Br. J. Pharmac. (1971), 43, 649–657.

Antibacterial activity of dihydro-1,3-oxazine derivatives condensed with aromatic rings in positions 5, 6

J. B. CHYLIŃSKA
Institute of Organic Chemistry, Polish Academy of Sciences, Warszawa 42
M. JANOWIEC
Institute of Tuberculosis, Warszawa
AND T. URBAŃSKI
Technical University (Politechnika), Warszawa 10, Poland

Summary

1. The antibacterial activity *in vitro* of dihydro-1,3-oxazine derivatives with aromatic rings condensed in positions 5, 6 was examined.

2. Of more than thirty compounds examined, two (T 615 and T 638) showed marked activity against various strains of *Mycobacterium tuberculosis* at concentrations below 2 μg/ml.

3. These two compounds also showed marked activity against *Escherichia coli, Clostridium pneumoniae* and *Salmonella typhi.*

4. Both showed marked activity *in vivo* against tuberculosis produced in mice and guinea-pigs by various strains of *Mycobacterium* such as human strain 'Sz', bovine 'An 5' and H37Rv non-resistant and resistant to isonicotinic acid hydrazide (INH), streptomycin (SM) and *p*-aminosalicylic acid (PAS).

Introduction

The biological activity of oxazine derivatives was reported as early as 1937 (Novelli & Adams, 1937). Later, several workers reported the fungistatic and bacteriostatic—including tuberculostatic—activity of these compounds (Urbański & Ślopek, 1951; Lane, 1953; Kay & Lane, 1953; Shono & Takahashi, 1954). We extended our examination of dihydro-1,3-oxazine derivatives as antibacterial and oncostatic agents (Chylińska & Urbański, 1959; Chylińska, 1962; Chylińska, Urbański & Mordarski, 1963; Chylińska, Grochowski, Mordarski & Urbański, 1964). The results of our experiments on the antibacterial activity of these compounds both *in vitro* and *in vivo* are the subject of this paper; the activity *in vitro* of phenols used to form the dihydro-1,3-oxazine derivatives was also examined.

Methods

The antimycobacterial activity of the compounds *in vitro* was tested by classical serial dilution in Youman's medium with 10% bovine serum added. All other bacteria were cultivated on ordinary broth. The following bacteria were examined: *Mycobacterium smegmae, Mycobacterium* 279, *Mycobacterium* 607, *Mycobacterium*

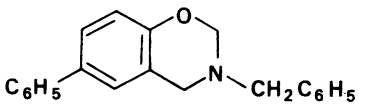
tuberculosis H37Rv, *Staphylococcus aureus* 209 P, *Escherichia coli, Klebsiella pneumoniae, Salmonella typhi* and *Shigella flexneri.*

Toxicity

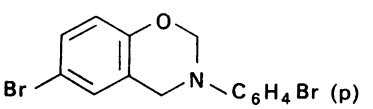
The acute toxicity LD50 was determined by the method of Kärber (1931). The compounds were injected intraperitoneally into white mice in the form of a suspension in an aqueous (2·5%) solution of tylose (methyl ether of cellulose). The toxicity was also tested by oral administration.

Activity in vivo

The activity of two compounds, T 615 and T 638,



T615



T638

which gave the best results *in vitro* was also examined *in vivo* in mice weighing 20 g and guinea-pigs weighing 300–350 g. Various strains of *Mycobacterium* were injected intravenously (0·1 mg/animal). They were: human strain 'Sz', bovine 'An 5', H37Rv non-resistant and resistant towards isonicotinic acid hydrazide (INH), streptomycin (SM) and *p*-aminosalicylic acid (PAS).

The drugs were given subcutaneously or orally once a day. When administered subcutaneously they were dissolved in aqueous gelatine or propylene glycol. If given orally, they were administered by stomach tube. The treatment was continued until all the control animals died.

The 'mean survival time' is the mean survival time (in days) of the animals during the course of the experiment which was stopped when all control (non-treated) animals died. All surviving animals in treated groups were allocated a survival time of the full duration of the experiment for the purpose of calculating the mean.

'Index of TB' indicates tuberculous changes in the organs in the animals compared with control animals, where the 'index of TB' is taken as 100% by definition. For this, the method of Feldmann, modified by Ślopek (1956) was used.

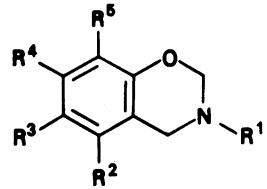
Materials

The dihydro-1,3-oxazine derivatives condensed with aromatic rings in positions 5, 6 were prepared according to methods previously described (Burke, 1949; Burke, Kolbezen & Wayne, 1952; Burke, Mordock & Ec, 1952; Chylińska & Urbański, 1959; Lane, 1953; Kay & Lane, 1953; quaternary ammonium salts of benzoxazines, Br. patent 699,550, Aug. 12; Noda, 1959; Rigterink, 1957; 3,4-dihydro-2H-1,3-benzoxazines. U.S. patents 2,806,031, Sept. 10; 2,811,532, Oct. 29; Shono & Takahashi, 1954).

Results

The results of the *in vivo* experiments are shown in Tables 4–9.

TABLE 1. *Antibacterial activity of* 3,4-*dihydro*-3-*alkyl/aryl/*-*benz*-1,3-*oxazine derivatives* in vitro

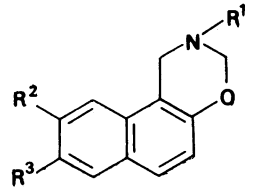


I

No.	R_1	R_2	R_3	R_4	R_5	Bacteriostatic concentration (μg/ml)								
						1 *Myc. smegm.*	2 279	3 607	4 $H_{37}Rv$	5 209P	6 *E. coli*	7 *Kl. pneum.*	8 *S. typh.*	9 *Sh. flex*
1	CH_3	H	Br	H	H	15·6	31·2	31·2	31·2	62·5	62·5	31·2	31·2	31·2
1c						31·2	31·2	62·5	31·2	31·2	31·2	31·2	12·5	31·2
2	CH_3	H	Br	H	Br	62·5	62·5	62·5	31·2	62·5	62·5	62·5	62·5	15·6
3	C_6H_{11}	H	Br	H	H	7·8	15·6	7·8	31·2	31·2	31·2	31·2	31·2	31·2
3c						7·8	3·9		7·8	25·6	25·6	25·6	25·6	
4	C_6H_{11}	H	Cl	H	H	7·8	3·9	3·9	15·6	62·5	31·2	31·2	31·2	31·2
4c						31·2	31·2	15·6	31·2	62·5	31·2	62·5	31·2	31·2
5	C_6H_{11}	H	C_6H_5	H	H	7·8	7·8	7·8	7·8	3·9	3·9	3·9	7·8	3·9
5c						7·8	7·8	7·8	3·9	3·9	15·6	15·6	7·8	7·8
6	$CH_2C_6H_5$	H	CH_3	CH_3	H	3·9	3·9	3·9	15·6	62·5	15·6	62·5	31·2	7·8
7	$CH_2C_6H_5$	H	H	CH_3	CH_3	3·9	3·9	3·9	15·6	250	250	500	500	250
7c						7·8	7·8	7·8	500	31·2	31·2	62·5	31·2	31·2
8	$CH_2C_6H_5$	H	C_6H_5	H	H	1·9	1·9	1·9	1·9	3·9	31·2	3·9	3·9	15·6
9c	$CH_2C_6H_5$	H	Br	H	H	7·8	3·9		3·9	12·8	25·6	6·4	6·4	
10	$CH_2C_6H_5$	H	Br	H	Br	62·5	62·5	62·5	62·5	125	125	31·2	62·5	15·6
10c						31·2	31·2	31·2	31·2	62·5	62·5	31·2	31·2	15·6
11	C_6H_4Br-*p*	H	CH_3	H	H	7·8	15·6	7·8	31·2	62·5	62·5	125	62·5	31·2
12	C_6H_4Br-*p*	H	Br	H	H	<1·9	<1·9	<1·9	7·8	<1·9	<1·9	3·9	<1·9	31·2
13	C_6H_4Br-*p*	H	Br	H	Br	15·6	31·2	31·2	62·5	7·8	62·5	62·5	62·5	62·5
14	C_6H_4Br-*p*	H	Cl	H	H	1·9	1·9	1·9	15·6	62·5	62·5	15·6	15·6	31·2
15	C_6H_4Br-*p*	H	Cl	H	Cl	7·8	7·8	7·8	62·5	3·9	15·6	31·2	7·8	15·6

Hydrochlorides of the bases are marked with letter c.

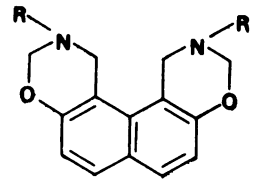
TABLE 2. *Antibacterial activity of* 2,3-*dihydro*-1*H*-*naphtho*-1,3-*oxazine derivatives* in vitro



II

No.	R_1	R_2	R_3	Bacteriostatic concentration (μg/ml) 1 *Myc. smegm.*	2 279	3 607	4 $H_{37}Rv$	5 209P	6 *E. coli*	7 *Kl. pneum.*	8 *S. typh.*	9 *Sh. flex*
16	CH_3	H	H	15·6	15·6	31·2	15·6	15·6	31·2	31·2	31·2	31·2
16c*				62·5	7·8	62·5	31·2	25·6	25·6	25·6	25·6	—
17	CH_3	OH	H	7·8	31·2	7·8	62·5	7·8	7·8	62·5	31·2	15·6
18	C_2H_5	OH	H	31·2	31·2	15·6	15·6	15·6	7·8	31·2	31·2	31·2
19	$CH_2C_6H_5$	OH	H	31·2	31·2	31·2	62·6	15·5	62·5	31·2	62·5	62·5
20	$CH_2C_6H_5$	H	SO_3Na	62·5	250	125	62·5	62·5	125	62·5	62·5	62·5
21	C_6H_4Br–*p*	H	H	125	125	62·5	31·2	125	125	31·2	62·5	62·5
22	$C_6H_4CH_3$–*p*	H	H	3·9	3·9	7·8	15·6	7·8	7·8	15·6	15·6	3·9

Antibacterial activity of 2,3,11,12-tetrahydro-1H,10H-naphtho [1,2-e:8,7-e'] bis [1,3]-oxazine derivatives *in vitro*.

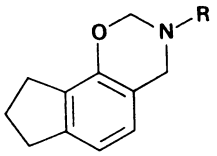


III

No.	R	Bacteriostatic concentration (μg/ml) 1 *Myc. smegm.*	2 279	3 607	4 $H_{37}Rv$	5 209P	6 *E. coli*	7 *Kl. pneum.*	8 *S. typh.*	9 *Sh. flex.*
23	CH_3	31·2	31·2	31·2	62·5	15·6	7·8	31·2	31·2	15·6
24	C_2H_5	62·5	31·2	31·2	15·6	62·5	62·5	62·5	62·5	62·5
25	$CH_2C_6H_5$	31·2	31·2	31·2	125	62·5	125	62·5	62·5	62·5

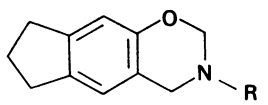
* Hydrochlorides of the bases are marked with letter c.

The chemical structures of the benzene and naphthalene derivatives of 1,3-oxazine and their antibacterial activities are shown in Tables 1 and 2. A few hexahydroindene derivatives (IV and V) were also examined:



IV

$R=CH_2C_6H_5$

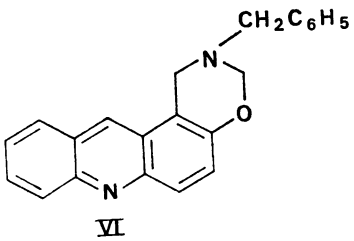


V

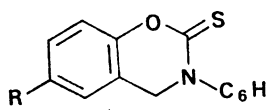
$R=CH_3, C_2H_5, CH_2C_6H_5$

They showed the same order of activity as the most active compounds I and II (Tables 1 and 2) with $R_1=CH_2C_6H_5$ and $C_6H_4CH_3$-p, respectively which are active against Mycobacteria at concentrations of 1·9–7·8 μg/ml.

The acridine derivative (VI) showed strong activity against *Mycobacterium* H37Rv (3·9 μg/ml) and low activity (62·5–125 μg/ml) against saprophytic strains. A few 2-thiono derivatives of benz-1,3-oxazine were also examined, and showed weaker activity (15·6–127 μg/ml) against Mycobacteria.



VI



VII

$R=CH_3, Cl$

TABLE 3. In vitro *activity of T* 615 *and T* 638 *against* Mycobacterium $H_{37}Rv$ *resistant to standard drug*

Strains	Tuberculostatic concentration of T 615	T 638
	μg/ml	
Normal	7·8	7·8
Resistant to		
INH	7·8–15·6	7·8–31·2
SM	7·8	7·8
PAS	7·8	15·6
INH and SM	7·8	15·6
INH and PAS	7·8	15·6
SM and PAS	7·8	15·6
INH, SM and PAS	7·8	7·8–31·2

TABLE 4. *Mice, twenty in each group infected with human strain 'Sz' of* Mycobacterium

Group	Drugs Name	Doses (mg/kg)	Mortality	Mean survival time (days)	Index of TB %
1	—	—	20	21·6	100·0
2	T 615	10	15	25·4	60·2
3	INH	10	3	29·4	25·4

Administration: subcutaneously as 10% solution in propylene glycol. Duration of the experiment, 34 days.

TABLE 5. *Mice, twenty in each group, infected with bovine strain 'An 5' of* Mycobacterium

Group	Drugs Name	Drugs Doses (mg/kg)	Mortality	Mean survival time (days)	Index of TB %
1	—	—	20	26·1	100·0
2	T 615	5	17	30·2	77·6
3	T 615	10	15	36·0	67·0
4	T 615	30	9	37·0	61·9
5	T 638	5	17	29·7	60·4
6	T 638	10	15	31·8	56·3
7	T 638	30	3	39·9	24·3
8	INH	5	1	40·1	15·6
9	SM	10	17	31·4	61·9

Subcutaneous administration of 10% solution in propylene glycol. Duration of the experiment, 41 days.

TABLE 6. *Guinea-pigs, ten in each group, infected with* Mycobacterium $H_{37}Rv$

Group	Drugs Name	Drugs Doses (mg/kg)	Drugs Administration	Mortality	Mean survival time (days)	Index of TB %
1	—	—	—	10	50·0	100·0
2	T 615	5	s.c.*	6	56·2	73·7
3	T 615	10	s.c.*	6	56·2	66·0
4	T 615	40	s.c.*	6	54·6	74·7
5	T 638	5	s.c.*	4	60·0	77·6
6	T 638	10	s.c.*	4	56·3	71·8
7	T 638	40	s.c.*	3	57·9	56·3
8	T 615	5	p.o.	5	61·5	63·1
9	T 615	10	p.o.	4	60·8	78·6
10	T 615	40	p.o.	3	59·8	61·1
11	T 638	5	p.o.	7	53·5	65·0
12	T 638	10	p.o.	6	57·0	52·4
13	T 638	40	p.o.	7	51·7	60·1
14	T 615	5	p.o.†	7	57·7	83·4
15	T 615	10	p.o.†	5	59·7	66·0
16	T 615	40	p.o.†	6	57·8	55·2
17	T 638	5	p.o.†	6	54·1	78·2
18	T 638	10	p.o.†	6	58·2	71·8
19	T 638	40	p.o.†	6	52·6	73·7
20	INH	5	s.c.‡	1	63·6	26·2
21	SM	10	s.c.‡	2	61·2	33·9
22	ETA	10	p.o.§	2	64·2	64·0
23	PZA	40	s.c.‡	8	50·9	81·5
24	PAZL	40	s.c.‡	8	54·8	77·6

Duration of the experiment, 66 days.
* In propylene glycol as a 10% solution. † After 30 days of inoculation. ‡ Aqueous solution.
§ In 1% aqueous solution of gelatine.

TABLE 7. *Guinea-pigs, ten in each group, infected with* Mycobacterium $H_{37}Rv$. *Effect of standard drugs*

Group	Drugs Name	Drugs Dose	Drugs Administration	Mortality	Mean survival time (days)	Index of TB %
1	—	—	—	10	51·4	100·0
2	INH	5	s.c.*	1	73·4	14·1
3	INH	1	s.c.*	8	57·5	29·2
4	ETA	10	p.o.†	3	67·5	65·4
5	PAS	100	s.c.‡	10	49·0	50·4
6	PAS	50	s.c.‡	10	48·6	57·5
7	PZA	100	s.c.*	5	56·9	59·2
8	PZA	50	s.c.*	7	48·4	57·5
9	SM	10	s.c.*	3	67·9	34·5
10	SM	5	s.c.*	7	52·6	54·8

Duration of the experiment, 78 days.
* In water. † In 1% aqueous gelatine. ‡ In propylene glycol, as 10% solution.

The activity of phenols—parent substances used for preparation of 1,3-oxazine derivatives—was markedly weaker than the activity of the latter. Thus *p*-bromophenol (the parent substance of T 638) was active against Mycobacterial strains at concentrations of 7·8–31·2 μg/ml and against *E. coli, Kl. pneum., S. typhi* and *Sh. flex.* at concentrations of 31·2, 15·6, 31·2 and 31·2 μg/ml respectively.

Substances 8 (code name T 615) and 12 (code name T 638) (Table 1) were further tested against *Mycobacterium* H37Rv, resistant towards the standard drugs. No difference in activity was found whether the strains were resistant to INH, SM, PAS or to various combinations of these (Table 3).

The intraperitoneal LD50 of T 615 and T 638 was 890 mg/kg and 300 mg/kg respectively. By oral administration no toxic effects were found at doses of 6,000 mg/kg. The toxicity of the parent phenols 4-hydroxydiphenyl (the parent substance of T 615) and *p*-bromphenol was much higher: 50 mg/kg.

TABLE 8. *Guinea-pigs, ten in each group, infected with* Mycobacterium $H_{37}Rv$

	Drugs						
Group	T 615 dose (mg/kg)	Name	Dose (mg/kg)	Administration	Mortality	Mean survival time (days)	Index of TB %
1	5	—	—	—	6	52·7	66·3
2	5	INH	1	s.c.*	2	74·0	8·8
3	5	ETA	10	p.o.†	4	59·7	56·6
4	5	PAS	100	s.c.‡	7	47·2	55·7
5	5	PAS	50	s.c.‡	8	43·5	53·0
6	5	PZA	50	s.c.*	7	47·9	60·1
7	5	SM	5	s.c.*	6	52·8	69·9
8	10	—	—	—	6	52·8	78·7
9	10	INH	1	s.c.*	2	74·5	5·3
10	10	ETA	10	p.o.†	5	62·5	29·2
11	10	PAS	100	s.c.‡	6	54·4	73·4
12	10	PAS	50	s.c.‡	6	51·7	65·4
13	10	PZA	50	s.c.*	6	51·9	68·1
14	10	SM	5	s.c.*	6	53·2	55·7

Duration of experiment, 76 days. T615, subcutaneous administration of 10% solution in propylene glycol with standard drugs.
* In water. † In 1% aqueous gelatine. ‡ In propylene glycol, as 10% solution.

TABLE 9. *Guinea-pigs, ten in each group, infected with* Mycobacterium $H_{37}Rv$

	Drugs						
Group	T 638 doses (mg/kg)	Name	Doses (mg/kg)	Administration	Mortality	Mean survival time (days)	Index of TB %
1	5	—	—	—	6	53·0	68·1
2	5	INH	1	s.c.*	1	73·4	5·3
3	5	ETA	10	p.o.†	5	61·0	37·1
4	5	PAS	100	s.c.‡	7	47·7	57·5
5	5	PAS	50	s.c.‡	8	47·0	62·8
6	5	PZA	50	s.c.*	6	52·9	66·9
7	5	SM	5	s.c.*	6	51·9	48·6
8	10	—	—	—	8	43·6	64·6
9	10	INH	1	s.c.*	3	30·8	13·2
10	10	ETA	10	p.o.†	6	59·5	46·9
11	10	PAS	100	s.c.‡	6	51·8	57·5
12	10	PAS	50	s.c.‡	7	47·3	64·6
13	10	PZA	50	s.c.*	7	47·1	69·9
14	10	SM	5	s.c.*	6	51·9	67·2

Duration of experiment, 76 days. T 638, subcutaneous administration of 10% solution in propylene glycol with standard drugs.
* In water. † In 1% aqueous gelatine. ‡ In propylene glycol, as 10% solution.

Discussion

It is difficult to make any general statements concerning the relationship between the structure of the compounds and their activity *in vitro*. However, a few conclusions can be drawn as follows: When methylamine or ethylamine was used to close the 1,3-oxazine ring the antibacterial property of the parent phenol was reduced. In contrast, the use of cyclohexylamine, benzylamine or *p*-bromoaniline to close the 1,3-oxazine ring can increase the antibacterial activity of the parent phenols and at the same time may reduce their toxicity (examples 8, T 615 and 12, T 638) (Table 9). *In vitro* experiments with mice indicate (Table 5) that the activity of T 615 and T 638 increases with increase of dose. At 30 mg/kg the activity of T 615 and T 638 was higher than that of SM (10 mg/kg) but lower than that of INH (5 mg/kg). From Table 1, T 638 seems to be superior to T 615 *in vitro*.

From the experiments with guinea-pigs (Table 6) the antitubercular activity of T 615 seems to be best when the substance is given orally and T 638 when administered subcutaneously. Both substances show greater activity when given immediately after inoculation than after 30 days from the day of infection. Both substances are inferior to INH and SM but are similar in action to ethionamide (ETA) and better than PAS and morinamide (piazoline, morfazinamide) (PAZL).

Simultaneous administration of T 615 and T 638 with other standard drugs indicates that the best results can be obtained when the substances, in doses of 5 mg/kg or 10 mg/kg are combined with small doses (1 mg/kg) of INH.

No improvement was found in the action of SM, ETA and pyrazinamide (PZA) after combined administration with T 615 and T 638.

The chronic toxicity of T 615 and T 638 will have to be examined before clinical experiments.

This work was supported by the Polish Pharmaceutical Industries 'Polfa'. The authors are greatly indebted for their financial help. We are also much indebted to Dr. M. Wilimowski for the toxicity testing.

REFERENCES

BURKE, W. J. (1949). 3,4-Dihydro-1,3,2H-benzoxazines. Reaction of *p*-substituted phenols with N,N-dimethylolamines. *J. Am. Chem. Soc.*, **71**, 609–612.

BURKE, W. J., KOLBEZEN, N. J. & WAYNE, S. (1952). Condensation of naphthols with formaldehyde and primary amines. *J. Am. Chem. Soc.*, **74**, 3601–3605.

BURKE, W. J., MORDOCK, K. C. & EC, G. (1952). Condensation of hydroxyaromatic compounds with formaldehyde and primary aromatic amines. *J. Am. Chem. Soc.*, **76**, 1677–1679.

CHYLIŃSKA, J. B. & URBAŃSKI, T. (1959). Derivatives of 3,4-dihydro-1,3-oxazine condensed with aromatic rings in the position 5,6. *Bull. Acad. Polon. Sci., Sér. Chim.*, **7**, 635–637.

CHYLIŃSKA, J. B. (1962). Derivatives of 3,4-dihydro-1,3-oxazine condensed with aromatic rings in the position 5,6. Thesis, Warsaw Politechnika (in Polish), 1–135.

CHYLIŃSKA, J. B., URBAŃSKI, T. & MORDARSKI, M. (1963). Dihydro-1,3-oxazine derivatives and their antitumour activity. *J. med. Chem.*, **6**, 484–487.

CHYLIŃSKA, J. B., GROCHOWSKI, E., MORDARSKI, M. & URBAŃSKI, T. (1964). Oncostatic properties of 1,3-oxazine derivatives. *Acta Union Intr. Contre le Cancer*, **20**, 118–121.

KÄRBER, G. (1931). Beitrag zur kollektiven Behandlung pharmakologischer Reihenversuche. *Archs exp. Path. Pharmak.*, **162**, 480.

KAY, E. & LANE, E. S. (1953). Quaternary ammonium salts of benzoxazines. *Chem. Abs.* (1954), **48**, 9412.

LANE, E. S. (1953). Benzoxazine derivatives. Brit. pat. 694, 489. July 22. *Chem. Abs.* (1954), **48**, 9412.

NODA, M. (1959). Reaction of 2,6-bis-(hydroxymethyl)-4-bromophenols with primary aromatic amines; N-(2-hydroxy-3-hydroxymethyl-5-brombenzyl)-arylamine and their derivatives. *J. Chem. Soc. Japan*, **62**, 743–747.

NODA, M. (1959). Condensation products of 2,6-bis-(hydroxymethyl)-4-chlorophenols with primary aromatic amines and their derivatives. *J. Chem. Soc. Japan*, **62**, 747–751. *Chem. Zentr.* (1960), **131**, 7856–7857.

NOVELLI, A. & ADAMS, R. (1937). Aminophenyl-2-pentoxazolines. *J. Am. Chem. Soc.*, **59**, 2259–2260.

RIGTERINK, R. H. (1957). Benzoxamine derivatives. U.S. Pat. 2,806,031; 2,811,523. *Chem. Abst.*, (1958). **52**, 8210, 5485.

SHONO, T. & TAKAHASHI, A. (1954). Condensation products of phenols with aldehydes XIX. Initial crystalline products, ammonia catalyst. *J. Chem. Soc. Japan*, **57**, 569–571. *Chem. Abs.* (1955), **49**, 6649.

ŚLOPEK, S. (1956). Estimation of methods of determining the activity of antitubercular agents. *Recent Problems in Antibiotics*, eds. Kurylowicz, Korzylski & Kowszyk. (Polish), p. 147: Warsaw PZWL, Polish Medical Publishers.

URBAŃSKI, T. & ŚLOPEK, S. (1951). New derivatives of nitroparaffins and their antitubercular and antirickettsial properties. *Nature, Lond.*, **168**, 562–565.

URBAŃSKI, T., GÜRNE, D., ECKSTEIN, Z. & ŚLOPEK, S. (1955). On the anti-tubercular properties of some derivatives of benzoxazine-1,3. *Bull. Acad. Polon. Sci. Cl. III*, **3**, 397–399.

URBAŃSKI, T., RADZIKOWSKI, CZ, LEDÓCHOWSKI, Z. & CZARNOCKI, W. (1956). Biological activity of benzoxazine-1,3 derivatives, particularly against experimental sarcoma. *Nature, Lond.*, **178**, 1351–1352.

(*Received July* 2, 1970)