Synthesis and Mass Spectral Studies of a Coumarin Analog of Chloramphenicol (1)

*Hanamanthsa S. Bevinakatti and Virupax V. Badiger**

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

Received May 23, 1980

Preparation of *dl-threo*-2-dichloroacetamido-1-(3-coumarinyl)propane-1,3-diol (**7**) is discussed. The structures of the final compound (**7**) as well as its two precursors (**5** and **6**) were confirmed by ir and nmr studies. Because of the larger side chain, the coumarin analog (**7**) breaks down in a well defined manner upon electron impact. Its mass spectral fragmentation patterns are described.

J. Heterocyclic Chem., **17**, 1701 (1980).

We have recently reported the synthesis (2), mass spectral and antimicrobial studies (3) of the benzofuran analog of chloramphenicol. In continuation of our study on different heterocyclic analogs of the well-known broad spectrum antibiotic chloramphenicol, we now wish to report the synthesis and mass spectral studies of *dl-threo*-2-dichloroacetamido-1-(3-coumarinyl)propane-1,3-diol.

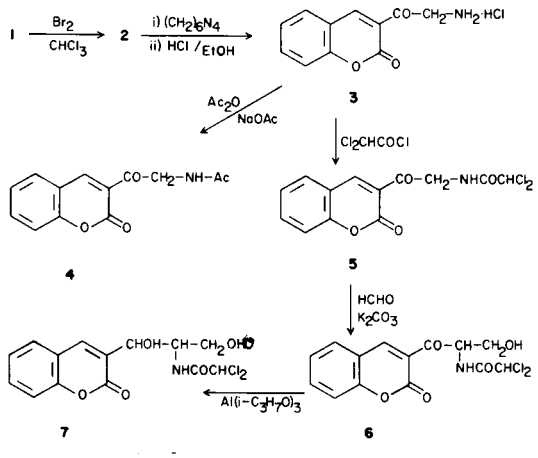
It was thought worthwhile to attach the coumarin nucleus to the active 2-dichloroacetamido propanediol side chain of chloramphenicol, because of the fact that, coumarin nucleus is the basis of various naturally occuring as well as synthetic compounds possessing several pharmacological and physiological activities such as antibacterial, tuberculostatic, antifungal, algal, anticarcinogenic, anticoagulant, antispasmodic, vasodilatory, stimulatory, diuretic and oestrogenic activities (4).

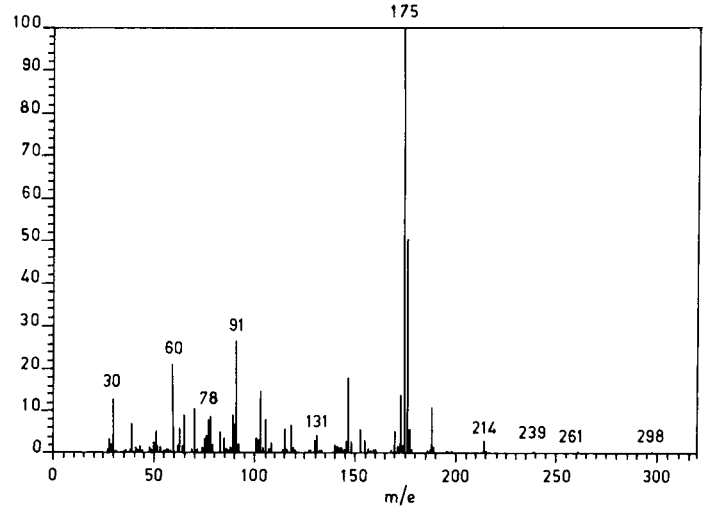
3-Acetylcoumarin (**1**) (5), which served as the starting material, on bromination in chloroform yielded 3-bromoacetyl coumarin (**2**) (6), which was further converted into the dichloroacetamide (**5**) according to the similar methods as described earlier (2). But at the hydroxymethylation stage, the problem was again the same as was observed in the preparation of the benzofuran analog of chloramphenicol (2). Of all the alterations tried, only the use of paraformaldehyde and potassium carbonate in methanol, yielded 2-dichloroacetamido-3-hydroxy-1-(3-coumarinyl)-1-propanone (**6**) as an impure yellow solid. Further, the purified product on Meerwein-Ponndorf-Verley reduction, yielded a red oil, which failed to produce the pure crystalline product even after passing through activated alumina column. Although some solid was obtained, it was impure. It neither gave a sharp melting point nor could it show sharp absorptions when its ir spectrum was taken. Hence it was thought to carry out the reduction according to the modified Meerwein-Ponndorf-Verley reduction method, suggested by Cutler, *et al.* (7). The red oil obtained from the reaction, on recrystallisations with ethylene chloride and benzene yielded the desired crystalline *dl-threo*-2-dichloroacetamido-1-(3-coumarinyl)propane-1,3-diol (**7**) (Scheme 1).

The structures of the compounds **5** and **6** were confirmed by their ir and nmr studies, as described in our earlier paper (2). Further, the position of the nmr signals due to -OH and -NH groups in compound **6** have been confirmed by deuterium oxide exchange studies. The structure of the final product (**7**) has been confirmed by ir and mass spectral studies.

2-Dichloroacetamido-1-(3-coumarinyl)propane-1,3-diol (**7**) breaks down in a well defined manner upon electron

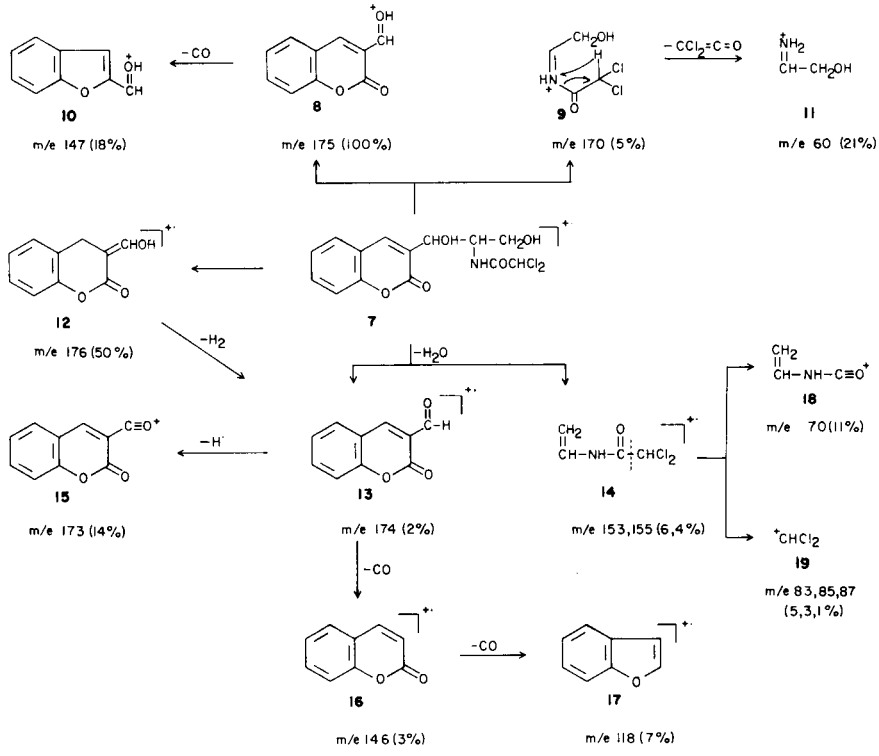
Scheme I





0022-152X/80/081701-03$02.25

Scheme 2



impact. Its larger side-chain makes the fragmentation pattern an interesting subject of study. The fragmentation pattern followed by the coumarin analog is the same as suggested by us for the benzofuran analog of chloramphenicol (3). Further, observation of the corresponding peaks in the mass spectra of the parent chloramphenicol (8) and the benzofuran analog of chloramphenicol (3) again confirms the fragmentation pattern suggested here.

Unlike the benzofuran analog of chlormaphenicol (2,3), the coumarin analog failed to give the molecular ion peak at an ionising potential of 70 eV, similar to that observed in the mass spectrum of the parent chloramphenicol (8). Because of the larger side-chain, the molecule can split in three different ways as follows.

The prinicpal fragmentation occurs in the same fashion as described for the benzofuran analog (2,3), to give the most abundant (100%) even electron ion **8**, which constitutes the base peak at m/e 175, and the olefinic even electron ion **9** appearing at a relatively lower abundance (5%) at m/e 170. The ion **8** may undergo ring contraction by losing a molecule of carbon monoxide to give the ion **10** (m/e 147, 18%) with the benzofuran nucleus. On the other hand, the side-chain fragment **9** may lose a molecule of $Cl_2C{=}C{=}O$ by the cleavage of the amide bond with the hydrogen transfer to give another odd electron ion **11**, which forms a peak at m/e 60.

Another major fragmentation in the molecular ion occurs by the McLafferty rearrangement involving the π-bond of the coumarin ring as shown in case of the benzofuran analog (3), to give the second most abundant ion **12**, which constitutes a peak at m/e 176 (50% of the base peak).

The third major fragmentation of the molecular ion may occur by another type of McLafferty rearrangement as seen in Scheme B of the benzofuran analog (3), to yield the two odd electron ions **13** (m/e 174) and **14** (m/e 153,155). The ion **13**, which can also be formed after the loss of a hydrogen molecule from ion **12**, may either lose an H-radical to give the even electron ion **15** (m/e 173) or it may lose a carbon monoxide molecule to give the odd electron ion **16** (m/e 146), which, in turn, can undergo ring contraction by losing another molecule of carbon monoxide to give the ion **17** (m/e 118). The ions with the benzofuran nucleus, further split according to the known patterns (3,9). On the other hand, the olefinic ion **14**, after the homolytic cleavage of the C-C bond, may give rise to two daughter ions **18** (m/e 70) and **19** (m/e 83, 85 and 87) (Scheme 2).

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 nmr spectra were determined at 60 MHz on a Varian A-60 Spectrophotometer with TMS as an internal reference. Mass spectrum was recorded on a Hitachi-Elmer Model RMU-7 mass spectrometer operating at an ionising potential of 70 eV, using direct inlet system at 150°.

3-Acetylcoumarin (**1**) (5) and 3-bromoacetylcoumarin (**2**) (6) were prepared in good yields according to the literature methods.

Aminomethyl 3-Coumarinyl 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 26.7 g. of 3-bromoacetylcoumarin in 600 ml. of dry chloroform in one lot. Immediately, a bright yellow solid mass separated out, which 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, m.p. 190-191° dec., yield 38.5 g. (95%).

The hexamine adduct (41 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 became clear. Then the mixture was cooled to 0° and filtered. The resulting solid was washed with slight acidic alcohol and then with dry ether to give the colourless amine hydrochloride, contaminated with paraformaldehyde and ammonium chloride. It weighed 28 g. (theoretical 24 g.) and decomposed above 225°. This compound was used directly for the next stage.

Acetamidomethyl 3-Coumarinyl Ketone (**4**).

To a suspension of 2.4 g. (0.01 mole) of aminomethyl 3-coumarinyl 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. The mixture was stirred for an hour at 0° and for two hours at room temperature. The solid was filtered, washed with water and dried to give 1.35 g. (55%) of acetamidomethyl 3-coumarinyl ketone, m.p. 234-236°. Recrystallisation in ethyl alcohol yielded colourless crystals, m.p. 236-237°.

Anal. Calcd. for $C_{13}H_{11}NO_4$: C, 63.66; H, 4.49; N, 5.71. Found: C, 63.45; H, 4.31; N, 5.83.

Dichloroacetamidomethyl 3-Coumarinyl Ketone (**5**).

A suspension of 24 g. (0.1 mole) of crude aminomethyl 3-coumarinyl ketone hydrochloride and 80 ml. of dichloroacetyl chloride was heated and stirred at 80° for about 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, m.p. 209-210°, yield 25 g. (80%). Recrystallisation from ethyl acetate gave colourless crystals, m.p. 211°; ir (potassium bromide): 3265 (NH), 1725 (C=O lactone), 1710 (C=O amide), 1660 cm^{-1} (C=O ketone); nmr (DMSO-d_6): δ 4.6-4.7 (m, 2H, $-CH_2-$), 6.7 (s, 1H, $-CHCl_2$), 7.3-8.3 (m, 5H, aromatic), 8.7-9.0 (m, 1H, -NH-).

Anal. Calcd. for $C_{13}H_9Cl_2NO_4$: C, 49.68; H, 2.87; N, 4.46. Found: C, 49.77; H, 2.81; N, 4.53.

2-Dichloroacetamido-3-hydroxy-1-(3-coumarinyl)-1-propanone (**6**).

To a mixture of 6.28 g. (0.02 mole) of the dichloroacetamido ketone and 1.2 g. of paraformaldehyde in 5 ml. of methanol, was added 0.12 g. of potassium carbonate. After stirring for 2 hours at room temperature, the clear yellow solution was cooled and poured into a 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 compound was sufficiently impure and weighed 6.0 g. It softened at 160-165° and melted in a range of 170-175° dec. The whole lot on fractional crystallisation from benzene-ethyl acetate mixture yielded 3.1 g. (45%) of 2-dichloroacetamido-3-hydroxy-1-(3-coumarinyl)-1-propanone as colourless crystals, m.p. 176-177° dec.; ir (potassium bromide): 3400-3360 (OH), 3260 (NH), 1715 (C=O lactone), 1690 (C=O amide), 1660 cm^{-1} (C=O ketone); nmr (deuteriochloroform): δ 3.3 (s, 1H, -OH), 3.95-4.10 (m, 2H, $-CH_2-$), 5.55-5.75 (m, 1H, -CH-), 6.35 (s, 1H, $-CHCl_2$), 7.15-7.90 (m, 5H, aromatic), 8.8-8.9 (m, 1H, -NH-); (deuteriochloroform + deuterium oxide): δ 3.95-4.10 (m, 2H, $-CH_2-$), 5.6-5.85 (m, 1H, -CH-), 6.35 (s, 1H, $-CHCl_2$), 7.1-7.85 (m, 5H, aromatic).

Anal. Calcd. for $C_{14}H_{11}Cl_2NO_5$: C, 48.83; H, 3.20; N, 4.07. Found: C, 48.51; H, 3.28; N, 4.19.

dl-threo-2-Dichloroacetamido-1-(3-coumarinyl)propane-1,3-diol (**7**).

A mixture of 3.44 g. (0.01 mole) of 2-dichloroacetamido-3-hydroxy-1-(3-coumarinyl)-1-propanone and 2.35 g. (0.011 mole) of aluminium isopropoxide in 30 ml. of dry iso-propanol was heated and refluxed on a steam bath for 3 hours. The excess isopropanol was removed by vacuum distillation. To the remaining red gummy residue, 16 ml. of 10% aqueous 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 ether under reduced pressure yielded a red oil which failed to produce a pure crystalline product on recrystallisations either with benzene or with ethylene chloride. However, this oily material was passed through activated alumina column using ethyl acetate-benzene mixture (5:1) as an eluting solvent. The fractions on evaporation to dryness *in vacuo*, yielded a pasty mass, which on recrystallisations with ethylene chloride and benzene yielded 0.84 g. (24%) of the desired *dl-threo*-2-dichloroacetamido-1-(3-coumarinyl)-propane-1,3-diol as colourless crystals, m.p. 138-139°; ir (potassium bromide): 3385-3345 (OH), 3280 (NH), 1690 (C=O lactone), 1665 cm^{-1} (C=O amide); ms: m/e (%), 188 (11), 177 (6), 176 (50), 175 (100), 173 (14), 170 (5), 147 (18), 131 (5), 115 (6), 106 (8), 103 (14), 91 (26), 90 (6), 89 (9), 83 (5), 78 (9), 77 (8), 63 (6), 60 (22).

Anal. Calcd. for $C_{14}H_{13}Cl_2NO_5$: C, 48.55; H, 3.76; N, 4.05. Found: C, 48.49; H, 3.79; N, 4.11.

Acknowledgment.

We thank Prof. E. S. Jayadevappa for his encouragement, and Drs. B. G. Ugarkar and M. V. Kulkarni for their help. One of us (H.S.B.) is grateful to the C.S.I.R., New Delhi, for a research fellowship.

REFERENCES AND NOTES

(1) Part of the Ph.D. thesis submitted by H. S. Bevinakatti, to Karnatak University, Dharwad, India, 1980.

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

(3) H. S. Bevinakatti and V. V. Badiger, *Arch. Pharm. (Weinheim)*, **313** (1980), in press.

(4) G. Feuer, "Progress in Medicinal Chemistry", Vol. 10, G. P. Ellis and G. B. West, Ed., North-Holland Publishing Co., Amsterdam, 1974, p. 85.

(5) F. Knoevenagel, *Ber.*, **31**, 732 (1898).

(6) C. F Koelsch, *J. Am. Chem. Soc.*, **72**, 2993 (1950).

(7) R. A. Cutler, R. J. Stenger and C. M. Suter, *ibid.*, **74**, 5475 (1952).

(8) C. Brunnee, G. Kappus and K. H. Maurer, *Z. Anal. Chem.*, **232**, 17 (1967). The paper reports the mass spectrum of chloramphenicol without its detailed fragmentation studies.

(9) B. Willhalm, A. F. Thomas and F. Gautschi, *Tetrahedron*, **20**, 1185 (1964).