	24	28	264
LXI	CH_3	CH=CH—$C_6H_4NO_2$-*p*	H	H	I	59; 17	29	264
LXII	CH_3	CH=CH—C_6H_5	H	H	I	14	43	264
LXIII	CH_3	CH=CH—C_6H_4Cl-*p*	H	H	I	38	—	264
LXIV	CH_3	CH=CH—$C_6H_4NO_2$-*m*	H	H	I	37	—	264
LXV	CH_3	CH=CHC$_6$H$_3$OH-*p*-(OCH_3)-*m*	H	H	I	16	—	264
LXVI	CH_3	CH=CH—$C_6H_4NH_2$-*p*	H	6-$NHCOC_6H_4$— —$NHCOCH_3$-*p*	CH_3CO	62	—	265
LXVII	CH_3	CH=N—$C_6H_4N(CH_3)_2$-*p*	4-Cl	6-OCH_3	Cl	21	43	273
LXVIII	C_2H_5	CH=CH—$C_6H_4(CH_3)_2$-*p*	H	H	I	43	—	265

a slight activity. However, it is noteworthy that many styryl-substituted quinolinium salts proved to be virtually inactive against these types of tumours [260,263,271,274-276]. Certain 2- and 4-*p*-dimethyl(diethyl)aminostyrylquinolinium salts also proved to be inactive against leukaemia and Ehrlich ascites carcinoma when administered in combination with irradiation by X-rays [277].

In a study of the activity of styrylquinolinium salts against other malignant tumours, it was found that 1-methyl-4-(*p*-dimethylaminostyryl)quinolinium iodide (LXIX) and chloride (LXX) are exceptionally active against lymphoma 8, [278,279] suppressing completely the tumours in rats. It is interesting to note that, whereas compound (LXX) is active only when administered orally, compound (LXIX) is also active when injected subcutaneously. Slight changes in the structure of styrylquinolinium have a very marked influence on its antitumour activity. The replacement of the *p*-dimethylamino-group by the *p*-diethylamino group greatly reduces the activity of the preparation [280].

The migration of the *p*-dimethylaminostyryl group from the 4-position in the quinoline ring to the 2-position involves a complete loss of antilymphoma activity. In a study of the effect of preparations of type (LXIX) and (LXX) on other types of tumours, it was found that adenocarcinoma 11 also regressed in the majority of animals, but the effect of the preparations on this tumour is somewhat weaker. However, in experiments on mice, both in the case of spontaneously generated carcinoma of mammary glands and the transplanted carcinoma, preparation (LXIX) proved to be inactive.

In a study of the activity of this preparation and 4-styrylquinolinium against the Walker tumour [250], the tertiary base proved to be more active [281-283]. Preparation (LXIX) was found to be inactive against Nelson mouse ascites tumour [284] and against leukaemia L1210. [285,286] Compounds (LXIX) and (LXX) and also an isomer of the former, containing the *p*-dimethylaminostyryl group in the 2-position of the quinoline ring (LXXI), exhibited a cytotoxic activity to an extent proportional to their antitumour activity [287-289].

Compound (LXXI) and its 1-ethyl homologue are inactive against lymphoma 8 [280] and leukaemia [285,286,290], but they do suppress the growth of Walker carcinoma 256. [291] In addition, the activity of (LXXI) was investigated *in vitro* on cells of sarcoma 180 of mice and on four human tissue cultures [292]. A study was also made of the suppression of glycolysis by these preparations [293].

Various derivatives and analogues of compounds (LXIX)–(LXXI) were also investigated in order to elucidate the relation between structure and antitumour activity [294,295]. It was found that the vinylogue of compound (LXIX) is completely inactive against lymphoma 8. [296] The replacement of the quinoline ring by the isoquinoline ring reduces the antilymphoma activity [297] and the replacement of the *p*-$N(CH_3)$ group by F causes a complete loss of activity [298].

In an examination of the mechanism of the action of styrylquinolinium salts on normal and neoplastic cells, it was suggested that the antitumour activity of these compounds is determined by the quinoline part of the molecule, while the aminostyryl group is involved in the attachment

of the molecule to important sections of the tumour cell[295]. According to Bahner et al.[299], the above salts interact with sulphydryl groups in cysteine. The fate of styrylquinolinium compounds in the animal organism was investigated[300] and a highly sensitive method for the detection of these compounds was developed. Certain of the styrylquinolinium salts and anil derivatives of quinolinium salts containing the mustard gas group in the benzene ring of the styryl substituent have been patented as effective anticancer preparations[301].

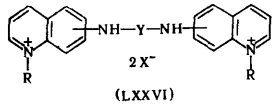
In 1963 Hirschberg[302] published a very brief compilation of the literature on the antitumour properties of certain styrylquinolinium salts.

Cyanine dyes with quinoline rings have also been tested for anticancer activity. It was found that compounds of type (XVI) are very weak carcinostatic agents or inactive. Thus compound (LXXIII) [XVI, $R^1 = CH_3$, $R^2 = 6\text{-}N(CH_3)_2$, $R^3 = C_6H_5$, and X = Cl] does not suppress sarcoma 180,[275] while its analogue with $R^1 = CH_2CH_2OH$ and $R^2 = 6\text{-}CH_3$ is inactive against carcinoma and leukaemia L1210, suppressing sarcoma very slightly (to the extent of 27%)[303]; compound (LXXI) [XVI, $R^1 = CH_3$, $R^2 = 6\text{-}CH_3$, $R^3 = C_5H_{11}$, and X = Cl] prolongs the life of animals suffering from leukaemia almost by a factor of 2.[304] 1-Methyl-4-[2′(4″-pyridyl)vinyl] quinolinium iodide is inactive against all three tumours[305]. Among symmetric quinocyanine dyes, cryptocyanine was tested for its activity against leukaemia. It proved to be inactive[306], although it suppresses the growth of a KB tissue culture to the extent of 50% at a concentration of 1.4×10^{-1} μg ml^{-1}.[268] Orthochrome T [bis-(1-ethyl-6-methylquinoline-2-yl)trimethinecyanine iodide] is also inactive against sarcoma 180, carcinoma, and leukaemia L2110.[265]

At the same time Quinolinium Blue at a dilution of 1 : 2000 proved to be very active against Ehrlich carcinoma[75,307]. The action of quinocyanine dyes with three rings against malignant tumours was also studied. Neocyanine (LXXV) suppresses sarcoma 180 to the extent of 21–51%.[265] Japanese investigators reported that it is also active against cancer tumours and its effectiveness is higher when administered orally than in local administration[308]. The use of compound (LXXV) in the treatment of Hodgkin's disease has been reported[309]. Mizuno[310] notes that cyanine dyes (the formulae and names are not quoted) suppress *in vitro* the growth of a tissue culture of Erlich carcinoma, sarcoma 180, and Yoshida sarcoma.

In a study of bisquinolinium salts of type (XXI) (X = Br), it was found that, when $n = 2$, the compound suppresses carcinoma to the extent of 45%, but the degree of suppression is only 24% when $n = 3$,[263] and when $n = 4$ the compound is inactive. The decamethylene derivative ($n = 10$) is also inactive against carcinoma but suppresses to the extent of 30% Erlich ascitices tumours[263]. A study was also made of the activity of compounds (XX) against sarcoma and carcinoma[267].

Bisquinolinium salts with a general formula (LXXVI) have recently attracted attention owing to their activity against leukaemia:



(LXXVI)

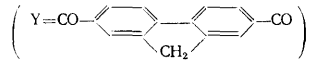
(LXXVII, Y = OC–C_6H_4–CO).

The activity of 6-substituted derivatives of quinoline is more pronounced with R = C_3H_7 and C_4H_9, falling rapidly in the case of higher homologues.

It has been found[311] that the physiological activity of compounds (LXXVI) is directly related to their lypophilic and hydrophilic properties. The replacement of the terephthaloyl residue by that of pyridine-2,5-dicarboxylic acid leads to some decrease of activity and its replacement by the isophthaloyl residue or the residue of an aliphatic dicarboxylic acid causes a loss of activity. A similar result is obtained when the –NHCOC_6H_4CONH– group joins the quinoline rings in the 5- and 7-position. A slight activity is also shown by derivatives of *p*-carboxyphenoxyacetic acid (LXXVI, Y = CO–C_6H_4–OCH_2CO).[311]

When the Y = COC_6H_4NHCONHC_6H_4CO group is introduced into (LXXVII), its antileukaemic activity is enhanced; the replacement of one of the quinoline rings by a pyridine ring has a similar effect[312].

When the phenyl group is Y = COC_6H_4CO is replaced by the biphenylyl group (Y = CO$C_6H_4C_6H_4$CO), the activity is retained; it is also retained when the Y group is in the 7-position[313]. This is believed[314] to be an indication that the minimum distance between the nitrogen atoms required for antileukaemic activity must be about 18 Å. When the benzene rings in the biphenylene group are fixed by a methylene bridge



the activity disappears[313].

The study of the activity of the most effective preparations of the type under consideration against various cancer tumours showed that they do not suppress carcinoma 180 and the spontaneous cancer of mammary glands. However, a distinct suppression of the tumour was observed in the case of lymphosarcoma induced by methylcholanthrene[311].

The activity of many quinolinium salts was studied by the method involving the suppression of the growth of a KB tissue culture[265,266,268,269,272,273,288,314,315].

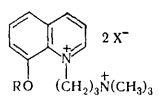
c. Other Radiomimetic Properties

Other radiomimetic properties of quinolinium salts have been investigated very little. There are reports of a mutagenic activity by compound (XXXIII), which is also known to be carcinogenic. It induces the mutation of strain B of *E. coli*[316] and *Saccharomyces cerevisiae*[317-319]. When the embryos of *Tritonia alpestris* and *Caenopus laevis* are treated in an early stage of development with preparation (XXXIII) at concentrations in the range 0.001 to 0.0001%, an abnormal course of development takes place (deformations, proliferation of tissues, and high mitotic activity), similar to the effect of X-rays at a dose of 120 to 500 roentgens[320].

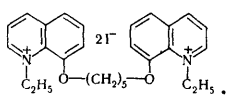
V. EFFECT OF QUINOLINIUM SALTS ON THE NEUROMUSCULAR SYSTEM AND ENZYMES

The effect of monoquaternary quinolinium salts on the neuromuscular system has been known for a long time. For example, Bamberger[321] reported in 1887 that *N*-phenylacylquinolinium bromide has a curare-like activity. However, these properties were investigated in greater detail much later. Schneider[322] and Denys and Levy[323] showed that 1-methyl-5,6-benzoquinolinium iodide is twice as active as eserine in suppressing the effect of acetylcholinesterase, but is slightly less active than Prostigmine;

it inhibits pseudocholinesterase more than the specific enzyme. The isomeric 1-methyl-7,8-benzoquinolinium iodide inhibits equally both acetylcholinesterases. High concentrations of the first preparation suppress the effect of acetylcholine on muscles. 1-(2'-Phenylcarbamoyloxyethyl)quinolinium iodide[324], 3-(diethoxyphosphinyloxy)-1-methylquinolinium methosulphate[325], and acetoxyquinolinium salts[326] also exhibit an antiacetylcholinesterase activity, 3-acetyl-1-methylquinolinium iodide being more active than the isomer containing the acetoxy-group in the 8-position of the quinoline ring. In a study of the effect of various quaternary ammonium salts on the rectus abdominis muscle, Iordache[327] found that 1-allylquinolinium bromide sensitises it with respect to acetylcholine. Quaternary salts of 8-alkoxyquinolinium have an analgesic effect[328]. In experiments on animals, 1-allyl-8-ethoxy- and 1-allyl-8-propoxy-quinolinium bromides showed a very satisfactory activity. 8-Hydroxy-1-methylquinolinium methosulphate has an analgesic effect in the treatment of the eye, associated with its ganglion-blocking activity[329]. Austin et al.[162] studied the curare-like activity of compound (X). It proved to be only twice as weak as (+)-curarine. Werner[330] suggested the use of quaternary quinolinium salts with a dioxanylalkyl residue at the nitrogen heteroatom as sympathomimetic preparations. Surrey and coworkers[331,332] synthesised mono- and di-quaternary salts of 4-dialkylaminoalkylquinolinium with hypotensive activity. Among other diquaternary quinolinium salts with hypotensive activity, mention should be made of the trypanocidal preparation antrycide (XVIII), which reduces blood pressure when administered in doses considerably below the therapeutic amount[333] and also causes the secretion of histamine[334]. The effect of compound (XVIII) on the cardiac activity of healthy cattle and cattle suffering from piroplasmosis has also been studied[335]. Gray and coworkers[336,337] synthesised and investigated diquaternary salts of type (LXXVIII).



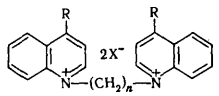
(LXXVIII)
(R = H, CH_3)



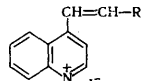
(LXXIX)

Many of these also exhibit a hypotensive activity. Quininebis(allyl bromide), which is also a diquaternary quinolinium salt, has an antiacetylcholine activity of the type of curare[337].

Bovet and coworkers[338,339] began an intensive study of the pharmacodynamic properties of bisquinolinium salts and in 1946 published data on the curare-like activity of compound (LXXIX) (RP-3381). Eserine and Prostigmine are antagonists of this preparation. Apart from the curare-like activity, compound (LXXIX) exhibits only physostigmine-like activity[340-342], inhibits pseudocholinesterase (but not the specific enzyme)[343,344], causes the contraction of the bronchi in guinea-pigs[345], and lowers the blood pressure in dogs[346]. Huidobro and Ugarte[347,348] studied the mechanism of the curare-like activity of the preparation. A number of patents have been obtained for preparations similar to compound (LXXIX)[349,350]. Barlow and coworkers[351,352] studied the curare-like activity of bisquinolinium salts of type (LXXX, R = H) with 3, 5, and 10 ethylene groups.



(LXXX)
n = 3, 5, 10



(LXXXI)

All three homologues exhibit a moderate curare-like activity and the highest member of the group shows in addition a considerable antiacetylcholinesterase activity. Reduction of the quinoline ring and the introduction of more than one OCH_3 group enhance the curare-like activity of the preparation[353-355]. Bhattacharya and Sen[356] studied compound (LXXX) with 20 methylene groups (n = 20). The preparation is antigonistic to acetylcholine but does not eliminate the effect of histamine and nicotine. Vyrbanova and Ivanov[357] studied the curare-like and anticholinesterase activity of compounds of type (LXXX, R = CH_3, n = 3–6, 8, or 10, X = Br). It was established that at a concentration of 10^{-6} M the anticholinesterase activity increases with the length of the polymethylene chain, but members with an odd number of CH_2 groups (n = 3 or 5) are somewhat more active. At the same time the curare-like activity is most pronounced in compounds with n = 4 and 6, i.e. those with the lowest anticholinesterase activity[358].

In a study of the effects of these compounds on the control of movement in rabbits, it was found that at a dose of 1 mg kg^{-1}, compounds with n = 3 and n = 10 enhance the control, while all other homologues lower it. The maximum decrease is observed with n = 5.[359]

The toxicity of polymethylenebislepidinium bromides (LXXX, R = CH_3, X = Br) is insignificant[360] and varies in parallel with their effect on subordination, reaching a maximum at n = 5. The compounds do not exhibit a local irritant activity when introduced into the conjunctival sac and also on subcutaneous and intramuscular administration.

Tarakhovs'kii and coworkers[361,362] showed that pentamethylenebisquinolinium bromide (pentaquinomethonium) (LXXX, R = H, n = 5, X = Br) lowers the blood pressure in experiments on cats and dogs in doses of 1–10 mg kg^{-1} and blocks the transmission of nerve impulses both via the sympathetic and parasympathetic ganglia of the vegetative nervous system. The preparation also exhibits a central cholinolytic activity. Kimenis[363,364] studied the effect of the quinolinium analogue of ditilin (preparation DS-3) on the neuromuscular system of warm-blooded animals. In its curare-like activity the compound is inferior to ditilin, but the duration of its action is longer. The antiacetylcholinesterase activity of compound DS-3 exceeds by severalfold that of proserene and is less toxic by a factor of 8.

At attempt has been made to establish a relation between the curare-like activity and the magnitude of the cationic charge of the nitrogen atoms. The ability of conjugated system to distribute the charge associated with the nitrogen atom leads to a decrease of the curare-like activity[365]. Maximum curare-like activity is observed with compounds in which the distance between the two positively charged nitrogen atoms is 15 Å.[366]

Certain quinolinium dyes also exhibit an appreciable activity. Although Brooker and Sweet[71] reported that cyanine dyes do not have an appreciable effect on α-amino-acid oxidase, cytochrome oxidase, succinate dehydrogenase glucosedehydrogenase, and glyoxalase and Ciaccio et al.[367] found that (LXX) and (LXX) are inactive in relation to lactate dehydrogenase and α-glycerolphosphate dehydrogenase and do not inhibit glycolysis, Hase and coworkers[368,369] showed that many cyanine and styryl dyes of the quinolinium series inhibit acetylcholinesterase.

It has also been established that the non-purified preparation (XVII) (the so called Lumin) has a marked influence on the respiration of animals [370-372]. Fuzimoto [373] investigated quinolinium dyes of type [LXXXI, R = piperidyl, $N(CH_3)_2$, $N(CH_3)C_6H_5$]. The preparations cause a dilatation of blood vessels and accelerate the peristalsis of the intestine. Many quinocyanine and quinostyryl dyes inhibit aerobic glycolysis [293,374]. Ogura et al. [375] made a kinetic study of the mechanism of the inhibition of catalase by compound (XVII).

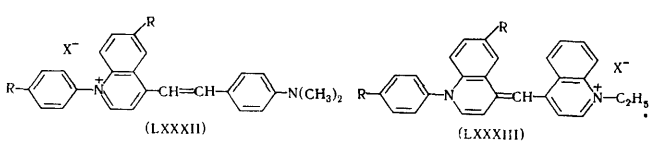
Recently styrylquinolinium compounds have also been investigated as inhibitors of choline acetyltransferase [376] and monoamine oxidase [377].

Among the numerous reviews dealing with the effect of quaternary ammonium salts on the neuromuscular system, only two [378,379] consider briefly bisquinolinium salts in this respect, on the basis of the literature between 1946 and 1951.

VI. QUINOLINIUM SALTS AS REGULATORS OF PLANT GROWTH AND DEVELOPMENT

The properties of quinolinium salts as regulators of plant growth began to be studied only 20 years ago by Japanese investigators. In 1949 Fujisawa and Ohba [380,381] made patent applications for the use of monomethinecyanine dyes, and particularly bis-(1-ethylquinolin-2-yl)-monomethinecyanine iodide, as stimulators of seed germination; Ogata and Shingu [382] studied the activity of a number of quaternary heterocyclic salts and cyanine dyes synthesised from them in tests on peas. The trinuclear quinocyanine dye (XVII) was investigated as a regulator of fungal growth [383]. The growth of fungi is stimulated when the preparation is diluted to 1 : 100 000–1 : 10 000 000 and is inhibited at a dilution of 1 : 10 000. The stimulation of the growth of certain medicinal plants by purified compound (XVII) was also investigated [384]. In the middle 1960's the work of Soviet scientists in this field was published. A method was proposed for increasing the crop of peas (to the extent of 117%) by soaking the seeds before sowing in 0.001% aqueous solution of (1,2-diphenylquinolin-4-yl). (1′-ethylquinolin-4′-yl)monomethinecyanine perchlorate [385]. Wheat grains treated with 0.001% solution of 4-*p*-dimethylaminostyryl-1,2-diphenylquinolinium perchlorate resulted in an increase of the growth of the green mass of wheat by the hydroponic method by 124%, [386] and treatment with a solution of 4-*p*-dimethylaminostyryl-1-β-naphthyl-5,6-benzoquinolinium perchlorate gave an increase of 117%. [387]

In a study of the activity of monomethinecyanine and styryl dyes derived from *N*-aryl-lepidinium on the growth of cucumbers and hemp [388], it was found that the dyes at a concentration of 0.01% inhibit the germination of the seeds or do not have an appreciable effect. The optimum concentrations proved to be 0.0001 and 0.00001% for cucumbers and 0.00001% for hemp. Experiments showed that lepidinium derivatives have unequal effects on the growth of various plant species.



(LXXXII) (LXXXIII)

Here R = H (a), CH_3 (b), OH (c), $OCOCH_3$ (d), or OCH_3 (e).

Thus in the case of cucumber seeds the best growth stimulating activity was shown by compounds (LXXXII, e), and (LXXXIII, b) and satisfactory activity was also shown by compounds (LXXXII, a, d) and (LXXXIII, a, c, e). In an identical experiment with hemp, the best stimulators proved to be (LXXXII, c, d) and (LXXXIII, a, c, d,). It is interesting to note that in experiments with cucumbers the preparations showed a somewhat lower activity than potassium heteroauxinate. However, in experiments with hemp, the latter proved less active than the lepidinium derivatives. Field tests on hemp showed that certain preparations increase the length of the internodal sections, enhance the saturation of tissues with water, and promote the accumulation of protein [388,389].

Preparations of type (LXXXII) and (LXXXIII) were also tested in the growth of tree seedlings, in particular fir seedlings [390]. Compounds (LXXXII, a, c, e,), (LXXXIII, a, c,), certain styryl derivatives, and monomethines synthesised from 1-aryl-5,6-benzolepidinium salts, and also Pinacyanol iodide [bis-(1-ethylquinolin-2-yl)trimethylcyanine iodide] proved to be the most active. It is interesting that, in order to stimulate the growth of tree seedlings, it is necessary to employ more concentrated solutions (0.005 and 0.001%). More water-soluble preparations (LXXX, LXXXII, a, X = Cl) and Pinacyanol chloride were tested *in vitro* on Belotserkovskaya 23 and Meris Widgen [spelling uncertain (Ed. of Translation)] wheat grains. The experiments showed that the activity of the preparations is almost equal to that of (LXXXIV) as regards the enhancement of the growth of the part of the plant above ground but is somewhat inferior as regards the stimulation of root growth [391]. The growth stimulating activity of compound (LXXXV) was also tested on leguminous plants [392]. In field tests the preparation increased the content of chlorophylls, reducing sugars, and the dry matter in the plant leaves during the flowering phase. The preparation is somewhat more active than (XXXIV). It increased the crop of broad beans by 108% and that of French beans by 114.6%.

In studies of the growth stimulating activity of dyes synthesised from 6-hydroxy-1-methyllepidinium chloride [393] in the initial phase of the growth of Belotserkovskaya 23 wheat and Nadezhnyi oats, a high activity of 1-methyl-4-*p*-dimethylaminostyryl- and 4-*p*-hydroxy-*m*-methoxystyryl-1-methyl-substituted 6-hydroxylepidinium chlorides was noted, being equal to that of compound (XXXIV).

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