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PYRROLE ANALOGUES OF CHLORAMPHENICOL. III. SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF *DL–THREO*–1–(1–METHYLSULFONYLPYRROLE–3–YL)–2–DICHLOROACETAMIDOPROPANE–1,3–DIOL

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Abstract: A seven–stage synthesis of a pyrrole analogue of chloramphenicol (**9**) is described. The compound exhibits a significant antibacterial activity, over the 3% to 50% range of the chloramphenicol activity; over the 6% to 100% range of the thiamphenicol activity and florfenicol.

Keywords: chloramphenicol; synthetic analogues of antibiotics; pyrrole analogue of chloramphenicol.

Among the synthesised over 2.000 compounds (1) of the structure similar to chloramphenicol, only three have found use in therapy: thiamphenicol, azidamphenicol and florfenicol (2,3). Quite recently (1980), a fluorine analogue of thiamphenicol – Florfenicol – was introduced into veterinary therapy. This analogue differs from the parent compound by the presence of a fluorine atom ($-CH_2OH \rightarrow -CH_2F$) (3;4). Analogues of chloramphenicol were synthesized, one or two fluorine atoms took place instead of one or two chlorine atoms in the acetamido group. These compounds are insignificantly active (5). Interesting, antibacterial activity show pyrrole analogues of chloramphenicol (6,7,8).

EXPERIMENTAL

Methanesulfonamide and dimethoxytetrahydrofurane were the starting substrates. The 1–methylsulfonylpyrrole (**1**) obtained was the subject to reaction with bromoacetyl bromide to afford a mixture of two isomeric ketones, *viz.* (**2**) and (**3**), which were separated by column chromatography. The transformation of bromoketone (**2**) into the target compound (**9**) was accomplished by means of the modified methods developed by Šorm (9) and Smoleński (10).

Bromoketone (**2**) reacts with hexamethylenetetraamine to yield a crystalline adduct (**4**) which, in turn, was transformed into aminoketone (**5**) as a result of hydrolysis. This compound was further transformed into amide (**6**) by means of dichloroacetyl chloride, and this was hydroxymethylated (11,12,13), while the main product of the reaction (**7**) was subjected to the Meerwein–Ponndorff reduction. This method enables to obtain mainly a compound of the desired configuration, i.e. *DL–threo* (**9**). The reaction scheme is outlined in Figure 1.

The antibacterial activity of compound **9** was determined using the method presented by Sahm (14).

^1H NMR and ^{13}C NMR spectra were recorded on a Bruker AC 200F spectrometer, using TMS as an internal standard. All the melting point data were measured with a Büchi 535 apparatus and are uncorrected. Analytical TLC was performed using Merck silica gel 60 F_{254} plates. The solvent systems used were (v:v): A = C_6H_{14}/AcOEt (1 : 2); B = C_6H_{12}/CH_2Cl_2 (1 : 1); C = AcOEt/EtOH/AcOH/H_2O (3 : 2 : 1 : 1); D = benzene/CH_2Cl_2/EtOH/AcOEt (5 : 5 : 2 : 1).

A column chromatography was performed with silica gel 60 (Merck) as the adsorbent.

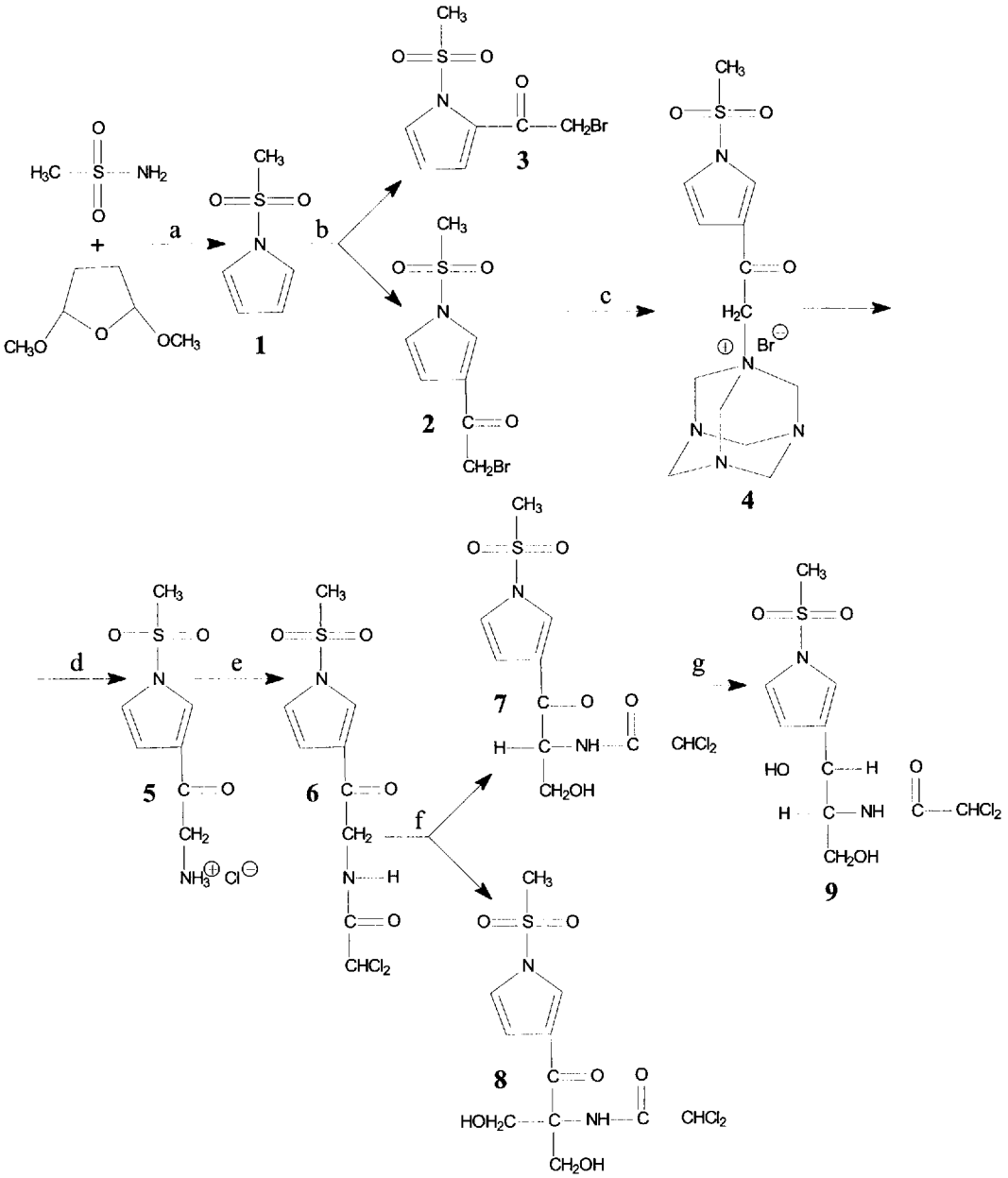
RESULTS

1–methylsulfonylpyrrole (**1**)

A mixture of methanesulfonamide (45.7 g, 0.48 M), dimethoxytetrahydrofurane (75.2 ml, 0.58 M) and AcOH (250 ml) was refluxed for 4 hours. The solution was concentrated under reduced pressure. Crude product (69.3 g) was crystallized from chloroform to give 51 g of compound **1**.

3–bromoacetyl–1–methylsulfonylpyrrole (**2**) and 2–bromoacetyl–1–methylsulfonylpyrrole (**3**)

To a mixture of 27.2 g (0.2 M) of $AlCl_3$ in 1,2–dichloroethane (340 ml), bromoacetyl bromide



Scheme 1. Synthesis of compound **9**.
Reagents and conditions: (a) AcOH; (b) Br–CH_2–COCl, $AlCl_3$, Cl–CH_2–CH_2–Cl; (c) $(CH_2)_6N_4$, $CHCl_3$; (d) HCl, H_2O/EtOH; (e) Cl_2–CH–COCl, Et_3N, Me_2CO; (f) CH_2O, $NaHCO_3$, H_2O/EtOH; (g) i-PrOH, $(i\text{-PrO})_3Al$.

(36.3 g, 0.18 M) was added. A solution of **1** (8.89 g, 0.06 M) in 1,2-dichloroethane (30 ml) was added within 0.5 h. The mixture was stirred for 2 h and then poured into crushed ice (300 g). This was stirred for 1 h at r.t. The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 150 ml). The combined organic layers were washed with brine (2 × 150 ml), dried (Na_2SO_4) and evaporated to give the crude products **2** and **3**. The two products were separated by column chromatography (system B) and rechromatographed to afford 11.26 g of **2** and 0.74 g of **3**.

N-[(1-methylsulfonylpyrrole-3-yl)-carbonylmethyl]-hexamethylenetetraminium bromide (**4**).

Compound **2** (17.38 g, 0.06 M) was dissolved in anhydrous $CHCl_3$ (250 ml) and the solution was warmed up to 50°C. Hexamethylenetetraamine

(12.7 g, 0.06 M) was dissolved in anhydrous $CHCl_3$ (100 ml), warmed up to 50°C and added to the solution of compound **2**. The mixture was stirred at 50°C for 4 h, then left overnight at 4°C. The product (**4**) was collected by filtration. From the mother liquors a second crop of **4** was obtained; total yield 26.52 g.

3–aminoacetyl–1–methylsulfonylpyrrole hydrochloride (**5**)

A mixture of conc. aq. HCl and 95% EtOH (19 ml + 38 ml) was added to 16.52 g (0.041 M) of compound **4** and the resulted suspension was stirred at 30°C for 1 h, then left overnight at 5°C. The crude compound **5**, containing NH_4Cl, was collected by filtration, and to the filter cake a mixture of conc. aq. HCl and H_2O (0.1 ml + 8.5 ml) was added. The suspension was stirred at 25°C for 15 min.. Next, it was cooled to 10°C and left at this temp. for 15 min. The pure product **5** (8.53 g) was collected by filtration.

N–[(1–methylsulfonylpyrrole–3–yl)–carbonylmethyl]–2,2–dichloroacetamide (**6**)

To a well–stirred at 0°C mixture of aminoketone **5** (8.54 g, 25 mM) and anhydr. acetone (90 ml) dichloroacetyl chloride (9.58 g, 65 mM) was slowly added, then anhydr. triethylamine (9.38 g, 67 mM) was added dropwise. The reaction mixture was stirred for 3 h at 0°C, then left overnight at 10°C. The precipitate was filtered off, and the filtrate was evaporated under reduced pressure to give a sirup, from which a product (2.90 g) crystallized within a few days. To the mother liquors, containing triethylamine hydrochloride, H_2O (40 ml) was added and the mixture was extracted with AcOEt (4 × 40 ml). The combined organic layers were dried (Na_2SO_4) and concentrated to give a second crop of the product **6** (0.37 g). The combined crops were recrystallized from 65 ml of methanol–acetone (2:1) to afford 3.27 g of pure **6**.

DL–2–dichloroacetamido–3–hydroxy–1–(1–methylsulfonylpyrrole–3–yl)–propan–1–one (**7**) and 2–dichloroacetamido–3–hydroxy–2–hydroxymethyl–1–(1–methylsulfonylpyrrole–2–yl)–propan–1–one (**8**)

A mixture of dichloroacetamide **6** (0.39 g, 1.2 mM), 36% formaldehyde aq. solution (0.37 ml, 4.42 mM), and $NaHCO_3$ (18 mg) in 96% EtOH (1.8 ml) was stirred for 2.5 h at r.t., then was concentrated in vacuo. TLC (system A) showed 2 products: **7** and **8**, which were separated by column chromatography (system A), yielding, respectively, 0.24 g of compound **7** and 0.14 g of compound **8**.

DL–threo–2–dichloroacetamido–1–(1–methylsulfonylpyrrole–3–yl)–propane–1,3–diol (**9**).

A mixture of **7** (1.39 g, 4.1 mM), 1M aluminum isopropoxide in anhyd. propan–2–ol (8.3 ml, 8.2 mM) and anhyd. propan–2–ol (13.2 ml) was heated for 10 h at 65°C, passing through the reaction pot a slow stream of dry argon. Afterwards, TLC showed no remaining starting material (system A). Then, to the reaction mixture EtOH and H_2O (9 ml + 2.7 ml) were added, and the solvent was evaporated under reduced pressure. Next, silica gel (3.9 g), EtOH (10 ml) and AcMe (19.3 ml) were added, and the solvent was removed under reduced pressure. The residue powder was poured on a column of silica gel (10 cm × 1.5 cm diam.). Elution with MeOH/AcMe/AcOEt (2:1:1) afforded crude **9**, which was purified by column chromatography (system A) to give compound **9** (1.04 g) as chromatographically homogeneous glassy solid, which crystallized on standing.

Elementary analysis of compound **9**:

calculated: C=34.78; H=4.06; N=8.12; Cl=20.58;
found: C=34.72; H= 4.12; N=8.21; Cl=20.45.

Physical and spectral data of compounds **1** – **9** are presented in Table 1.

Determination of antibacterial activity

The antibacterial activity of compound **9** was determined by establishing their minimal inhibitory concentrations (M.I.C.) against strains of microorganisms, as described by Sahm (14).

Simultaneously, the M.I.C.'s of chloramphenicol and thiamphenicol were determined.

Results of the antibacterial spectrum assay are presented in Table 2.

DISCUSSION

The seven–stage synthesis of compound **9** was performed by means of the classical method used then, when the derivatives of pyrrole are obtained as well as by means of some selected methods used for the forming of the three–carbon aliphatic fragment of chloramphenicol. There is no information in the literature on the compounds which we have synthesized, i. e. **2** – **9**.

Compound **2** during its reaction with urotropine (15;16) was subjected to the transformation into a quaternary ammonium salt **4**. The hydrolysis (15;16;17) of this salt gave hydrochloride of aminoketone **5**, easily subjected to the decomposition in alkaline or neutral media, even during a chromatographic procedure on silica gel. The transformation of aminoketone **5** into amide **6** (18;19) was carried out with an excess of

Table 1. Physical and spectral data of compounds **1 – 9**

Compd.	Formula	Molecular mass	R_f (system)	M.p. [°C]	Yield [%]	^{1}H NMR, δ (ppm) solvent	^{13}C NMR, δ (ppm) solvent
1	$C_5H_7NO_2S$	145	–	58	73	3.12 (s, 1H, CH_3), 6.35 (t, 2H, $C_3H + C_4H$, Ar, J = 2.28), 7.10 (t, 2H, $C_2H + C_5H$, Ar, J = 2.31) $CDCl_3$	42.59 (CH_3), 113.37 ($C_3 + C_4$, Ar), 120.31 ($C_2 + C_5$, Ar) $CDCl_3$
2	$C_7H_8BrNO_3S$	266	A=0.77 B=0.32	112.2	69.1	3.71 (s, 3H, CH_3), 4.31 (s, 2H, CH_2), 6.34 (t, 1H, C_4H, Ar, J = 3.24), 7.22 (dd, 1H, C_5H, Ar, J = 1.64, 3.86) 7.61 (dd, 1H, C_2H, Ar, J = 1.64, 3.17) $CDCl_3$	31.16 (CH_3), 42.95 (CH_2), 110.51 (C_4, Ar), 125.66 (C_2, Ar), 129.76 (C_3, Ar), 131.08 (C_5, Ar), 180.79 (C=O) $CDCl_3$
3	$C_7H_8BrNO_3S$	266	A=0.70 B=0.19	117.5	4.6	3.28 (s, 3H, CH_3), 4.23 (s, 2H, CH_2), 6.78 (dd, 1H, C_3H, Ar, J = 1.65, 3.32), 7.15 (dd, 1H, C_5H, Ar, J =2.14, 3.29), 7.82 (t, 1H, C_4H, J = 1.9) $CDCl_3$	31.20 (CH_3), 43.21 (CH_2), 112.76 (C_4, Ar), 121.65 (C_3, Ar), 125.26 (C_5, Ar), 125.62 (C_2, Ar), 186. 43 (C=O) $CDCl_3$
4	$C_{13}H_{20}BrN_5O_3S$	406	–	176.7(R)	96.5	3.88 (s, 3H, CH_3), 4.53 and 4.59 (2 × d, 6H, 3 × CH_2N, $J_{Ha,Hb}$ = 12.60), 4.76 (s, 2H, CH_2), 5.51 (s, 6H, 3 × CH_2N), 6.53 (t, 1H, C_4H, Ar, J = 3.39), 7.77 (2 × dd, 2H, $C_2H + C_5H$, Ar) DMSO–d_6	42.67 (CH_3), 57.50 (CH_2), 70.58 and 78.93 (6 CH_2, urotropin), 111.03 (C_4, Ar), 125.69 (C_2, Ar), 129.95 (C_3, Ar), 131.50 (C_5, Ar), 179.07 (C=O) DMSO–d_6
5	$C_7H_{11}ClN_2O_3S$	238.5	C=0.47	217.3(R)	87.9	3.77 (s, 3H, CH_3), 4.49 (s, 2H, CH_2), 6.45 (t, 1H, C_4H, Ar, J = 3.23), 7.55 (dd, 1H, C_5H, Ar, J = 1.65, 3.95), 7.72 (dd, 1H, C_2H, Ar, J = 1.69, 3.15) CD_3OD	2.67 (CH_3), 45.33 (CH_2), 111.65 (C_4, Ar), 127.34 (C_2, Ar), 129.84 (C_3, Ar), 132.33 (C_5, Ar), 181.54 (C=O) CD_3OD
6	$C_9H_{10}Cl_2N_2O_4S$	313	A=0.74 D=0.54	129.5	41.4	3.72 (s, 3H, CH_3), 4.64 (d, 2H, CH_2, J = 4.64), 6.03 (s, 1H, $CHCl_2$), 6.36 (t, 1H, C_4H, Ar, J = 3.5), 7.27 (dd, 1H, C_5H, Ar, $J_{5,2}$ = 1.58, $J_{5,4}$ = 2.7) 7.54 (bs, 1H, NHCO), 7.65 (dd, 1H, C_2H, Ar, J = 1.60, 3.11) $(CD_3)_2CO$	43.03 (CH_3), 46.42 (CH_2), 65.99 ($CHCl_2$) 110.85 (C_4, Ar), 125.04 (C_2, Ar), 129.64 (C_3, Ar), 131.09 (C_5, Ar), 164.16 (NC=O), 182.31 (C=O) $(CD_3)_2CO$
7	$C_{10}H_{12}Cl_2N_2O_5S$	343	A=0.54	150.4	55.8	3.78 (s, 3H, CH_3), 3.96 (m, 2H, CH_2OH), 4.54 (m, 1H, CH_2OH), 5.27 (m, 1H, CO–CH–N), 6.41 (t, 1H, C_4H, Ar, J = 3.4), 6.53 (s, 1H, $CHCl_2$), 7.56 (dd, 1H, C_5H, Ar, J = 1.65, 3.85), 7.62 (dd, 1H, C_2H, Ar, J = 1.64, 3.17), 8.05 (bs, 1H, NHCO) $(CD_3)_2CO$	43.03 (CH_3), 58.77 (CHNH), 63.16 (CH_2OH), 67.14 ($CHCl_2$), 111.19 (C_4, Ar), 126.30 (C_2, Ar), 131.43 (C_3, Ar), 131.52 (C_5, Ar), 164.41 (NC=O), 186.09 (C=O) $(CD_3)_2CO$
8	$C_{11}H_{14}Cl_2N_2O_6S$	373	A=0.18	158.3	30.4	3.69 (s, 3H, CH_3), 4.07 (s, 4H, 2 × CH_2OH), 6.30 (t, 1H, C_4H, Ar, J = 3.4), 6.31 (s, 1H, $CHCl_2$), 7.43 (dd, 1H, C_5H, Ar, J = 1.63, 3.88), 7.59 (dd, 1H, C_2H, Ar, J = 1.64, 3.20) CD_3OD	43.12 (CH_3), 62.19 (CH_2OH), 67.11 ($CHCl_2$), 69.49 (CNH), 110.43 (C_4, Ar), 124.36 (C_2, Ar), 130.31 (C_5, Ar), 131.49 (C_3, Ar), 165.05 (NC=O), 189.44 (C=O) CD_3OD
9	$C_{10}H_{14}Cl_2N_2O_5S$	345	A=0.33	133.4	74.3	3.43 (s, 3H, CH_3), 3.72 (m, 2H, CH_2OH), 4.24 (bs, 1H, CH_2OH), 4.30 (m, 1H, CHN), 4.83 (d, 1H, CHOH, J = 4.91), 5.52 (m, 1H, CH–Ar), 6.21 (t, 1H, C_4H, Ar, J = 3.40), 6.34 (dd, 1H, C_5H, Ar, J = 1.68, 3.39), 6.46 (s, 1H, $CHCl_2$), 7.11 (dd, 1H, C_2H, Ar, J = 1.76, 3.30), 7.61 (d, 1H, NHCO, J = 9.06) $(CD_3)_2CO$ 3.33 (s, 3H, CH_3), 3.58 (m, 2H, CH_2OH), 4.21 (m, 1H, CHN), 5.33 (d, 1H, CH–Ar, J = 2.75) 6.17 (t, 1H, C_4H, Ar, J = 3.40) 6.29 (dd, 1H, C_5H, Ar, J = 1.68, 3.39), 6.31 (s, 1H, $CHCl_2$), 7.04 (dd, 1H, C_2H, Ar, J = 1.74, 3.73) $D_2O \rightarrow (CD_3)_2CO$	43.14 (CH_3), 55.55 (CNH), 62.55 (CH_2OH), 64.89 ($CHCl_2$), 67.55 (CH–Ar), 111.64 (C_4, Ar), 113.49 (C_2, Ar), 123.45 (C_5, Ar), 135.86 (C_3, Ar), 164.64 (NC=O) $(CD_3)_2CO$

Table 2. M.I.C.'s (μg/ml) of chloramphenicol and its analogues.

Microorganisms	Compound			
	Chloramphenicol (*D–threo–*)	Thiamphenicol (*D–threo–*)	Florfenicol (*D–threo–*)	Compound **9** (*DL–threo–*)
Staphylococcus aureus Cowan ATCC 12600	0.5	0.5	0.5	8
*Streptococcus pyogenes** 5603	2	4	1	64
*Streptococcus pneumoniae** 3546	2	2	2	32
Bacillus subtilis ATCC 6051	1	2	0.5	8
Pseudomonas aeruginosa CCM 1960	16	32	16	32
*Pseudomonas aeruginosa** 5172	256	256	256	32
Escherichia coli ATCC 11775	2	4	2	16

* – clinical isolates

dichloroacetyl chloride in order to avoid the decomposition of the substrate in the presence of triethylamine. The aldol condensation of compound **6** with formaldehyde (12;13;20) in the presence of $NaHCO_3$ has resulted, according to the expectations, in a mixture of two compounds, being the products of the addition of 1 or 2 M of HCHO, i. e. **7** and **8**. The structure of these compounds was confirmed by means of the NMR spectrometry.

The reduction of the oxo– group in compound **7** can, depending on the used reducing reagents, result in a product having either a *threo–* or *erythro–* configuration. It is possible to obtain the desired compound **9** with the *threo–* configuration, due to the reduction with aluminum isopropoxide according to the Meerwein–Ponndorff method (10). The hardly filtrated aluminum hydroxide was eliminated by its precipitation on silica gel, while compound **9** was extracted and purified by means of column chromatography.

^1H NMR and ^{13}C NMR spectra of the final product were compared with the spectra of chloramphenicol as well as with the data presented in the literature (1), regarding the spectra of *erythro–*chloramphenicol isomer. The data thus obtained, clearly indicate that compound **9** has a *threo–* configuration; its *erythro–* configuration was excluded. The $J_{1',2'}$ coupling constants are practically identical for compound **9** and for chloramphenicol (2.75 Hz and 2.4 Hz). A great similarity of signals of the aliphatic fragment for compound **9** and chloramphenicol also confirms the same configuration of these fragments. *Erythro–*chloramphenicol has $J_{1',2'}$ value 6.0 Hz (1) within the limits of the work ^1H NMR spectra of chloramphenicol and thiamphenicol made, which were compared with NMR spectra of compound **9** (Table 3). The values $J_{1',2'}$ has matched the literature data (21;22;23).

Table 3. ^1H NMR data chloramphenicol and thiamphenicol.

Compounds	^1H NMR δ (ppm) solvent
Chloramphenicol	3.57 – 3.80 (m, 2H, CH_2OH), 4.11 (m, 1H, CHN), 5.15 (d, 1H, CH–Ar, J = 2.55), 6.23 (s, 1H, $CHCl_2$), 7.65 and 8.17 (2 × d, 4H, Ar) CD_3OD
Thiamphenicol	3.10 (s, 3H, CH_3), 3.60 – 3.80 (m, 2H, CH_2OH), 4.11 (m, 1H, CHN), 5.14 (d, 1H, CH–Ar, J = 2.65), 6.24 (s, 1H, $CHCl_2$), 7.64 and 7.85 (2 × d, 4H, Ar) CD_3OD

The results of the efforts to establish the minimal concentration inhibiting the growth of microorganisms have indicated that compound **9**, being the racemate (*DL*), is 2–16 times less active than chloramphenicol. The derivative inhibited clinical strain of the *Pseudomonas aeruginosa*, resistant to chloramphenicol, thiamphenicol and florfenicol.

A great number of data, presented in the professional literature regarding the activity of

D–threo– enantiomers of various analogues of chloramphenicol and their proper racemates (*DL–threo–*) indicate that the antibacterial activity of a racemate is always twofold less as the activity of the corresponding *D–threo–* compound. When calculating it per *D–threo–*enantiomer, present in the racemate **9**, its activity is 2–8 times smaller than that of a *D–threo–*chloramphenicol, i. e. it is closer to the activity of thiamphenicol (2) or cetophenicol (24).

The presence of biological activity in compound **9** can suggest that other derivatives of chloramphenicol, which contain pyrrole rings and other electronegative groups linked to them, can indicate greater activity than that of chloramphenicol, but with a lesser toxicity at the same time. It can be suspected that the biotransformation of the 1–methylsulfonylpyrrole fragment is carried out through a different path than that of the 4–nitrophenyl group.

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