Analogues of Chloramphenicol. Part I.

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The nitro-group of chloramphenicol has been replaced by cyano-, carbamoyl, ethoxycarbonyl, and thiazolyl groups. The dichloroacetamido-group of chloramphenicol has been replaced by a ureido-group and attempts have been made to replace the nitro- by a ureido-group.

This paper describes variation of the chloramphenicol molecule, starting from DL-*threo*-2-acetamido-1-*p*-aminophenylpropane-1 : 3-diol (I; R = NH_2, R′ = Ac) which is prepared by catalytic hydrogenation of the readily available *p*-nitro-derivative. The amino-compound was converted by the Sandmeyer reaction into the cyano-compound, from which the ethoxycarbonyl derivative (I; R = CO_2Et, R′ = H) was prepared by the action of dry hydrogen chloride and ethanol, the acetyl group being removed. The free base, isolated as a gum, was acylated by treatment with methyl dichloroacetate. The carbamoyl compounds (I; R = NH_2·CO, R′ = Ac and $CHCl_2$·CO) were made by the action of alkaline hydrogen peroxide on the corresponding nitriles and the thiocarbamoyl compound by that of alcoholic ammoniacal hydrogen sulphide on (I; R = CN, R′ = Ac). This was used in

p-R·C_6H_4·CH(OH)—CH(NHR′)·CH_2·OH (I)

the preparation of the thiazoles (I; R = 4-methyl- and 4-*p*-nitrophenyl-2-thiazolyl, R′ = Ac or $CHCl_2$·CO) by reaction with the appropriate halogeno-ketone. The thiocarbamoyl derivative was not obtained when the *N*-dichloroacetyl-*p*-cyano-compound reacted with hydrogen sulphide in cold pyridine and triethylamine (cf. Fairful, Lowe, and Peak, *J.*, 1952, 742) or with alcoholic ammoniacal hydrogen sulphide. In the former reaction only triethylamine hydrochloride was obtained, along with oily decomposition products; this instability of the dichloroacetyl group in the presence of tertiary bases is in keeping with the observations of Van der Meer, Kofman, and Veldstra (*Rec. Trav. chim.*, 1953, **72**, 236).

The optically active ureido-compound (I; R = NO_2, R′ = CO·NH_2) from D-(−)-*threo*-2-amino-1-*p*-nitrophenyl-1 : 3-propanediol was prepared by means of potassium cyanate and hydrochloric acid. The racemic ureido-derivatives (I; R = CO·NH_2, R′ = Ac or CO·NH_2) were prepared in the same manner from the appropriate amines. The former was subjected to acid hydrolysis to effect deacetylation and gave intractable gums when attempts were made to prepare dichloroacetyl derivatives.

Antibacterial tests on the dichloroacetyl compounds described above showed activities less than 10% of that of chloramphenicol.

Experimental

DL-threo-2-*Acetamido*-1-p-*aminophenylpropane*-1 : 3-*diol*.—The corresponding nitro-compound (100 g.) in methanol (500 c.c.) was hydrogenated at room temperature and pressure in presence of 5% palladised strontium carbonate (1 g.). Absorption was rapid (*ca.* 1 l./min.) and the hot solution obtained owing to the exothermic reaction was filtered and cooled, to give the *amino*-compound as short needles (*ca.* 90%), m. p. 179—180° (Found: C, 59·0; H, 7·4; N, 12·5. $C_{11}H_{16}O_3N_2$ requires C, 58·9; H, 7·2; N, 12·5%).

DL-threo-2-*Acetamido*-1-p-*cyanophenylpropane*-1 : 3-*diol*.—The above amine (64 g.), dissolved in concentrated hydrochloric acid (80 c.c.), was diazotised with sodium nitrite (23 g.) in water (150 c.c.). The resulting solution was neutralised by sodium carbonate (15·3 g.) and added to a cold solution of sodium cyanide (51·6 g.) and nickel chloride (55·4 g.) in water (200 c.c.) which had been made alkaline with sodium carbonate (15·3 g.). The temperature was kept below 5° throughout. The solution was set aside overnight and filtered with "Hyflo Supercel," and the filtrate was extracted with hot ethyl acetate. From the extract the *nitrile* (42·9 g.) was obtained as pale yellow needles, m. p. 146—147° (Found: C, 61·2; H, 6·3; N, 11·9. $C_{12}H_{14}O_3N_2$ requires C, 61·5; H, 6·0; N, 12·0%).

DL-threo-2-*Dichloroacetamido*-1-p-*ethoxycarbonylphenylpropane*-1 : 3-*diol*.—The foregoing nitrile (10 g.) in ethanol (200 c.c.) was refluxed for 3½ hr. in a stream of dry hydrogen chloride. The alcohol was removed by distillation and the residue washed with ether, dissolved in water (30 c.c.), and heated on the steam-bath for 20 min. The solution was cooled and made alkaline with sodium hydroxide solution, to give an oil, which was extracted with ethyl acetate and dried, then recovered and heated in methanol (50 c.c.) on the steam-bath with methyl dichloroacetate for 1 hr. On working up in the usual manner the *ester* was obtained as needles [from ethyl acetate–light petroleum (b. p. 40—60°)] (3 g.), m. p. 109—110° (Found: C, 48·0; H, 5·1; N, 4·55; Cl, 21·6. $C_{14}H_{17}O_5NCl_2$ requires C, 48·0; H, 4·9; N, 4·0; Cl, 20·25%).

DL-threo-1-p-*Cyanophenyl*-2-*dichloroacetamidopropane*-1 : 3-*diol*.—The foregoing nitrile (5 g.) was deacetylated by dilute sulphuric acid (25 c.c.) on the steam-bath for 1 hr. The cooled solution was made alkaline and extracted with *n*-butanol, the base being isolated as a gum. This was refluxed in methanol with methyl dichloroacetate (4 c.c.) for 1 hr.; by working up in the usual manner the *dichloroacetyl* derivative (1 g.) was obtained as needles, m. p. 126—127° [from ethyl acetate–light petroleum (b. p. 40—60°)] (Found: C, 46·7; H, 4·1; N, 8·85; Cl, 21·7. $C_{12}H_{12}O_3N_2Cl_2$ requires C, 47·4; H, 4·0; N, 9·2; Cl, 23·4%).

DL-threo-2-*Acetamido*-1-p-*carbamylphenylpropane*-1 : 3-*diol*.—The cyano-compound (7·2 g.), obtained from the diazonium reaction above, was dissolved in ethanol (10 c.c.) and diluted with water (40 c.c.). 30% Hydrogen peroxide solution (6 c.c.) and 5N-sodium hydroxide (2 c.c.) were added. A vigorous reaction occurred and the temperature was kept at 20° by cooling. When the reaction had subsided, the temperature was raised to 40° for 10 min. The total reaction time was approx. 30 min. Extraction of the cold solution with *n*-butanol gave a pale brown resin which crystallised from *iso*propanol–ethyl acetate, to give the *amide* (3·6 g.), m. p. 157—158° after drying in a high vacuum (Found: C, 57·2; H, 6·7; N, 11·0. $C_{12}H_{16}O_4N_2$

requires C, 57·1; H, 6·4; N, 11·1%). The corresponding *dichloroacetamido*-compound, obtained analogously, had m. p. 137—138° [small needles from ethyl acetate–light petroleum (b. p. 40—60°)] (Found: C, 45·1; H, 4·6; N, 8·6; Cl, 21·0. $C_{12}H_{14}O_4N_2Cl_2$ requires C, 44·9; H, 4·4; N, 8·7; Cl, 22·1%).

DL-threo-2-*Acetamido*-1-p-*thiocarbamoylphenylpropane*-1 : 3-*diol*.—The corresponding cyano-compound (4·6 g.) in ethanol (25 c.c.) was added to a solution of ammonia in alcohol and a stream of hydrogen sulphide passed into the mixture until a green colour appeared. The solution was then heated in a pressure bottle at 70° for 1 hr.; after evaporation, the residue crystallised from boiling water, to give the *thioamide* as yellow prisms (3·5 g.), m. p. 211—212° (Found: C, 53·45; H, 6·0; N, 10·2; S, 11·9. $C_{12}H_{16}O_3N_2S$ requires C, 53·7; H, 6·0; N, 10·4; S, 12·0%). The 2-dichloroacetamido-derivative could not be obtained by this technique or by the passage of dry hydrogen sulphide for 2 hr. through a cold solution of the corresponding cyano-compound (1·6 g.) in dry pyridine (5 c.c.) and triethylamine (1·5 c.c.). Repeated washing with light petroleum and crystallisation of the residue from ethyl acetate gave triethylamine hydrochloride as needles, m. p. 251—252° (Found: C, 52·5; H, 11·7; N, 9·8; Cl, 24·1. Calc. for $C_6H_{16}NCl$: C, 52·3; H, 11·7; N, 10·2; Cl, 25·8%).

4-[p-(DL-threo-2-*Acetamido*-1 : 3-*dihydroxypropyl*)*phenyl*]-2-*methylthiazole*.—The corresponding thioamide (1·34 g.) was refluxed in ethanol (20 c.c.) and chloroacetone (0·4 c.c.) for 1 hr. The solvent was removed by distillation, the residue made alkaline with sodium hydrogen carbonate solution, and the product obtained as an oil by extraction with ethyl acetate. Crystallisation from ethyl acetate gave the *thiazole* (0·4 g.), m. p. 193—194° (Found: C, 58·1; H, 6·0; N, 9·0; S, 10·9. $C_{15}H_{18}O_3N_2S$ requires C, 58·8; H, 5·9; N, 9·15; S, 10·5%). The corresponding *dichloroacetamido*-derivative was obtained by heating the acetamido-derivative (1 g.) with 2N-sulphuric acid (10 c.c.) for 30 min. on the steam-bath and treating the free base, obtained by use of alkali and extraction with ethyl acetate, with methyl dichloroacetate in methanol for 15 min. on the steam-bath. The thiazole crystallised from methanol as needles, m. p. 204—205° (Found: C, 49·1; H, 4·5; N, 8·1; Cl, 20·0; S, 9·3. $C_{15}H_{16}O_3N_2SCl_2$ requires C, 48·0; H, 4·3; N, 7·5; Cl, 19·8; S, 8·55%).

4-[p-(DL-threo-2′-*Acetamido*-1′ : 3′-*dihydroxypropyl*)*phenyl*]-2-p-*nitrophenylthiazole*.—The thioamide (2·54 g.) was refluxed in ethanol (100 c.c.) with *p*-nitrophenacyl bromide (2·44 g.) for 3 hr. A yellow crystalline solid was formed which was isolated, washed with sodium hydrogen carbonate solution and water, and dried; it formed small prisms (2·3 g.), m. p. 236° (Found: C, 57·3; H, 4·7; N, 9·9; S, 8·3; $C_{20}H_{19}O_5N_3S$ requires C, 58·1; H, 4·6; N, 10·2; S, 7·75%). The corresponding *dichloroacetyl* derivative was obtained by isolation of the dry base and gradual extraction thereof (Soxhlet) into methanol and methyl dichloroacetate; it formed yellow needles, m. p. 234°, from methanol (Found: C, 49·9; H, 3·8; N, 8·5; Cl, 14·5; S, 6·4. $C_{20}H_{17}O_5N_3Cl_2S$ requires C, 49·8; H, 3·55; N, 8·7; Cl, 14·7; S, 6·6%).

D-threo-1-p-*Nitrophenyl*-2-*ureidopropane*-1 : 3-*diol*.—Chloramphenicol base (4·24 g.) was treated in the cold with 2N-hydrochloric acid (10 c.c.) and potassium cyanate (2 g.) in water (10 c.c.) and set aside overnight. The mixture was evaporated to dryness and the *ureido*-compound obtained by crystallisation from ethanol as needles, m. p. 170—171° (Found: C, 47·2; H, 5·5; N, 17·0. $C_{10}H_{13}O_5N_3$ requires C, 47·1; H, 5·1; N, 16·5%).

DL-threo-2-*Acetamido*-1-p-*ureidophenylpropane*-1 : 3-*diol*.—DL-*threo*-1-Acetamido-2-*p*-aminophenylpropane-1 : 3-diol (4·48 g.) was treated as in the preceding preparation, and the *ureido*-compound crystallised from water as needles, m. p. 218° (decomp.) (Found: C, 54·3; H, 6·7; N, 15·4. $C_{12}H_{17}O_4N_3$ requires C, 53·9; H, 6·4; N, 15·7%).

DL-threo-2-*Ureido*-1-p-*ureidophenylpropane*-1 : 3-*diol*.—DL-*threo*-2-Amino-1-*p*-aminophenylpropane-1 : 3-diol (3·64 g.) was treated as in the preceding preparation with 2N-hydrochloric acid (20 c.c.) and potassium cyanate (4 g.). The *diureido*-derivative was obtained from aqueous ethanol as a white microcrystalline solid, m. p. 199° (decomp.) (Found: C, 48·3; H, 6·2; N, 21·4. $C_{11}H_{16}O_4N_4$ requires C, 49·3; H, 6·0; N, 20·9%).

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