A Benzofuran Analog of Chloramphenicol

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Preparation of *dl-threo*-2-dichloroacetamido-1-(2-benzofuranyl)propane-1,3-diol (VI), adopting the method of Sorm, *et al*, has been described. The structures of the final compound (VI) as well as of the two precursors (V and IV) have been confirmed by ir, nmr and mass spectral studies.

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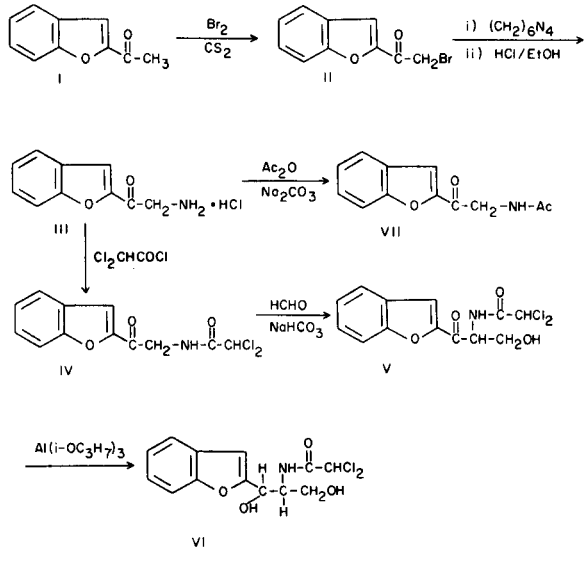
It is needless to overemphasize the importance as well as the chemical stability of the antibiotic chloramphenicol (1). Since, no experimental difficulties are encountered in attaching the active 2-dichloroacetamide side chain to various systems, interest has been manifested in synthesizing various analogs of this antibiotic. Although many variations in the structure have been carried out to improve the pharmacological activity of this antibiotic, the specific structural requirements responsible for the activity still remain unexplored. Attachment of biologically active heterocyclic moieties to the 2-dichloroacetamido-1,3-propanediol side chain may enhance the microbiological activity of the antibiotic, because of their flat surface as well as their ability to incorporate electron rich sites, thus coming in contact with the enzyme systems easily (2,3). Studies have been made in this direction (4-7) and the recent reports of the "in vitro" and "in vivo" screenings of the quinoline analog (8) seem to be interesting.

On the basis of these interesting observations and as a part of our general program (9,10) in the continued search for new antibacterial agents, we thought of preparing a benzofuran analog of chloramphenicol, in view of the fact that the benzofuran nucleus has shown promising pharmacological activities and possesses various physiological properties such as pesticidal and insecticidal, anthelmintic, parasiticidal, nematocidal, bactericidal, antifungal, antibiotic, estrogenic, antispasmodic and vasodilating activities (11).

This paper reports the preparation and ir, nmr and mass (12) (in brief) spectral studies of 2-dichloroacetamido-1-(2-benzofuranyl)-1,3-propanediol.

The modified route of Sorm (13) *et al*, [modification over Long and Troutman's method (14)] was adopted (Scheme).

Scheme I



2-Acetylbenzofuran (I) (15a,b) served as the starting material for the reaction sequence. The ketone, I, on bromination in carbon disulfide yielded 2-bromoacetylbenzofuran (II) (16). Treatment of the bromomethyl ketone II with hexamethylenetetramine in dry chloroform, followed by the hydrolysis of the quaternary salt with concentrated hydrochloric acid at room temperature readily produced the amino ketone, III, as the hydrochloride. Acetylation of the same was carried out below 5° in aqueous solution using acetic anhydride and sodium carbonate to give the acetamidomethyl-2-benzofuranyl ketone (VII). The hydrochloride III was treated with dichloroacetyl chloride at 80° to give the corresponding dichloroacetamide IV, in good yields.

However, difficulty was enountered in obtaining the pure hydroxymethylated compound, V. The dichloroacetamide IV on hydroxymethylation in 95% ethanol solution using 38% formaldehyde solution and sodium bicarbonate at room temperature gave a pale yellow solid which was impure and showed the characteristics of a mixture with a wide melting point range. This, on repeated crystallisations, yielded a white crystalline compound with a sharp melting point. Either the use of potassium carbonate instead of sodium bicarbonate or the use of paraformaldehyde instead of formaldehyde solution yielded a pasty yellow mass. The variations in the other reaction conditions such as solvent and temperature also were of no utility. Difficulties in hydroxymethylation have been reported earlier also (14,17). The resulting 2-dichloroacetamido-3-hydroxy-1-(2-benzofuranyl)-1-propanone (V) on Meerwein-Ponndorf-Verley reduction gave a viscous red oil, which on repeated crystallisations and on freezing for 2-3 days in ethylenechloride yielded yellow crystals of the desired *dl-*

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threo-2-dichloroacetamido-1-(2-benzofuranyl)propane-1,3-diol (VI). The *dl-threo* configuration was assigned by analogy with the work of the earlier workers (18).

All three compounds IV, V and VI exhibit ir bands due to, -NH (3290-3350 cm^{-1}) and amide carbonyl (1730 cm^{-1}). The band due to the ketone carbonyl (1680 cm^{-1}) shown by both the compounds IV and V is absent in VI, which confirms the reduction of the carbonyl group in the final product VI. An additional band around 3400 cm^{-1} due to -OH is observed in both V and VI. Further these structures have been confirmed by their nmr spectral studies. These data are given in experimental part. The shift of the singlet peak corresponding to the single aromatic proton of the furan ring, to the lower δ values (19) in the final compound VI clearly indicates the reduction of the ketone carbonyl group in V to give the secondary alcoholic group in VI.

The mass spectral analysis (12) of VI gives a molecular ion peak at m/e 318 (2%), thus confirming its structure (Mol. Wt. 318). The base peak was obtained at m/e 147 (100%).

EXPERIMENTAL

All melting points are uncorrected. The infrared spectra were recorded on a Perkin-Elmer 257 spectrophotometer; nmr spectra were determined at 60 MHz on a varian A-60 NMR spectrophotometer with TMS as an internal reference. Mass spectra was taken on a CEC 21-110B mass spectrometer.

2-Acetylbenzofuran (15a,b) (I).

This was prepared by condensing equimolar quantities of salicylaldehyde and bromoacetone in alcoholic potassium hydroxide. However, the yields were very low.

2-Bromoacetylbenzofuran (16) (II).

This compound was prepared according to Shriner's method in very good yields. Repeated washings of the crude brownish compound with alcohol gave a pale greenish yellow compound which on recrystallisation with alcohol gave colourless needles, m.p. 90° (lit. 90-91°).

Aminomethyl 2-Benzofuranylketone Hydrochloride (III).

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 23.9 g. (0.10 mole) of II in 160 ml. of dry chloroform in one lot. A bright yellow solid mass separated immediately 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, yield, 33-36 g.(87-95%). The adduct softens at 156-158° and melts at 180° dec.

Thirty-eight g. (0.81 mole) of the hexamine adduct was stirred in a solution of 45 ml. of concentrated hydrochloric acid and 90 ml. of ethanol. The mixture became clear after about half an hour and immediately a white solid separated. The resulting suspension was stirred for another hour, frozen and filtered. It was washed with slight acidic alcohol and then with ether to give the colourless amine hydrochloride contaminated with paraformaldehyde and ammonium chloride. It weighed 23.5 g. (theoretical 21.15 g.) and decomposes above 230°. This compound was directly used for the next stage.

Acetamidomethyl 2-Benzofuranyl Ketone (VII).

To a suspension of 2.1 g. (0.01 mole) of III in 20 ml. of ice cold water was added, 2.5 ml. of acetic anhydride with stirring and cooling to 0°. This was followed by the gradual addition of 2-2.5 g. of sodium carbonate. The temperature of the mixture was kept below 5°, by the addition of ice from time to time. When the evolution of carbon dioxide had ceased, an additional 0.3 ml. of acetic anhydride was added and stirring was continued for 15 minutes. It was filtered, washed with cold water and dried, to give 1.2 g. (55%) of VII m.p. 137-139°. Recrystallisation in ethanol yielded white crystals m.p. 140-141°.

Anal. Calcd. for $C_{12}H_{11}O_3N$: C, 66.34; H, 5.07; N, 6.45. Found: C, 66.21; H, 5.19; N, 6.53.

Dichloroacetamidomethyl 2-Benzofuranyl Ketone (IV).

A suspension of 21.1 g. (0.1 mole) of crude III and 100 ml. of dichloroacetyl chloride was heated and stirred at 80° for 30 minutes. The mixture was cooled in a freezing mixture while about 500 g. of chipped ice was slowly added to it with constant stirring. It was well stirred until the crystalline amide IV separated out. It was filtered and washed thoroughly with cold water, to give 20 g. (70%) of solid, m.p. 158-160°. Recrystallization from ethyl acetate gave pure colourless needles, m.p. 166°; ir (potassium bromide): 3350 (NH), 1730 (C=O amide), 1680 cm^{-1} (C=O ketone); nmr (DMSO-d_6): δ 4.70-4.85 (m, 2H, O=C-CH_2-), 6.75 (s, 1H, -$CHCl_2$), 7.3-8.1 (m, 5H, aromatic), 9.2-9.4 (m, 1H, -NHC=O).

Anal. Calcd. for $C_{13}H_9Cl_2O_3N$: C, 50.71; H, 3.17; N, 4.89. Found: C, 50.47; H, 3.21; N, 4.85.

2-Dichloroacetamido-3-hydroxy-1-(2-benzofuranyl)-1-propanone (V).

A mixture of 5.72 g. (0.02 mole) of the dichloroacetamido ketone in 25 ml. of 37-38% aqueous formaldehyde and 60 ml. of 95% ethanol containing a small amount of sodium bicarbonate was stirred at room temperature. Care was taken about the quantity of sodium bicarbonate which was to be added. It was just sufficient to make the stirring mixture clear after 1 to 1½ hours (variations in the quantity of sodium bicarbonate largely affected the purity of the compound V). After stirring for 2 hours, the clear yellow coloured solution was poured on ice, a small amount of sodium chloride was added and stirred well. A small pasty yellow mass separated. The whitish colloidal solution was decanted and kept at 0° for 2 days to give a pale yellow solid which was filtered and dried. The weight of this impure solid was 5.3 g., which melted between a range of 160-171°. This compound on repeated crystallisations from a benzene-ethyl acetate mixture yielded 2.1 g. (33%) of pure hydroxymethylated compound in the form of white silky needles, m.p. 181-182° dec.; ir (potassium bromide): 3395-3365 (OH), 3290 (NH), 1730 (C=O amide), 1680 cm^{-1} (C=O ketone); nmr (DMSO-d_6): δ 3.3 (s, 1H, -OH), 3.90-4.05 (m, 2H, -CH_2OH), 4.95-5.10 (m, 1H, O=C-CH), 6.6 (s, 1H, -$CHCl_2$), 7.2-7.9 (m, 5H, aromatic), 8.8-8.9 (m, 1H, -NH-C=O).

Anal. Calcd. for $C_{13}H_{11}Cl_2O_4N$: C, 49.37; H, 3.48; N, 4.43. Found: C, 49.49; H, 3.37; N, 4.49.

dl-threo-2-Dichloroacetamido-1-(2-benzofuranyl)-propane-1,3-diol (VI).

Compound V (3.78 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. flask equipped with a small vigreux column packed with glass helices. The solution attained a reddish brown colour immediately. Refluxing and slow distillation was continued until the distillate no longer gave a positive test for acetone (6-7 hours). Eight ml. of water was added to the thick residue, refluxed for 15 minutes and filtered. The residue was refluxed twice with 80% absolute alcohol and filtered. The combined filtrates were evaporated *in vacuo*, to yield a thick red oil. Trituration in different solvents was tried in vain. On repeated crystallisations in ethylene chloride and freezing the solution for 2-3 days finally yielded 0.8 g. (21%) of VI as pale yellow needles, m.p. 150-151°. An analytically pure sample was recrystallised from nitromethane in colourless silky needles, m.p. 152°; ir (potassium bromide): 3430-3390 (OH), 3320 (NH), 1730 cm^{-1} (C=O amide); nmr (DMSO-d_6): δ 3.35-4.30 (m, 4H, -CH_2OH, -CHOH), 4.90-5.15 (m, 1H, -CH-NH-), 6.05-6.15 (m, 1H, -CHOH-), 6.6 (s, 1H, $CHCl_2$), 6.75 (s, 1H, furan-aromatic H), 7.1-7.8 (m, 4H, aromatic), 8.3-8.5 (m, 1H, -NH-); m/e (%), 318 (2, M^+), 147 (100).

Anal. Calcd. for $C_{13}H_{13}Cl_2O_4N$: C, 49.06; H, 4.09; N, 4.39. Found: C, 49.21; H, 4.18; N, 4.34.

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