5-Bromobenzofuran Analog of Chloramphenicol (1)

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dl-threo-2-Dichloroacetamido-1-[2-(5-bromobenzofuranyl)] propane-1, 3-diol (**7**) was synthesised according to Sorm's method. The fragmentation of 2-dichloroacetamido-3-hydroxy-1-[2-(5-bromobenzofuranyl)]-1-propanone (**6**) under electron impact is reported. The base peak is due to the rupture of the central bond whereas loss of water and McLafferty rearrangement also lead to important fragmentation pathways.

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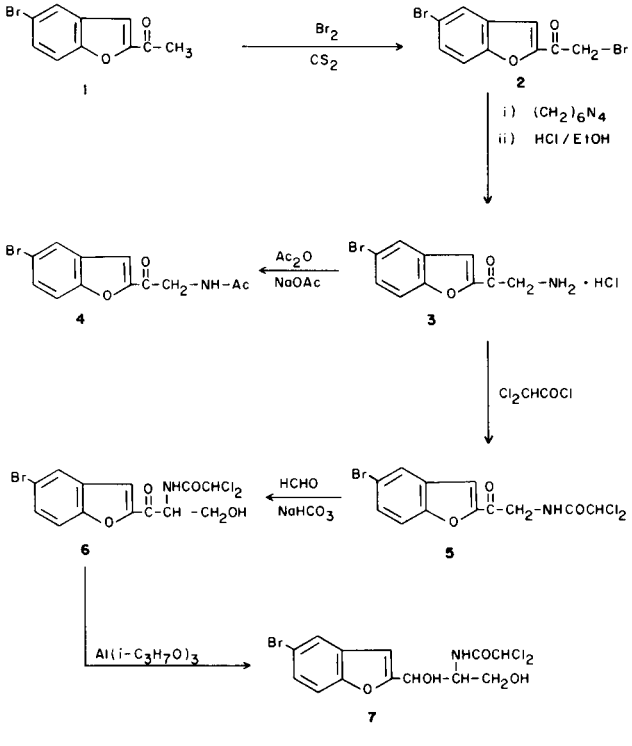
As a result of the continuing interest in studying the structure-activity relationship of the antibiotic chloramphenicol, we have synthesised different heterocyclic analogs of chloramphenicol. In the three preceding papers of this series, we have reported the synthesis, mass spectral and antimicrobial studies of the benzofuran and coumarin analogs of chloramphenicol (2-4).

Motivated by the suggestion of Bambas, *et al.*, that a halogen atom rather than a nitro group in the aromatic ring might enhance the activity of chloramphenicol (5), and also increase the electron richness of the aromatic ring which is another important factor that increases the biological activity of the antibiotic, we have now extended our interest in preparing the bromo substituted benzofuran analog of chloramphenicol (2-4).

This paper reports the synthesis and the ir and nmr studies of *dl-threo*-2-dichloroacetamido-1-[2-(5-bromobenzofuranyl)]-1-propanone (**7**), together with the mass spectral studies of its precursor, 2-dichloroacetamido-3-hydroxy-1-[2-(5-bromobenzofuranyl)]-1-propanone (**6**). The modified route due to Sorm, *et al.*, was adopted (Scheme 1).

Scheme I



2-Acetyl-5-bromobenzofuran (**1**), which served as the starting material, was prepared in lower yields by the equimolar condensation of 5-bromosalicylaldehyde and bromoacetone [instead of chloroacetone (6)]. The ketone **1** was further converted to the dichloroacetamide (**6**) after several stages as described earlier (2). But as expected, difficulty was again encountered in getting the pure hydroxymethylated compound (**6**). However, by using the similar procedure as described in our previous paper (2), 2-dichloroacetamido-3-hydroxy-1-[2-(5-bromobenzofuranyl)]-1-propanone (**6**) could be obtained as colourless silky needles in lower yields. The resulting compound even after repeated crystallizations and freezing failed to yield crystalline material. However, the oily material thus obtained was passed through activated neutral alumina column using ethyl acetate-benzene mixture (1:1) as an eluting solvent. The fractions on evaporation yielded a pasty mass, which on repeated crystallizations with benzene or ethyene chloride yielded the desired crytalline compound **7**.

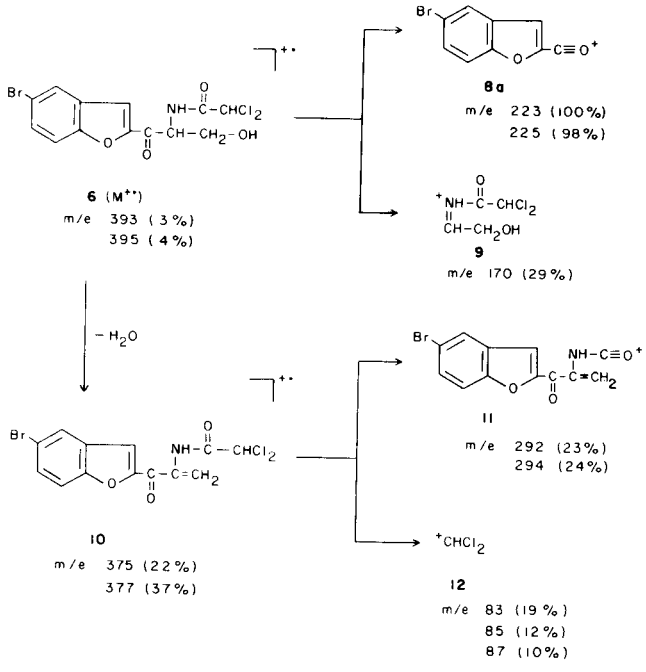
The structures of the compounds **5**, **6** and **7** were confirmed by their ir and nmr studies, as described in our earlier papers (2-4).

As a support to the mass spectral fragmentations suggested by us for the benzofuran and coumarin analogs of chloramphenicol (3,4), and also because of the difficulty encountered in the hydroxymethylation stage, it was thought to confirm the structure of 2-dichloroacetamido-3-hydroxy-1-[2-5-bromobenzofuranyl)]-1-propanone (**6**) by studying its effect of the bromine atom to give double peaks of equal intensity after each splitting makes the fragmentation pattern of compound **6** an interesting subject of study. These isotopic peaks have been observed for all the fragments containing a bromine atom.

As expected, the two molecular ion peaks (M^+) at m/e 393 and 395 with equal relative abundances have appeared in the mass spectrum of compound **6**. The principal fragmentations occur either by the cleavage of the central C-C bond or by the loss of a water molecule or by

McLafferty rearrangement in the molecular ion as described below.

Scheme A

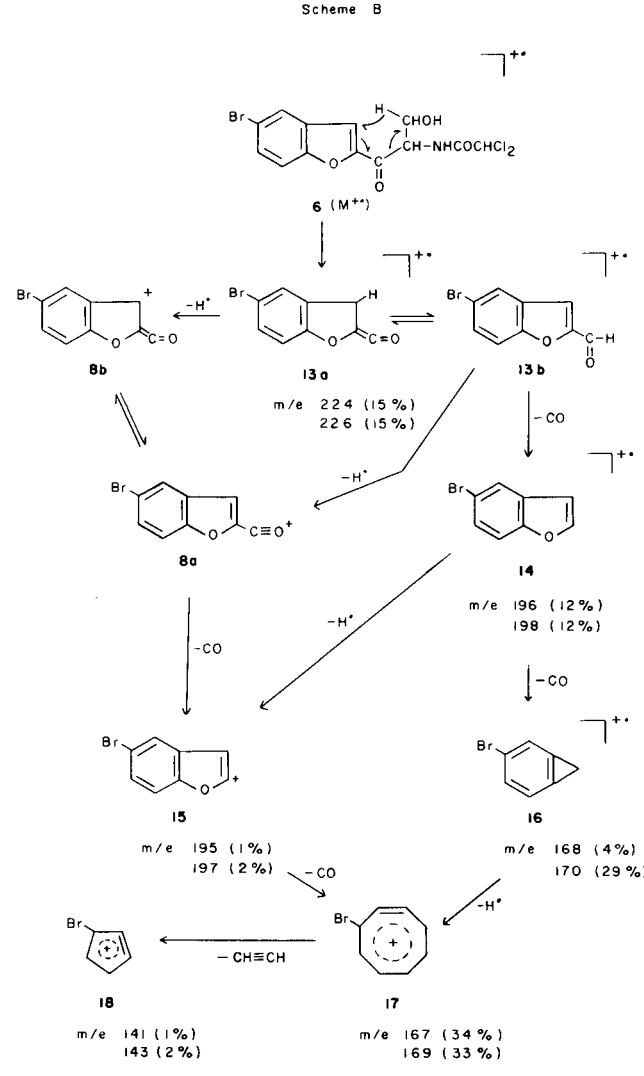


The principal fragmentation occurs by the homolytic cleavage of the central C-C bond at the ketone carbonyl group to give the most abundant (100%) even electron ion **8a**, to constitute the base peaks at m/e 223 and 225. The other side-chain fragment **9**, obtained after this cleavage, competes for the positive charge and forms a peak of relatively lower intensity (29%) at m/e 170.

The peaks due to $(M\text{-}H^{\circ}O)^{+}$ fragment (**10**), have appeared with sufficiently high relative abundances at m/e 375 and 377. The fragment **10**, may then undergo the homolytic cleavage of the C-C bond at the amide carbonyl to give the two daughter ions **11** (m/e 292, 294) and **12** (m/e 83, 85 and 87).

The molecular ion, on McLafferty rearrangement involving the transfer of a hydrogen from the methylene group to the π-bond of the aromatic furan ring, loses a neutral molecule of the olefin with mass 169, to produce the odd electron ion **13a**, capable of existing as **13b** also (m/e 224, 226). Both these resonating structures **13** (a and b) may either lose a *H*-radical to give the most abundant ion **8** (a or b), or the ion **13b** may lose a molecule of carbon monoxide to yield the odd electron ion **14**, to constitute the isotopic peaks at m/e 196 and 198. The ion **14**, in turn, may either lose a *H*-radical, so as to retain the furan nucleus in the even electron ion **15**, or it may eliminate a carbon monoxide molecule to break the furan ring so as to give the odd electron ion **16** (m/e 168, 170). The ion **15** can also be obtained on loss of a molecule of carbon monoxide

Scheme B

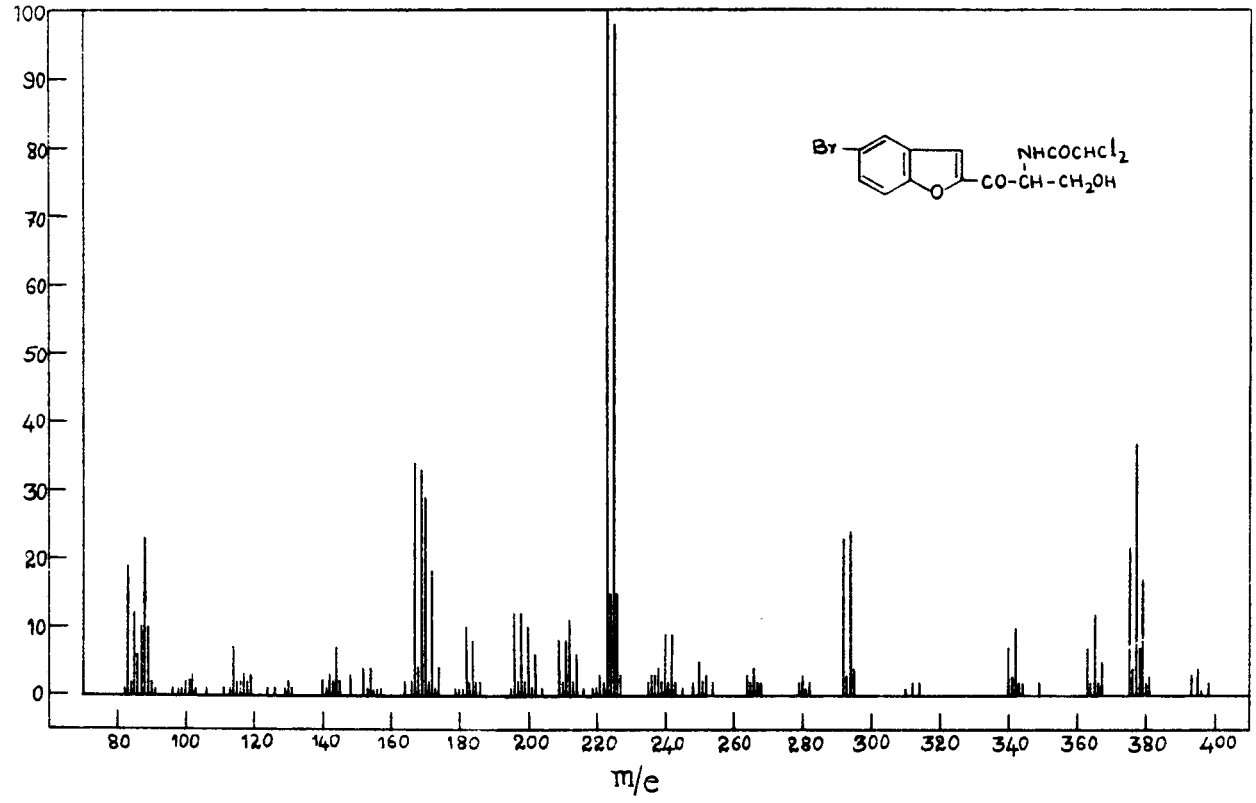


from the most abundant ion **8a**. Further, both these ions **15** and **16**, become the same fragment **17** after losing a carbon monoxide molecule and *H*-radical respectively. The fragment **17** constitutes the two isotopic peaks at a relatively high abundance (33 and 34%) at m/e 167 and 169 respectively. This seven membered ion **17**, may then undergo ring contraction by losing an acetylene molecule to give the five membered fragment **18** which accounts for the peaks at m/e 141 and 143.

It is quite interesting to note in the mass spectrum of this hydroxymethylated compound (**6**), that the corresponding peaks arising due to the rearrangements of the two *H*-atoms of the reduced carbonyl group (3,4), are absent.

EXPERIMENTAL

All melting points were taken on a electrically heated Buchi capillary melting point apparatus and are uncorrected. The infrared spectra were recorded on a Perkin-Elmer 137B spectrophotometer and nmr spectra were determined at 60 MHz on a varian A-60 nmr spectrophotometer



with TMS as an internal reference. Mass spectrum was determined with A.E.I. MS 902 spectrometer operating at an ionising potential of 70 ev.

2-Acetyl-5-bromobenzofuran (**1**).

5-Bromosalicylaldehyde (201 g, 1 mole) dissolved in 600 ml of hot, dry ethyl alcohol was heated with 61 g of alcoholic potassium hydroxide until the solution of the salt was achieved. To this, 137 g (1 mole) of bromoacetone was slowly added from a dropping funnel while stirring the contents with a mechanical stirrer. After the vigorous reaction subsided, the mixture was kept overnight. Then it was diluted with an equal amount of water and the excess alcohol was distilled off. The partly oily, partly crystalline 2-acetyl-5-bromobenzofuran was washed several times with aqueous alcohol to give a reddish brown solid. The whole lot on recrystallising twice from ethyl alcohol, yielded 87 g (37%) of 2-acetyl-5-bromobenzofuran in the form of colourless needles, mp 107° (lit (6) 109-110 °).

2-Bromoacetyl-5-bromobenzofuran (**2**).

A solution of 17.6 g (0.11 mole) of bromine in 100 ml of carbon disulfide was added dropwise, with stirring, into a solution of 23.9 g (0.1 mole) of 2-acetyl-5-bromobenzofuran in 300 ml of carbon disulfide. Bromine was added during a period of two hours and at the end of this time, carbon disulfide was removed at reduced pressure to leave 30 g (94%) of pale brown solid residue. The residue was washed twice with ethyl alcohol and recrystallised from ethanol-dioxan mixture to give the pure product in the form of shiny yellow crystals, mp 135-136°, yield, 25 g, (79%).

Aminomethyl 2-(5-Bromobenzofuranyl) 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 31.8 g (0.1 mole) of 2-bromoacetyl-5-bromobenzofuran in 200 ml of dry chloroform in one lot. Within no time, a bright yellow solid mass separated which was stirred at room temperature for two more hours, cooled to 5° and filtered. The resulting solid was thoroughly washed with chloroform to remove the coloured impurities. The colourless adduct weighed 42 g (92%), mp 150-152% dec.

The hexamine adduct (45.8 g, 0.1 mole) was stirred in a solution of 55 ml of concentrated hydrochloric acid and 110 ml of ethyl alcohol. The mixture became clear after about half an hour and immediately a colourless solid separated. The resulting suspension was stirred for another hour, frozen and filtered. It was washed with slightly acidic alcohol and then with ether to give the colourless amine hydrochloride, contaminated with paraformaldehyde and ammonium chloride. It weighed 32 g (theoretical, 29.1 g) and decomposed above 225°. This compound was directly used for the next stage.

Acetamidomethyl 2-(5-Bromobenzofuranyl) Ketone (**4**).

To a suspension of 2.9 g (0.01 mole of aminomethyl 2-(5-bromobenzofuranyl) ketone hydrochloride in 20 ml of ice cold water, was added 2.5 ml of acetic anhydride and 1 g solid sodium acetate with stirring and cooling to 0° and one hour at room temperature. The solid was filtered, washed with water and dried to give 1.5 g (51%) of acetamidomethyl 2-(5-bromobenzofuranyl) ketone, mp 190-191°. Recrystallisation in ethyl alcohol yielded colourless crystals, mp 193°.

Anal. Calcd. for $C_{12}H_{10}BrNO_3$: C, 48,65; H, 3.38; N, 4.73
Found: C, 48,54; H, 3.43; N, 4.87.

Dichloroacetamidomethyl 2-(5-Bromobenzofuranyl) Ketone (**5**).

A suspension of 29.1 g (0.1 mole of crude aminomethyl 2-(5-bromobenzofuranyl) ketone hydrochloride in 90 ml of dichloroacetyl chloride was heated and stirred at 80° for 30 minutes. The mixture was cooled in freezing mixture while about 500 g of chipped ice was slowly added to it with constant stirring. It was well stirred until the crystalline dichloroacetamide separated out. It was filtered and washed thoroughly with cold water and then with a little ethyl acetate to give 25 g (68%) of pale yellow compound, mp 183-184°. Recrystallisation from ethyl acetate gave colourless needles, mp 186-187°, ir (potassium bromide): cm^{-1} 3300

(NH), 1695 (C=O amide), 1645 (C=O ketone); nmr (DMSO-d_6): δ 4.6-4.7 (m, 2H, -CH_2-), 6.7 (s, 1H, -$CHCl_2$), 7.78.1 (m, 4H, aromatic), 8.8-9.1 (m, 1H, -NH-).

Anal. Calcd. for $C_{12}H_8BrCl_2NO_3$: C, 39.46; H, 2.19; N, 3.83. Found: C, 39.41; H, 2.11; N, 3.80.

2-Dichloroacetamido-3-hydroxy-1-[2-(5-bromobenzofuranyl)]-1-propanone (**6**).

A mixture of 7.3 g (0.02 mole) of the dichloroacetamido ketone in 25 ml of 37-38% aqueous formaldehyde and 80 ml of 95% ethyl alcohol containing a small amount (just sufficient to make the solution clear within an hour) of sodium bicarbonate was stirred at room temperature for two hours. The clear yellow solution was cooled and poured on ice to give a yellow colloidal solution, which on freezing for 2-3 days yielded a yellow crystalline solid. This was filtered and dried. This crude yellow solid weighed 7.6 g (96%) and melted in a range of 160-190°, without any sharp melting point. This compound, on fractional crystallisation with benzene-ethyl acetate mixture yielded 3.1 g (39%) of pure 2-dichloroacetamido-3-hydroxy-1-[2-(5-bromobenzofuranyl)]-1-propanone in the form of colourless silky needles, mp 174° dec; ir (potassium bromide): cm^{-1} 3480-3440 (OH), 3280 (NH), 1665 (C=O amide), 1650 (C=O ketone); nmr (DMSO-d_6): δ 3.35 (s, 1H, -OH), 3.9-4.0 (m, 2H, -CH_2-), 4.95-5.15 (m, 1H, -CH-), 6.55 (s, 1H, -$CHCl_2$), 7.65-8.1 (m, 4H, aromatic) 8.9-9.0 (m, 1H, -NH-).

Anal. Calcd. for $C_{13}H_{10}BrCl_2NO_4$: C, 39.50; H, 2.53; N, 3.54. Found: C, 39.55; H, 2.50; N, 3.49.

dl-threo-2-Dichloroacetamido-1-[2-(5-bromobenzofuranyl)]-propane-1,3-diol (**7**).

2-Dichloroacetamido-3-hydroxy-1-[2-(5-bromobenzofuranyl)]-1-propanone (4.74 g, 0.012 mole) was added to a hot solution of 3.6 g (0.018 mole) of aluminium isopropoxide in 36 ml of dry 2-propanol in a 50 ml round-bottomed flask equipped with a small vigreux column packed with glass helices. The solution attained a reddish brown colour after refluxing for about 15 minutes. Refluxing and slow distillation were continued until the distillate no longer gave a positive test for acetone (6-7 hours). Water (8 ml) was added to this thick residue, refluxed for another 15 minutes and filtered while hot only. The residue was refluxed twice with 80% absolute alcohol and filtered. The combined filtrates were evaporated *in vacuo* to yield a thick red oil, which failed to yield the crystalline compound even after repeated crystallizations in different solvents and freezing for for 3-4 days. However, the oily material thus obtained, was passed through activated alumina column using ethyl acetate-benzene mixture (1:1) as an eluting solvent. The fractions on evaporation *in vacuo* yielded a pasty mass, which repeated crystallizations with benzene yielded 0.8 b (17%) of the final product as pale yellow crystals, mp 127-128°; ir (potassium bromide): cm^{-1} 3420-3380 (OH), 3330 (NH), 1660 (C=O amide); nmr (DMSO-d_6): δ 3.35 (s, 1H, -CH_2OH), 3.4-3.7 (m, 1H, -CH(OH)-1), 3.8-4.3 (m,2H, -CH_2OH), 4.8-5.1 (m, 1H, -CH-NH-), 6.1-6.2 (m, 1H, -CH(O*H*)-). 6.5 (s, 1H -$CHCl_2$), 6.7 (s, 1H, furan-aromatic H), 7.1-7.7 (m, 3H, aromatic), 8.2-8.4 (m, 1H, -NH-).

Anal. Calcd. for $C_{13}H_{12}BrCl_2NO_4$: C, 39.29; H, 3.02; N, 3.53. Found: C, 39.34; H, 3.09; N, 3.50.

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