A 6-Bromocoumarin Analog of Chloramphenicol [1]

Ramachandra V. Joshi and Virupax V. Badiger*

Department of Chemistry, Karnatak University,
Dharwad-580003, India

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dl-threo-2-Dichloroacetamidol-1-[3-(6-bromocoumarinyl)]propane-1,3-diol (**7**) was synthesized according to Sorm's method. The fragmentation of dichloroacetamidomethyl 3-(6-bromocoumarinyl)ketone (**4**) under electron impact is reported. The results of *in vitro* antibacterial screening of the newly synthesized compounds have been presented.

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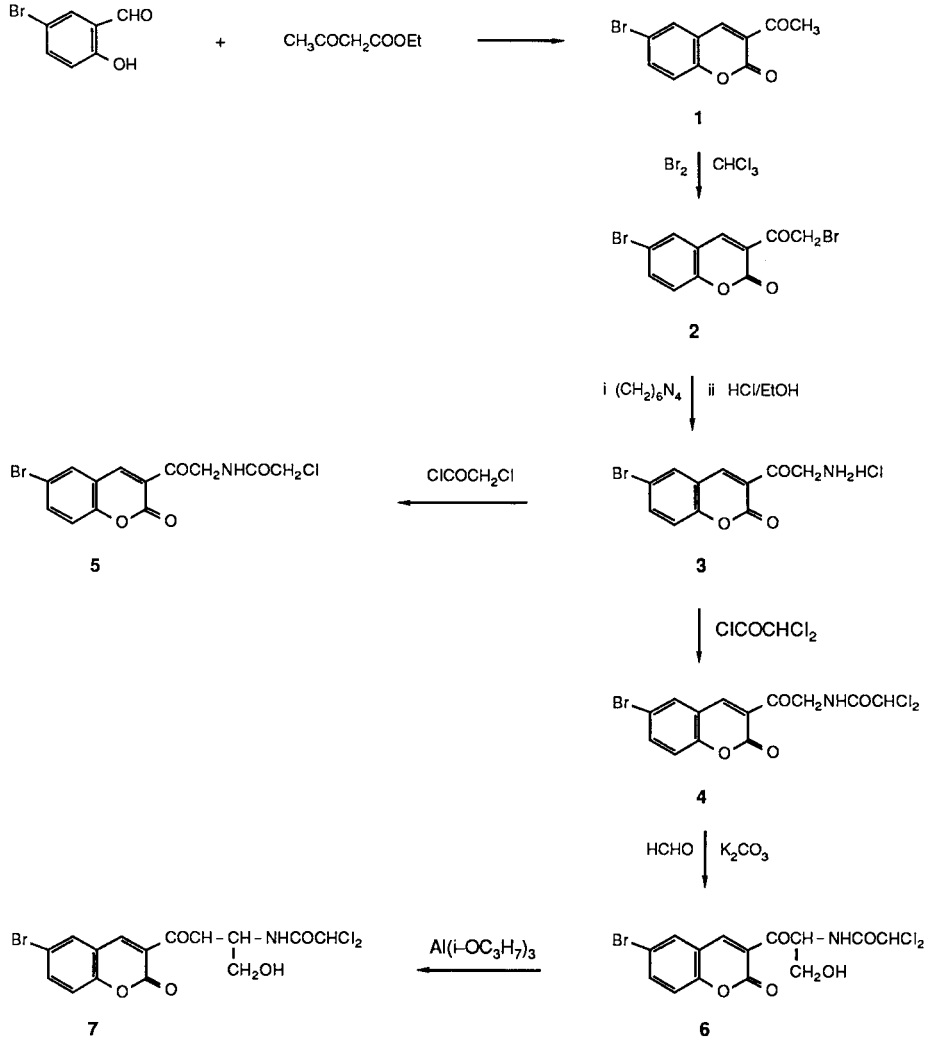
Although a large number of analogs of chloramphenicol have been prepared and studied in biological system specific structural requirements for maximum antibacterial activity have not been fully determined. However comparison of the relative activities of various analogs suggest that optimum microbiological activity may be dependent on the presence of a flat surface (phenyl moiety) with an electron rich substituent in the para position.

On the basis of these observations and in continuation of the synthesis and antimicrobial studies of various heterocyclic analogs of chloramphenicol [2-5], we have extended our interest in preparing the bromosubstituted coumarin analog of chloramphenicol in view of the fact that coumarin derivatives are well known for the antibac-

Scheme 1



terial activity [6].

This paper reports the synthesis, the ir and nmr studies of *dl-threo*-2-dichloroacetamido-1-[3-(6-bromocoumarinyl)]-propane-1,3-diol (**7**), together with the mass spectral studies of dichloroacetamidomethyl 3-(6-bromocoumarinyl)ketone (**4**). It also describes the result of *in vitro* antibacterial screening of compounds **4-7**. The modified route due to Sorm, *et al.* was adopted (Scheme 1).

3-Acetyl-6-bromocoumarin (**1**) [7] served as the starting material for the reaction sequence. This was further converted to the dichloroacetamide **4** after several stages as described earlier [2-4]. Similarily the chloroacetamide **5** was obtained. But as expected difficulty was again encountered in getting the pure hydroxymethylated compound **6**. However by using similar procedure as described earlier [3], 2-dichloroacetamido-3-hydroxy-1-[3-(6-bromocoumarinyl)]-1-propanone could be obtained as colourless silky needles. This compound on modified Meerwein-Pondorf Verley reduction method suggested by Cutler, *et al.* [8] gave a red oil which on repeated crystallisation either with benzene or ethylene chloride yielded the desired compound **7**.

The structures of the compounds **2,4,6** and **7** were confirmed by their ir and nmr studies whereas that of compound **5** was confirmed by the ir spectra.

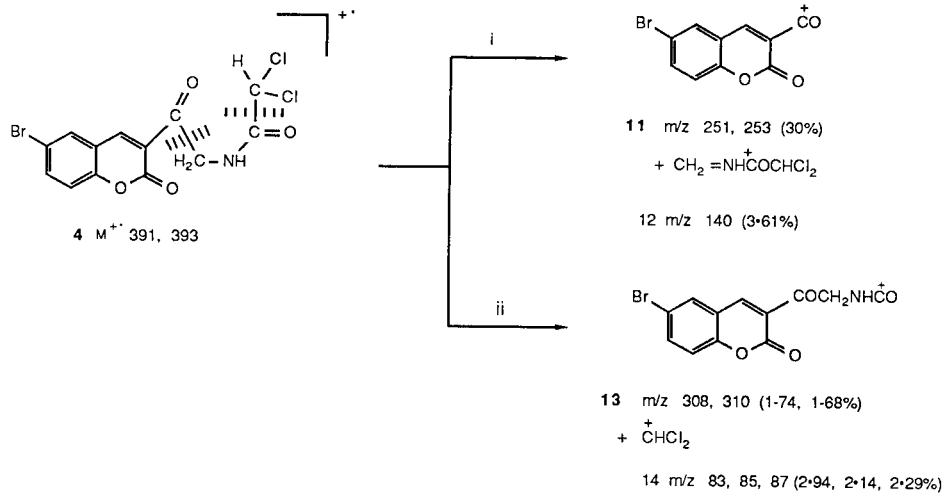
In continuation of the mass spectral fragmentations of benzofuran and coumarin analogs of chloramphenicol and their precursors [3-5] it was thought worthwhile to confirm the structure of the compound **4** by a fragmentation pathway.

As expected [3,9-11] the fragmentation of **4** is shown in Scheme 2 and the bar graph data are shown in Figure 1.

Antibacterial Activity.

Applying the well known cup-plate method [12] all of the newly synthesized compounds **4-7** were screened *in vitro* for antibacterial activity against *Esch. coli., Bacillus cirroflagellosus, Staph. aureus* and *Shigella sonnei.* In this method 10 mm diameter cups were made by punching into set agar and seeded with the test organism. To these cups 0.1 ml of solution of the test compound (1000 μg/ml of dimethylformamide) was placed and the plates were incubated for 24 hours at 37°. The zone of inhibition of bacterial growth around the cup was observed taking chlor-

Scheme 2



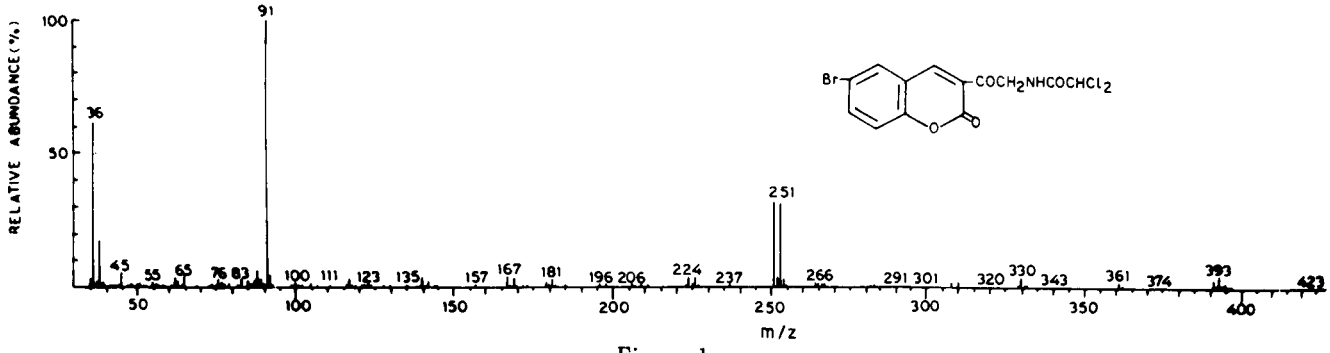


Figure 1

amphenicol as the standard. The screening results given in Table 1 indicated that all the compounds exhibited antibacterial activity.

Table 1

Antibacterial Activities of Compound **4-7**

Compound No. [a]	*Esch. coli*	*B. cirroflagellous*	*S. aureus*	*S. sonnei*
4	+ [b]	+ +	+	+
5	+ +	+ +	+ +	+
6	+ + +	+ + +	+ +	+ +
7	+	+ +	+ +	+ +
Std.	+ + +	+ + +	+ + +	+ + +

[a] Compound numbering is same as described in the Experimental. [b] Zone of inhibition: 12-15 mm = +; 15-24 mm = + +; 24-36 mm = + + +.

EXPERIMENTAL

All melting points were taken on an electrically heated Buchi capillary melting point apparatus and are uncorrected. The infrared spectra were recorded on a Perkin-Elmer 257 spectrophotometer and pmr spectra were determined at 60 MHz on a Varian A-60 spectrophotometer with TMS as an internal reference. Mass spectrum was recorded at an ionisation potential of 70 eV with a Finnigan 4121 GC mass spectrometer consisting of (ci/ci system) using a direct inlet system.

3-Bromacetyl-6-bromocoumarin (**2**).

To a solution of 26.7 g (0.1 mole) of 3-acetyl-6-bromocoumarin in 100 ml of alcohol-free chloroform was added 17.6 g (0.11 mole) of bromine in 10 ml of chloroform. Bromine was added during a period of three hours with intermittent shaking and warming the mixture to decompose the addition product. The mixture was heated for an hour on waterbath to expel most of the hydrogen bromide, then cooled and filtered. The solid was washed with ether. Crystallisation from acetic acid gave pale yellow crystals, mp 177-180°, yield 30 g (91%); ir (nujol): 1725 (C=O lactone), 1660 (C=O ketone) cm^{-1}; nmr (deuteriodimethyl sulphoxide): δ 4.5 (s, 2H, $-CH_2-$), 7.3-8.3 (m, 4H, aromatic).

Aminomethyl 3-(6-Bromocoumarinyl)ketone Hydrochloride (**3**).

Powdered anhydrous hexamethylenetetramine (16.8 g, 0.12 mole) was dissolved in 200 ml of dry chloroform. To this stirred mixture was added a clear solution of 34.6 g (0.1 mole) of 3-bromoacetyl-6-bromocoumarin in 760 ml of dry chloroform all at once. Immediately a bright yellow solid mass separated out. It was stirred at room temperature for two hours, cooled to 5° and filtered. The resulting solid was thoroughly washed with chloroform to remove the coloured impurities. The colourless adduct weighed 44 g (90%) mp 200-205° dec.

The hexamine adduct (48.6 g, 0.1 mole) was stirred in a solution of 50 ml of concentrated hydrochloric acid and 100 ml of ethyl alcohol for 3-4 hours at room temperature. The mixture never becomes clear. Then the mixture was cooled to 0° and filtered. The resulting solid was washed with slightly acidic alcohol and then with dry ether to give the colourless amine hydrochloride contaminated with paraformaldehyde and ammonium chloride. It weighed 32 g (theoretical 30.6 g) and decomposed above 225°. This compound was used directly for the next stage.

Dichloroacetamidomethyl 3-(6-Bromocoumarinyl) Ketone (**4**).

A suspension of 31.8 g (0.01 mole) of crude aminomethyl 3-(6-bromocoumarinyl) ketone hydrochloride in 90 ml of dichloroacetyl chloride was heated and stirred at 80° for 45 minutes. The mixture was cooled and filtered. The yellow solid was washed thoroughly with cold water and then with ethyl acetate to give sufficiently pure product, mp 210-212°, yield 33 g (84%). Recrystallisation from ethyl acetate gave colourless crystals mp 230-232°; ir (nujol): 3265 (NH), 1725 (C=O lactone), 1690 (C=O amide), 1660 (C=O ketone) cm^{-1}; nmr (deuteriodimethyl sulphoxide): δ 4.5-4.6 (m, 2H, $-CH_2-$), 6.7 (s, 1H, $-CHCl_2$), 7.3-8.3 (m, 4H, aromatic), 8.7-8.9 (m, 1H, -NH-).

Anal. Calcd. for $C_{13}H_8BrCl_2NO_4$: C, 39.8; H, 2.01; N, 3.57. Found: C, 39.5; H, 2.00; N, 3.49.

Chloroacetamidomethyl 3-(6-Bromocoumarinyl) Ketone (**5**).

A suspension of 3.18 g (0.01 mole) of crude aminomethyl 3-(6-bromocoumarinyl) ketone hydrochloride in 9 ml of chloroacetyl chloride was heated and stirred at 80° for 30 minutes. The mixture was cooled and poured into a mixture of ice and water. On stirring the crystalline chloroacetamide separated out. It was filtered and washed thoroughly with cold water and then with a little ethyl acetate to give 2 g (62%) of the material. Recrystallisation from ethyl acetate gave colourless crystals, mp 210-212°; ir (potassium bromide): 3310 (NH), 1740 (C=O lactone), 1700 (C=O amide), 1680 (C=O ketone) cm^{-1}.

Anal. Calcd. for $C_{13}H_9BrClNO_4$: C, 43.63; H, 2.51; N, 3.91. Found: C, 43.60; H, 2.49; N, 3.87.

2-Dichloroacetamido-3-hydroxy-1-[3-(bromocoumarinyl)]-1-propanone (**6**).

To a mixture of 3.92 g (0.01 mole) of dichloroacetamido ketone and 0.600 g of paraformaldehyde in 5 ml of methanol was added 0.060 g, of potassium carbonate. There was little evidence for the reaction at the room temperature. When the mixture was stirred with intermittent warming to 60° on water bath for two hours, the solid material became more dense. The mixture was cooled and poured into the mixture of ice and water. On stirring, the colloidal solution with a small quantity of sodium chloride, a yellow solid separated which was filtered and dried. The entire lot on fractional crystallisation from benzene-ethyl acetate mixture yielded 1.5 g (39%) of 2-dichloroacetamido-3-hydroxy-1-[3-(6-bromocoumarinyl)]-1-propanone as colourless crystals, mp 215-217° dec; ir (nujol): 3480-3440 (OH), 3300 (NH), 1725 (C=O lactone), 1690 (C=O amide), 1660 (C=O ketone) cm^{-1}; nmr (deuteriodimethyl sulphoxide): δ 3.35 (s, 1H, -OH) 3.9-4.0 (m, 2H, $-CH_2-$), 4.7-4.8 (m, 1H, -CH-), 6.55 (s, 1H, $-CHCl_2$), 7.3-8.85 (m, 4H, aromatic), 8.8-8.9 (m, 1H, NH).

Anal. Calcd. for $C_{14}H_{10}BrCl_2NO_5$: C, 39.8; H, 2.37; N, 3.32. Found: C, 39.6; H, 2.30; N, 3.29.

dl-threo-2-Dichloroacetamido-1-[3-(6-bromocoumarinyl)]-propane-1,3-diol (**7**).

A mixture of 4.22 g (0.01 mole) of 2-dichloroacetamido-3-hydroxy-1-[3-(6-bromocoumarinyl)]-1-propanone and 2.35 g (0.011 mole) of aluminium isopropoxide in 30 ml of dry 2-propanol was heated and refluxed on a steam bath for 3 hours. The excess 2-propanol was removed by vacuum distillation. To the remaining red gummy residue, 16 ml of 10% aquous sodium chloride solution was added and refluxed for another 15 minutes. The precipitated aluminium hydroxide was removed from the hot solution by filtration and the filter cake was washed thoroughly with several portions of ether. The combined ether filtrates and the ether extracts of the original aqueous filtrate were combined and dried over sodium sulfate. Removal of the ether under reduced pressure yielded an oil which on cooling and repeated crystallisations from benzene yielded a pale yellow crystals, 0.80 g (19%), mp 150-151°; ir (potassium bromide): 3800-3350 (-OH), 3250 (-NH), 1690 (C=O amide), 1725 (C=O lactone) cm^{-1}; nmr (deuteriodimethyl sulphoxide): δ 3.3 (s, 1H, $-CH_2$-OH), 3.4-3.6 (m, 1H, -CH(OH)-1), 3.6-3.8 (m, 2H, $-CH_2OH$), 4.5-4.7 (m, -1H, -CHNH-), 6.0-6.1 (m, 1H, -CHOH), 6.5-6.6 (s, 1H, $-CHCl_2$), 7.0-8.3 (m, 4H, aromatic), 8.7-8.9 (m, 1H, -NH-).

Anal. Calcd. for $C_{14}H_{12}BrCl_2NO_5$: C, 39.64; H, 2.83; N, 3.30. Found: C, 39.37; H, 2.93; N, 3.28.

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REFERENCES AND NOTES

[1] R. V. Joshi, Ph. D. Thesis, Karnatak University, Dharwad, India, 1986.

[2] H. S. Bevinakatti and V. V. Badiger, *J. Heterocyclic Chem.*, **17**, 613 (1980).

[3] H. S. Bevinakatti and V. V. Badiger, *J. Heterocyclic Chem.*, **17**, 1701 (1980).

[4] H. S. Bevinakatti and V. V. Badiger, *Arch Pharm* (Weinheim)., **314**, 162 (1981).

[5] H. S. Bevinakatti and V. V. Badiger, *J. Heterocyclic Chem.*, **19**, 69 (1982).

[6] G. Fever, "Progress in Medicinal Chemistry", Vol **10**, G. P. Ellis and G. B. West, eds, North Holland Publishing Co, Amsterdam, 1974, p 85.

[7] Ng. Ph. Buu-Hoi, T. B. Loc and Ng. D. Xyong, *Bull. Soc. Chim. France*, 561 (1957); *Chem. Abstr.*, **51**, 128595e (1957).

[8] R. A. Cutler, R. J. Stenger and C. M. Suter, *J. Am. Chem. Soc.*, **74**, 5475 (1952).

[9] R. A. W. Johnstone, B. J. Millard, F. M. Dean and A. W. Hill, *J. Chem. Soc.* (*C*)., 1812 (1966).

[10] G. Saint Ruf, A. De, S. A. Brunskill and H. Jaffrey, *J. Heterocyclic Chem.*, **17**, 81 (1980).

[11] P. I. Zekharov, *Zh. Org. Khim.*, **7**, 388 (1971); *Chem. Abstr.*, **74**, 124380w (1971).

[12] H. W. Seeley and P. J. Vandamark, in "Microbes in Action", W. H. Freeman and Co, 1972, pp 75-100.