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Searching for New Drugs

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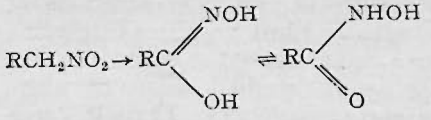
IN his chemical research the author was mainly concerned with the chemistry of nitro compounds and while searching for new drugs he was particularly on the look out for biologically active compounds belonging to one of the following three groups:

(a) Isomers of nitro compounds, such as hydroxamic acids, which are isomeric to primary nitroalkanes and are potential bearers of an amino group



...(A)

(b) Derivatives of nitroalkanes which contain the unchanged nitro group.

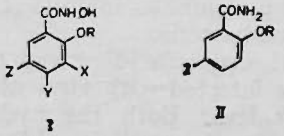
(c) Aromatic compounds with a nitro group.

It is known that some among the important antibiotics (such as chloramphenicol) and synthetic drugs (such as flagyl) contain a nitro group and that some nitro compounds (e.g. picric acid) do not show excessive toxicity. Of course, particular attention should be paid to the problem of toxicity (both acute and chronic) when examining the possibility of using a compound with a nitro group as a drug.

Hydroxamic Acids

The author suggested in 1948 the use of salicylhydroxamic acid (I, X=Y=Z=R=H) (which will be called SH) as an antitubercular agent[1]. The suggestion was based on the hypothesis that the hydroxamic group can act as an aminating agent either as a source of hydroxylamine[2-5] or through the Lossen degradation, and the effect of the administration of the drug might be similar to that of *p*-aminosalicylic acid (PAS), a well-known antitubercular drug. The results with SH on experimental tuberculosis in animals were encouraging. The acute toxicity of the compound was found to be extremely low (LD_{50} by oraladministration was >3·0 g/kg), but the antitubercular activity in clinical experiments was insignificant.

In search for more potent agents among the derivatives of SH, 5-bromosalicyl hydroxamic acid (I, X=Y=R=H, Z=Br) was prepared[6]. It will be referred to as BSH. Like SH, it has shown a very low toxicity[7]. McIsaac and Williams[8,9] explained the low toxicity of both the compounds from a study of their metabolism. They found that both SH and BSH are metabolized mainly by direct conjugation with glucuronic acid and sulphuric acid, thus producing I, X=Y=Z=H, R=$C_6H_9O_6$ or R=SO_3H and I, X=Y=H, Z=Br, R=$C_6H_9O_6$ or SO_3H respectively.



I II

In addition, SH and BSH are partly reduced to amides in man, rat and mouse, yielding II, Z=H, R= $C_6H_9O_6$ or SO_3H and II, Z = Br, R = $C_6H_9O_6$ or SO_3H respectively. In rabbit, there is the remarkable difference between SH and BSH in it that the former is not reduced to an amide (II) to a great extent, whereas the latter is. McIsaac and Williams[8,9] also found that *in vitro*, the tuberculostatic activity of 5-bromosalicylamide (II, Z—Br) is about half that of BSH.

BSH gave promising results in a few hundred clinical cases. Particularly interesting were the cases which did not respond to the treatment with streptomycine, but positive results were obtained with BSH[7,10].

BSH was made at this stage on industrial scale by reacting ethanolic solution of methyl ester of

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5-bromosalicylic acid with conc. aqueous solution of hydroxylamine[11].

Further clinical experiments have shown that BSH inhibits the formation of strains of *Mycobacterium tuberculosis* ($H_{37}Rv$) resistant to isoniazid[12,13].

From another series of clinical experiments carried out in Canada it has been found[14] that BSH effectively inhibits the acetylation of isoniazide (which is known to produce inactivation of this important drug)[15]. This experimental finding opened a new field for the possible application of BSH. It is well known that acetic ion is the precursor of cholesterol in rat[16], and the biosynthesis of cholesterol in man starts from acetate[17-19]. Subsequently, Czyzyk and Urbanski[20] anticipated that BSH, while inhibiting the acetylation of isoniazide, might also inhibit the formation of cholesterol in the blood serum. This proved to be correct and in many clinical cases, BSH reduced the cholesterol level significantly

To continue this line, a number of halogen substituted derivatives of SH were prepared[21]. All of them caused marked lowering of the cholesterol level. The strongest activity was shown by 3,5-dibromosalicylhydroxamic acid (I, X=Z=Br, Y=R=H) and the next best was 3-bromo-5-fluorosalicylhydroxamic acid (I, X=Br, Z=F, Y=R=H). The trihalogen substituted product (I, X=Z=Br, Y=F, Y=R=H) was less active.

Monosubstituted derivatives were less effective than the disubstituted derivaties mentioned above, but 5-chlorosalicylhydroxamic acid (I, X=Y=R=H, Z=Cl) was more effective than BSH. Unsubstituted SH proved to be practically inactive.

Experiments on the toxicity and pharmacodynamic action of 3,5-dibromosalicylhydroxamic acid (DBSH) are now in progress.

In another series of studies, salicylhydroxamic acid proved to be of interest as an antifungal agent. When taken orally, it inhibited various types of deep skin mycoses[22]; particularly striking results were obtained with ring worm in children[23].

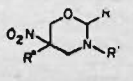
Buu-Hoi[24] confirmed the antitubercular activity of halogen derivatives of salicylhydroxamic acid, and more recently, Gale and Hawkins[25] found that hydroxamic derivatives of some α-amino acids — glycine and β-alanine — inhibit the growth of pathogenic mycobacteria.

β-Alanyl hydroxamic acid proved to be effective *in vivo* in mice infected with virulent strains of *M. tuberculosis* ($H_{37}Rv$). Both the hydroxamic acids were found to have low toxicity ($LD_{50} > 2{\cdot}0$ g/kg).

1,3–Oxazines

Two kinds of 1,3-oxazine derivatives were examined with regard to their biological activity: (i) tetrahydro-1,3-oxazine derivatives with the nitro group in position 5, and (2) dihydro-1,3-oxazine derivatives condensed with aromatic rings in 5,6-positions.

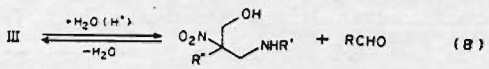
Tetrahydro-1,3-oxazines — 5-Nitrotetrahydro-1,3-oxazines (III, R=H; R′=H) were prepared by Hirst *et al.*[26,27] from 1-nitropropane by condensation with formaldehyde and ammonia. Nitroethane and higher primary nitroalkanes were also used[28-31].



III

Senkus[32,33] used primary amines instead of ammonia to obtain compounds III (R= alkyl, R′=H, R″= alkyl).

The most important property of compounds III is their ability to react in dilute hydrochloric acid (usually conc. hydrochloric acid diluted with ethanol) by splitting off carbon (2) with substituents, to yield aldehydes RCHO and 3-amino-2-nitro-alcohols (IV) through hydrolysis. The reaction is reversible and in a neutral or slightly basic medium, the original tetrahydro-1,3-oxazine (III) is formed (reaction B).



(B)

IV

The presence of an active group at carbon (2) suggested to the author that compounds III should possess biological activity due to C(2)HR group, which (after being split off the compound) may act as an alkylating or cross-linking agent. It is known that alkylating agents are most common antitumour compounds.

Indeed, compounds III proved to be active both *in vitro* and *in vivo*[32,33] as antitubercular and antirickettsial compounds. They also show a definite antitumour activity[34] and the latter property was considered to be particularly important. Hence, the screening of compounds III has since 1958 been concentrated on the evaluation of the antitumour activity of this group of compounds[35-37]. The work has been recently summarized by Mordarski *et al.*[38]. The report gives the results of examination of 110 derivatives of 5-nitrotetrahydro-1,3-oxazine.

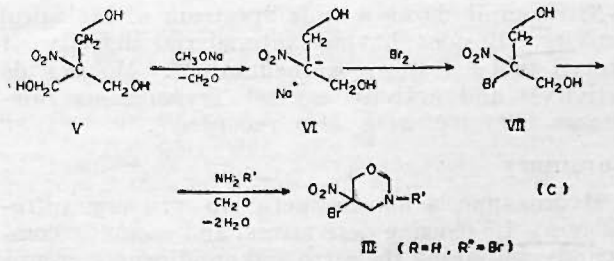
In vitro experiments were carried out by evaluating the dehydrogenase activity of tumour cells, incubated *in vitro* with various concentrations of the compounds studied. Ehrlich ascites carcinoma and amytal ascites sarcoma served as standard cells.

Antitumour activity was studied *in vivo* in white mice with subcutaneous tumours: Ehrlich carcinoma, sarcoma 180, Nemeth-Kellner lymphoma and amytal sarcoma. The compounds studied were injected subcutaneously in doses of 50-200 mg/kg. The results were analysed statistically.

Many of the compounds exhibited strong cytotoxicity for tumour cells (*in vitro*) and some of them markedly inhibited the growth of transplantable tumours. Not infrequently, they caused as high as 70% inhibition of the development of the tumours as compared with the control group.

Three compounds proved to be most interesting and are being subjected to preclinical trials. They are (in order of diminishing activity): (1) T 398 (III, R=H, R′–R″=CH_3); (2) T 307 (III, R=H, R′=$CH_2C_6H_5$. R″=CH_3); and (3) T 306 (III), R=H, R′=$CH_2C_6H_5$R″=C_2H_5).

5-Bromo-5-nitrotetrahydro-1,3-oxazines (antiprotozoal compounds — 5-Bromo derivatives of III (R=H, R″=Br) were prepared (reaction C) starting from 2-nitro-2-hydroxymethyl-propane-1,3-diol (nitroisobutylglycerol) (V) through the retroaldolic break of one C-C bond by acting with sodium methoxide to yield the sodium salt of 2-nitropropane-1,3-diol (VI), which in turn (by acting with bromine) was converted into 2-bromo-2-nitropropane-1,3-diol (VII). By acting with primary amines $R'NH_2$ and



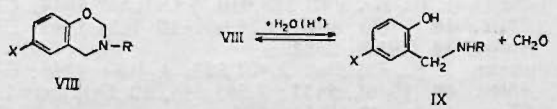
formaldehyde, compounds III (R=H, R″=Br) were obtained. R^1 was CH_3, C_2H_5 or $CH_2C_6H_5$. Of these three compounds, the benzyl derivative ($R^1=CH_2C_6H_5$) showed the lowest toxicity (LD_{50} = 381 mg/kg in mice) and high activity against *Trichomonas vaginalis*[39]. The effective dose *in vitro* was found to be 22 γ/ml, killing 50% of protozoa after 10 min. The dose of 4γ/ml produced the same effect after 30 min. The same was found to be a potent amoebicide against *Entamoeba moshkovskii*[40]. The effective dose *in vitro* was 2·5-20 mg/ml.

Dihydro-1,3-Oxazine Derivatives Condensed with Aromatic Rings in Positions 6,5(VIII)

This group of compounds is known since 1900, when Betti obtained[41] the first representative by reacting an aliphatic aldehyde (e.g. isovaleraldehyde) with an aromatic primary amine (e.g. *p*-toluidine) on α-naphthol. Rohde and Schartel[42] formed a similar ring system by condensing salicylaldehyde with aniline and potassium cyanide.

More recently, Burke[43,44] worked out a simple method, which involves condensing phenols substituted in *para* position or naphthols with formaldehyde and primary amines. This method was used in our work.

Compounds VIII possess chemical properties similar to those of compounds III; when warmed with dilute hydrochloric acid, the heterocyclic ring is opened up through the splitting off of group $C(2)H_2$ by hydrolysis yielding formaldehyde and the *o*-aminomethyl derivative of the phenol (IX). The reaction is reversible and IX when heated with aqueous formaldehyde in a neutral or slightly basic medium gives back VIII. It has been found that benzdihydro-1,3-oxazines (VIII) possess biological properties similar to those of III. They show antitumour[37,45,46] and antitubercular activities[47]. The antitumour activity was confirmed by American workers[48]. However, our experiments have shown[37] that the anticancer activity of these compounds is weaker than that of compounds III; on the contrary, the antitubercular activity of VIII seemed to offer greater promise.



Two compounds, T 615 (VIII, X=C_6H_5, R=$CH_2C_6H_5$) and T 638 [VIII, X=Br, R=C_6H_4Br (*p*)] gave encouraging results in respect of antitubercular activiteis.

The *in vitro* activity of both the compounds was manifested at concentrations 7·8-31·2 mg/ml against *M. tuberculosis* $H_{37}Rv$. The *in vivo* activity in mice and gunea-pigs was similar to the activity of streptomycin, but lower than that of INH.

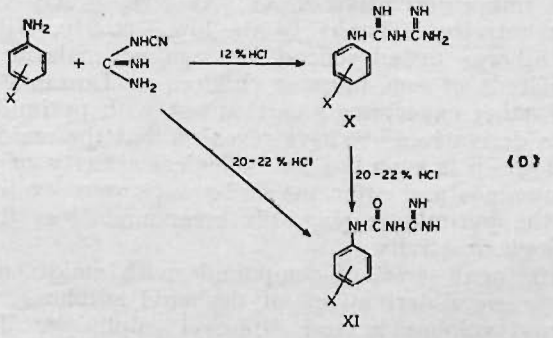
Table 1 — Biological Activities of the Most Potent Dihydro-1,3-oxazine Derivatives Condensed with Aromatic Rings in 5,6-Positions and the Parent Phenols

Compound	Activity *in vitro* against				Toxicity (LD_{50}) g/kg
	M. tuberculosis $H_{37}Rv$	*S. typhi*	*Esch. coli*	*Cl. pneumoniae*	
	in mg/ml				
T 615	7·8	1·9	1·9	3·9	0·50
p-Hydroxy diphenyl	—	—	200	—	0·05
T 638	1·9	3·9	31·2	3·9	0·50
p-Bromophenol	—	31·2	31·2	15·6	0·05

Both the compounds in addition showed a marked activity against *Esch. coli*, *Clostridium pneumoniae* and *Salmonella typhi*. From the chemical and pharmacodynamic points of view, one fact is of interest: the antibacterial activity of phenols — parent substances used in the preparation of 1,3-oxazine derivatives — was markedly weaker than the activity of the compounds VIII. At the same time, the toxicity of the parent phenols was higher (Table 1). These results indicate that cyclization of phenols to dihydro-1,3-oxazines increases their antibacterial activity and lowers their toxicity.

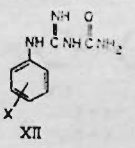
Guanidine Derivatives

It is well known that primary aromatic amines react with cyanoguanidine when boiled in dilute (~12%) hydrochloric acid to yield the so-called biguanides (X). Urbanski *et al.*[50,51] found that increase in the concentration of hydrochloric acid to 20-22% produces relatively little known compounds — derivatives of amidineurea (XI). They can also be formed by the hydrolysis of X in 20-22% hydrochloric acid (reaction D).

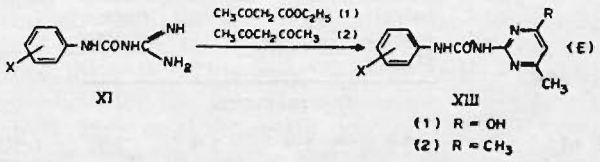


Compounds XI were known since 1923, but they were prepared in more complicated ways[52]. Also, isomeric substances, XII, were known[53,54].

On comparing the chemical properties and spectra of XI and XII obtained by various known methods with the properties and spectra of the compounds prepared by us with the suggested structure XI,



we came to the conclusion that the structure of amidineureas (XI) should be assigned to our compounds[56]. The final proof for this structure was obtained later, when compounds XI were reacted with acetylacetic ester or acetylacetone[57,58] to form pyrimidine derivatives (XIII) (reaction E).



The same N^1, N^2 substituted ureas (XIII) were prepared in another known way by the addition of 5-aminopyrimidines to arylisocyanates.

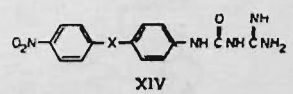
It is known that some biguanides, such as 'Paludrine', possess strong antimalarial activities[59]. It seemed advisable to try some of the amidineureas from this point of view. The first compound which showed antimalarial activity was compound XI ($X=p-NO_2$) given the code name "T 72" and now known as "Nitroguanil". The first experiments were carried out in China at the Institute of Materia Medica, Academy of Medical Sciences, Peking. A relatively strong antimalarial activity against *Plasmodium gallinaceum* in chicken was found along with a low toxicity[60,61]. The following were the main findings in respect of its activity *in vivo*. Nitroguanil cleared the blood off parasites at doses of 50 mg/kg and Paludrine produced the same effect at doses of 20 mg/kg. Thus, the activity of Nitroguanil was lower, but the toxicity of Paludrine was considerably higher, the lethal dose (LD_{50}) being 1200 mg/kg for nitroguanil and 45 mg/kg for Paludrine.

The above findings emerged from oral administration of the compounds. The low toxicity of Nitroguanil was recently confirmed by Aviado and coworkers[62].

It is worth recording that the *p*-chloro and *p*-bromo derivatives of phenylamidineurea (XI, $X=p-Cl$ or *p*-Br) are completely inactive and the amino derivative of XI ($X=NH_2$-*p*) has very low activity. Thanks to its low toxicity, Nitroguanil was tested successfully against malaria on hundreds of semi-immune children in Tanzania[63].

Further experiments carried out with pyrimidine urea derivatives[57,58] have revealed that the amidine end group is essential for biological activity of the compounds and after the end groups were cyclized to the pyrimidine ring, the compounds lost their biological activity.

The next series of compounds with amidineurea group were derivatives of diphenyl sulphone, diphenyl sulphoxide and diphenyl sulphide[64]. Two amidineurea derivatives (XIV, $X=SO_2$ and X=S) were relatively active. Experiments have shown that the presence of one nitro group is essential for the antimalarial activity of the compounds. However, more recent investigations[65] have shown that fluorine as a substituent (instead of the nitro group in compounds of the type XIV, $X=SO_2$) also favours building up of antimalarial activity.



"T 1213" X = S
"T 1215" X = SO_2

Nitroguanil shows a wide spectrum of biological activity. Besides having antimalarial activity, it proved to be a strong anthelmintic[66]. Moluscicide activity[66] and activity against *Trypanosoma gambiensae* in mice were also recorded[67].

Summary

Hydroxamic acids (isomeric to primary nitroalkanes), 1,3-oxazine derivatives, and aromatic compounds containing the nitro and amidineurea groups have been suggested by the author as new drugs.

Salicylhydroxamic acid (SH) proved to be a potent systemic fungicide. Its 5-bromo derivative was found to be effective as an auxiliary agent in treating tuberculosis; it inhibits the development of resistance of mycobacteria towards streptomycine and also inhibits the acetylation (and deactivation) of isoniazid. Halogen derivatives of SH proved to be effective in reducing the cholesterol level in blood serum.

5-Nitrotetrahydro-1,3-oxazines were found to be antitubercular and antirickettsial agents. However, their activity against cancer was much more prominent. The inhibition of the growth of tumour in animals was found to reach 70%. Bromo derivatives of 5-nitrotetrahydro-1,3-oxazine possess antiprotozoal activity.

Dihydro-1,3-oxazine derivatives condensed with aromatic rings in 5,6-position were found to be strong antitubercular agents effective against mycobacteria both non-resistant and resistant to the common antitubercular drugs. Their activity *in vivo* is the same order as that of streptomycine.

Amidineurea derivatives of aromatic compounds containing a nitro group were found to have antimalarial activity. The simplest of these compounds 'Nitroguanil' has a very wide spectrum of activity. In addition to antimalarial activity it is a strong anthelmintic and moluscicide, and is also active against trypanosomes.

Acknowledgement

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