compound. This finding is additional support for the hypothesis that the benzylic CH bond is broken in the kinetically determining step of chloramphenicol action and it is consistent with the idea that the antibiotic blocks an enzyme covalently.

Experimental Section

Optical rotation measurements were performed using an automatic polarimeter (Perkin-Elmer Model 141, Überlingen/Bodensee, West Germany). A Perkin-Elmer Model F 900 was used for the glc method and analysis was performed according to ref 11.

D-α-Dichloroacetylamino-β-hydroxy-p-nitropropiophenone (D-Ketone IV).—40 g of D-*threo*-chloramphenicol was dissolved in 1 l. of Me_2CO and mixed with 100 ml of H_2O and 40 ml of AcOH. To this soln 30 g of NBS was added, and the mixt was allowed to stand for 15 hr at room temp. After evapn of the solvent the product was recrystd from Et_2O, 15.8 g of white needles, mp 124–125°, $[\alpha]^{25}D$ + 20.8° (*c* 2.5 g/100 ml, EtOH).

D-*threo*-α-Deuteriochloramphenicol.—Reduction of IV with $Ca(BD_4)_2$ was carried out in EtOH at −30 to −35° as described according to ref 18 for chloramphenicol itself. The resulting raw material was recrystd 5 times from H_2O. All crystn steps were induced by inoculation with a trace of D-*threo*-chloramphenicol; white needles, mp 150–151°, $[\alpha]^{25}D$ + 17.0° (*c* 5.00 g/100 ml, EtOH).

Acknowledgments.—The authors wish to thank Doz. Dr. Prox for determining the isotopic purity of the chloramphenicol-d_1, Dr. Daneck for performing the glc analysis, and Dipl.-Chem. W. R. Ulrich for excellent technical assistance.

(18) Egyesült Gyógyszer és Tapszergyár, Budapest, German Auslegeschrift (published patent application), No. 1,117,136, Nov 11, 1961.

Chemotherapeutic Nitroheterocycles. 7.[1] Substituted 5-Alkylthiomethyl-3-(5-nitro-2-imidazolyl)methyleneamino-2-oxazolidinones[2]

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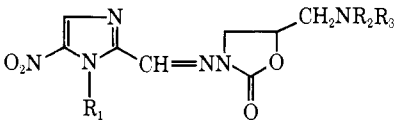
The syntheses of title compds were accomplished by condensation of 1-substituted 5-nitroimidazole-2-carboxaldehydes with 5-alkylthio-3-amino-2-oxazolidinones. The substances were highly active against *Trichomonas vaginalis in vitro* (Table I). 5-*n*-Butylthiomethyl-3-(5-nitro-2-imidazolyl)methyleneamino-2-oxazolidinone (**7d**) was the most effective compd *in vivo* showing ED_{50} 16.5 mg/kg.

In a previous paper[1] the effectiveness of substituted 5-aminomethyl-3-(5-nitro-2-imidazolyl)methyleneamino-2-oxazolidinones (**1**) against *Trichomonas vaginalis* both *in vitro* and *in vivo* was reported. As the antitrichomonal drug nifuratel[3] (**2**) has a similar structure, it was interesting to synthesize substituted 3-(5-nitro-2-imidazolyl)methyleneamino-2-oxazolidinones with 5-alkylthiomethyl side chains (**7**) and to investigate their antimicrobial activity.



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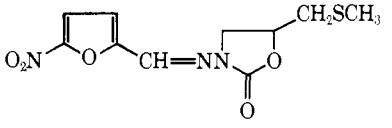
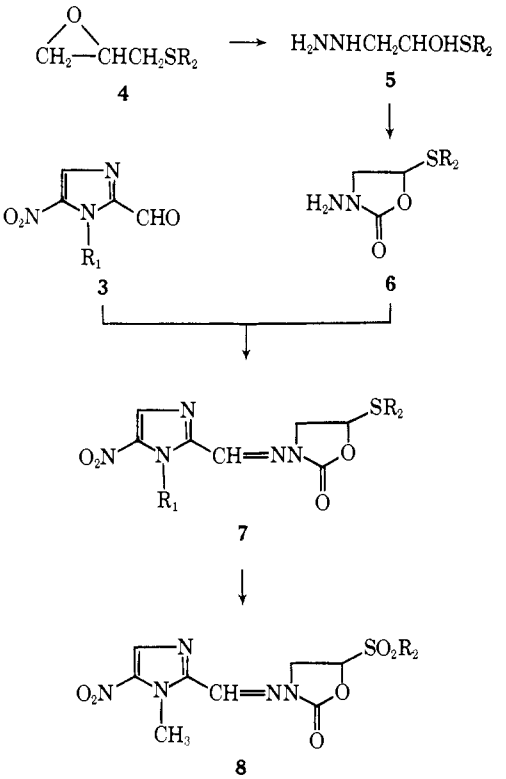


2

Chemistry.—5-Alkylthio-3-(5-nitro-1-methyl-2-imidazolyl)methyleneamino-2-oxazolidinones (**7a–7f**, Table I) were synthesized by condensation of 5-nitro-1-methylimidazole-2-carboxaldehydes[1] (**3**, R_1 = CH_3) with 5-alkylthiomethyl-3-amino-2-oxazolidinones (**6**) in MeOH–HCl. These compds were prepared according to known procedures[4] from 1-alkylthio-2,3-epoxypropanes[5] (**4**) *via* ring opening with hydrazine to **5** and reaction with diethyl carbonate. When 5-nitro-1-(2-acetoxyethyl)imidazole-2-carboxaldehyde[1] (**3**, R_1 = $C_2H_4OCOCH_3$) was condensed with **6** (R_2 = *n*-C_4H_9)



4 5 3 6 7 8

(1) Part 6: C. Rufer, H.-J. Kessler, and E. Schröder, *J. Med. Chem.*, **14**, 94 (1971).

(2) A preliminary report of part of this work has been presented at the VIth International Congress of Chemotherapy, Tokyo, August 1969.

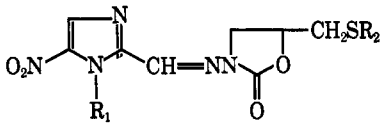
(3) R. Scuri and L. Failla, *Farmaco Ed. Sci.*, **19**, 301 (1964).

(4) Polochimica Sap S.p.A., Belgian Patent Application, 635,608 (1963); *Chem. Abstr.*, **61**, 16069 (1964).

(5) T. K. Todsen, C. B. Pollard, E. G. Reitz, *J. Amer. Chem. Soc.*, **72**, 4000 (1950).

TABLE I

SUBSTITUTED 5-ALKYLTHIOMETHYL-3-(5-NITRO-2-IMIDAZOLYL)METHYLENEAMINO-2-OXAZOLIDINONES (7)



Compd	R_1	R_2	Yield, %	Crystn solvent	Mp, °C	Formula	Analyses	Activity against *T. vaginalis*, *in vitro* MIC, μg/ml	*in vivo*[a]
a	CH_3	CH_3	30	1-Butanol	174	$C_{10}H_{13}N_5O_4S$	S	0.2	−
b	CH_3	C_2H_5	22	MeOH	134	$C_{11}H_{15}N_5O_4S$	N, S	0.1	*b*
c	CH_3	$CH(CH_3)_2$	47	EtOH	150	$C_{12}H_{17}N_5O_4S$	N, S	0.05	*b*
d	CH_3	n-C_4H_9	42	MeOH	120	$C_{13}H_{19}N_5O_4S$	N, S	0.05	+
e	CH_3	n-C_6H_{13}	17	MeOH	117	$C_{15}H_{23}N_5O_4S$	N, S	0.4	−
f	CH_3	n-C_8H_{17}	18	MeOH–water	103	$C_{17}H_{27}N_5O_4S$	N, S	0.4	Nt
g	C_2H_4OH	n-C_4H_9	35	2-Propanol–ether	134	$C_{14}H_{21}N_5O_5S$	S	0.1	−
Metronidazole								1.6	+

[a] Mice, sc infected with approx 10^6 living parasites, one daily oral treatment with 50 mg/kg for 5 subsequent days, first treatment immediately after infection. Therapeutic activity was detd on the 10th day on the presence or absence of living parasites at the site of infection. + = active ($p \leq 0.05$); − = non active ($p \leq 0.05$); Nt = not tested. [b] Active ($p \leq 0.05$) at a dose level of 200 mg/kg.

under acidic conditions, the ester was saponified and **7g** (Table I) was isolated. Compds **7a** and **7b** (Table I) were oxidized with H_2O_2 to the corresponding sulfones **8** (R_2 = CH_3 or n-C_4H_9, resp). In addition to the analytical data, measurements of the ir, uv, or nmr spectra which are in accordance with the structures shown have been carried out for all compds.

Biological Results.—No compd showed interesting *in vitro* activity against bacteria and fungi (disk assay and tube dilution assay, resp), but all of them were active *in vitro* against *T. vaginalis* (tube dilution assay). The minimal inhibitory concns (MIC values) of the title compds are listed in Table I; metronidazole[6] was taken as reference substance.

When the substituent R_1 at the imidazole moiety was Me (**7a–7f**) the optimal number of C atoms in the S side chain R_2 seems to be 3–4 (**7c,d**). This is in good accordance with the *in vivo* activity within the series; **7d** proved to be active when given orally at a dose level of 50 mg/kg to sc infected mice (Table I), in the same model the oral ED_{50} value was 16.5 mg/kg. A hydroxyethyl substituent at the N^1 atom of the imidazole ring system does not enhance the activity when R_2 is n-Bu (**7g**).

The sulfonyl compds (**8**, R_2 = CH_3, MIC = 3.1 μg/ml and R_2 = n-C_4H_9, MIC = 1.6 μg/ml, resp) are less active *in vitro* than the parent thio compds (**7a** or **7b**, resp).

Experimental Section[7]

5-Alkylthiomethyl-3-amino-2-oxazolidinones (6).—1-n-Hexylthio-2,3-epoxypropane[5] (**4**, R_2 = n-C_6H_{13}) (12 g, 69 mmoles) was added to $N_2H_4 \cdot H_2O$ (17 g) preheated to 90°. The temp rose to 110° and was maintained for 2 hr. $N_2H_4 \cdot H_2O$ was thoroughly removed *in vacuo*. The residue (**5**, R_2 = n-C_6H_{13}) was very hygroscopic, mp 45–50°. The crude material in 11 ml of MeOH and diethyl carbonate (7.8 g, 67 mmoles) was added to a soln of 78 mg (3.3 mg-atoms) of Na in 3 ml of MeOH. The mixt was heated to bp and solvent was distd during 1.5 hr (17 ml of dist; theor amt, 14 ml of MeOH and 6.2 ml of EtOH). The crude residue (**6**, R_2 = n-C_6H_{13}), 14.7 g (94%), was used for condensn. 1-n-Octylthio-2,3-epoxypropane (**4**, R_2 = n-C_8H_{17}) was prepd according to the method of Todsen, *et al.*,[5] bp 78–81° (0.05 mm), $n^{25}D$ 1.4706, and yielded **6** (R_2 = n-C_8H_{17}) in 77% yield by the procedure described above. All the other compds (**6**) were known from the lit.[4]

Substituted 5-Alkylthiomethyl-3-(5-nitro-2-imidazolyl)methyleneamino-2-oxazolidinones (7) (Table I).—Compd **3**[1] (0.01 mole) and **6** (0.01 mole) in 6 ml of MeOH were refluxed for 2 hr with 0.9 ml of satd MeOH–HCl (about 12.5 N). The mixt was cooled, and the ppt was filtered (**7a**), or the substance was pptd with H_2O and recrystd (**7b–7f**), or the substance was pptd with i-PrOH–Et_2O and recrystd (**7g**). Starting material for **7g** was 5-nitro-1-(2-acetoxyethyl)imidazole-2-carboxaldehyde (**3**, R_1 = $C_2H_4OCOCH_3$).

5-Methylsulfonylmethyl-3-(5-nitro-1-methyl-2-imidazolyl)methyleneamino-2-oxazolidinone (8, R_2 = CH_3).—H_2O_2 (2 ml, 30%) was added dropwise to **7a** (0.6 g, 2 mmoles) in 12 ml of HOAc. After 3 days at 20° solvent was removed *in vacuo* and the residue was triturated with H_2O. The ppt was filtered and recrystd from Me_2CO–H_2O, yield 0.17 g (26%), mp 218°. *Anal.* ($C_{10}H_{13}N_5O_6S$) S.

5-n-Butylsulfonylmethyl-3-(5-nitro-1-methyl-2-imidazolyl)methyleneamino-2-oxazolidinone (8, R_2 = n-C_4H_9).—Synthesized as described for **8** (R_2 = CH_3), but when the mixt was kept overnight at 20°, the substance pptd. It was filtered off and recrystd from EtOAc–2-PrOH, yield 0.7 g (94%), mp 162°. *Anal.* ($C_{13}H_{19}N_5O_6S$) S.

(6) C. Cosar, *Arzneim.-Forsch.*, **16**, 23 (1966).

(7) Melting points are uncor and taken on a Tottoli melting point apparatus (Fa. W. Büchi, Switzerland). Where anal. results are indicated only by symbols of the elements or functions, values found for those elements or functions were within ±0.4% of the calcd values.