Synthesis and Properties of the Pyrrole Analogs of Chloramphenicol

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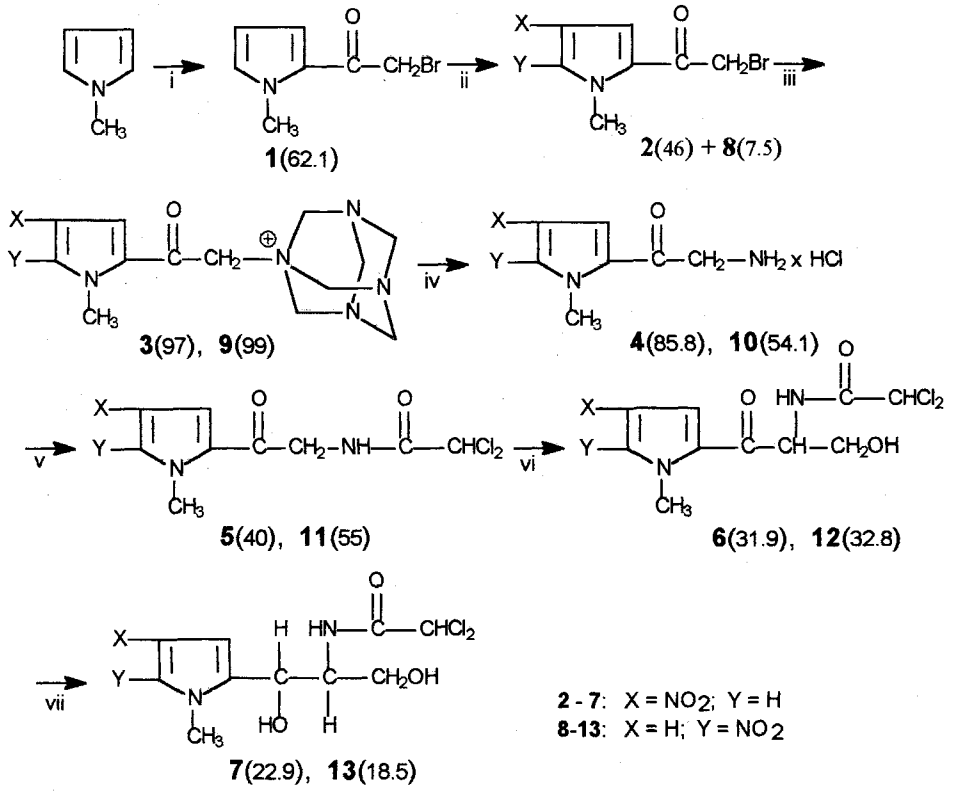
(Received for publication July 26, 1999)

Among the synthesised over 2,000 compounds[1] of the structure similar to chloramphenicol, only three found use in therapy: thiamphenicol, azidamphenicol and florfenicol [2,3]. Chloramphenicol esters are also used. The only derivative with the activity greater than chloramphenicol is perchlorylchloramphenicol ($-NO_2 \rightarrow -ClO_3$), a compound possessing explosive properties[4]. The heteroaromatic analogs of chloramphenicol are insignificantly active or inactive. The only exception is the thiophene analogue, DL-*threo*-1-(5-nitro-2-thienyl)-2-dichloroacetamido-propane-1,3-diol, with the activity of 50% in relation to the racemic chloramphenicol[5]. Pyrrole analogs are not known. Remote toxicity, specific for chloramphenicol, is probably caused by the presence of a fragment of nitrobenzene, which is subject to metabolisation to, among others, an aniline derivative ($-C_6H_4-NO_2 \rightarrow -C_6H_4NH_2$) and other metabolites of the nitro group.[6] The substitution of either the nitro group or the benzene ring by other fragments of the molecule shall result in different metabolites with perhaps a reduced or eliminated remote toxicity.

In the present paper we are presenting the synthesis of two pyrrole analogs of chloramphenicol, compounds **7** and **13** (Scheme 1). We had expected that the presence of the $N-CH_3$ group shall cause: (a) the reduction of the toxic properties, (b) the preventing of the N–H pyrrole participation in the undesired adverse reactions and (c) the blocking of the creation of a new system of hydrogen bonds

Scheme 1. Synthesis of **7** and **13**.



Reagents and conditions: i) $BrCH_2COBr$, $AlCl_3$, Et_2O; ii) HNO_3, Ac_2O, CH_2Cl_2, (-) 55°C, then SiO_2; iii) $(CH_2)_6N_4$, $CHCl_3$; iv) HCl, H_2O/EtOH; v) $Cl_2CHCOCl$, Et_3N, Me_2CO; vi) CH_2O, $NaHCO_3$, H_2O/EtOH; vii) i-PrOH, $(i\text{-}PrO)_3Al$.

Synthetic yields (%) in each step were presented in parentheses.

Table 1. Physico-chemical properties of compounds **7** and **13**.

No.	R_f (Solvents)	MP (°C)	IR (ν_{max}, nujol, cm^{-1})	^1H NMR (200 MHz; $D_2O \rightarrow (CD_3)_2CO$; δ ppm; J Hz)	^{13}C NMR (50 MHz; CD_3OD; δ ppm)
7	0.43 ($CHCl_3$-MeOH= =85:15)	110	3400, 1690, 1460 and 1376	3.67 (2H, m, CH_2), 3.79 (3H, s, NCH_3), 4.23 (1H, m, C*H*NH), 5.18 (1H, d, $J_{1',2'}$ = = 2.84, C*H*OH), 6.46 (1H, s, $CHCl_2$), 6.62 and 7.69 (2H, 2 × d, $J_{3,5}$ = 1.94, pyrrole $C_3H + C_5H$)	35.30 (NCH_3), 55.29 (CHNH), 61.85 (CH_2), 64.55 ($CHCl_2$), 67.41 (CHOH), 103.98 and 124.69 ($C_3 + C_5$, pyrrole), 135.13 and 135.89 ($C_2 + C_4$, pyrrole), 164.87 (CONH)
13	0.52 (C_6H_6-CH_2Cl_2- -EtOH-AcOEt = = 5:5:2:1) 0.54 ($CHCl_3$-MeOH= =85:15)	146.4	3400, 1670, 1460 and 1373	[a] 3.76 (2H, m, CH_2), 3.97 (3H, s, NCH_3), 4.20 (1H, m, C*H*NH), 5.13 (1H, d, $J_{1',2'}$ = = 2.94, C*H*OH), 6.29 (1H, s, $CHCl_2$), 6.25 and 7.13 (2H, 2 × d, $J_{3,4}$ = 4.48, pyrrole $C_3H + C_4H$)	34.12 (NCH_3), 55.64 (CHNH), 61.36 (CH_2), 64.71 ($CHCl_2$), 66.97 (CHOH), 108.66 and 114.16 ($C_3 + C_4$, pyrrole), 139.17 and 142.65 ($C_2 + C_5$, pyrrole), 166.30 (CONH)

[a] - In CD_3OD

by the pyrrole N–H group and aliphatic fragment of the molecule, destabilizing the specific conformation of this fragment[1,7].

N-Methylpyrrole was the substrate, which was subject to reaction with bromoacetyl bromide in the presence of $AlCl_3$. The obtained crude 2-bromoacetyl-1-methylpyrrole **1** was nitrated, obtaining a mixture of 2-bromoacetyl-1-methyl-4-nitropyrole **2** and 2-bromoacetyl-1-methyl-5-nitropyrrole **8**. These compounds were separated by means of column chromatography (silicagel, $C_6H_6/CH_2Cl_2 = 1:1$). The transformation of the two bromoketones into the target compounds **7** and **13** was conducted by means of the modified methods of ŠORM[8] and SMOLEŃSKI[9], used in the industrial production of chloramphenicol. Compound **2** was then subject to reaction with hexamethylenetetraamine, obtaining quaternary ammonium salt **3**, which, in turn, was transformed into aminoketone **4** in result of hydrolysis (HCl/H_2O - EtOH). This compound was further transformed into amide **5** by means of dichloroacetyl chloride and was hydroxymethylated while the product of reaction **6** was subject to Meerwein-Ponndorff reduction. The use of this method selectively results in a compound **7** with the desired DL-*threo* configuration, with a minimum addition of the DL-*erythro* product. Nitroketone **8** was identically transformed into compound **13**.

The structures of compounds **2**~**13** were confirmed by means of ^1H NMR and ^{13}C NMR spectrometry. The *threo* configuration of the aliphatic fragment of compounds **7** and **13** have confirmed the $J_{1',2'}$ values (2.84 Hz and 2.94 Hz, respectively) close to the $J_{1',2'}$ value of chloramphenicol

Table 2. MIC's (μg/ml) of chloramphenicol and its analogs

Strain No.	Derivative			
	I	II[a]	**7**[b]	**13**[b]
Sarcina lutea[c]	1		4	>250
Staphylococcus aureus ATCC 12600	0.5	25	4	>250
Bacillus subtilis ATCC 6051	0.5		8	>250
Pseudomonas aeruginosa CCM 1960	16	100	64	>250
Proteus mirabilis[c]	8		64	32
Escherichia coli ATCC 11775	2	50	16	4
Salmonella typhi[c]	2		16	8

I - D-*threo*-chloramphenicol
II - D-*threo*-thiamphenicol
[a] - Literature data [10]. Microorganisms: *S. aureus* 209; *Ps. aeruginosa* 211; *E. coli* 198;
[b] - DL-*threo*
[c] - Clinical isolates

(2.4 Hz)[1]. *erythro*-Chloramphenicol has $J_{1',2'}$ value=6.0 Hz[1]. The direct comparison of the ^{1}H and ^{13}C NMR spectra of compounds **7** and **13** with chloramphenicol spectra have shown significant similarity of their aliphatic fragments.

The antibacterial activity of compounds **7** and **13** was determined using the method presented by SAHM[11]. The obtained initial results allow to state that the racemic compound **7** shows the activity 4~16 times smaller than that of chloramphenicol; when calculated into the included D-*threo* enantiometer −2 to 8 times smaller. Compound **13** (DL-*threo*) presents the selective significant activity only with regard to strains from the Enterobacteriaceae family.

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