59. *Three New Analogues of Chloramphenicol.*

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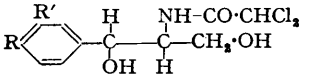
In continuation of our work on the relation between constitution and antibiotic activity in the chloramphenicol series, three further analogues of chloramphenicol have been synthesised for biological testing.

As has been reported recently, the antibacterial properties of chloramphenicol (chloromycetin) are qualitatively more connected with the *threo*-configuration of the molecule and the presence of a *p*-substituent in the phenyl nucleus than with the nature of that substituent (Buu-Hoï and Khoï, *Compt. rend.*, 1949, **229**, 1343; 1950, **230**, 967; Buu-Hoï, Hoán, Jacquignon, and Khoï, *ibid.*, 1950, **230**, 662; *J.*, 1950, 2766). In view of these results, three further substances having a molecular configuration akin to that of chloramphenicol (I), namely, *threo*-2-dichloroacetamido-1-*p*-tolyl- (II), -1-*p*-methoxyphenyl- (III), and -1-(3 : 4-dichlorophenyl)-propane-1 : 3-diol (IV), have now been prepared for biological testing. The method used



(I) : R = NO_2, R′ = H (III) : R = OMe, R′ = H.

(II) : R = Me, R′ = H. (IV) : R = R′ = Cl.

started from *p*-methyl-, *p*-methoxy-, and 3 : 4-dichloro-acetophenone, and followed the pattern frequently described (Long and Troutman, *J. Amer. Chem. Soc.*, 1949, **71**, 2469; Buu-Hoï *et al.*, *locc. cit.*). It is to be noted that in the condensation of formaldehyde with ω-acetamido-*p*-methyl- and -3 : 4-dichloro-acetophenone, the introduction of only one hydroxymethyl group was again observed; another feature of the present syntheses was the formation of a single secondary alcohol (believed by reason of analogy to be the *threo*-compound) in the Ponndorf–Meerwein reduction of ω-acetamido-β-hydroxy-*p*-methyl-, α-acetamido-β-hydroxy-*p*-methoxy-, and ω-acetamido-3 : 4-dichloro-β-hydroxy-propiophenone.

Screening bacteriological tests showed compounds (II) and (III) to have an extremely low degree of activity against *Escherichia coli* and *Staphylococcus aureus*. Compound (III) showed notable activity against *Shigella paradysenteriae* and *St. aureus*.

Experimental.

Preparation of Intermediates.—The large-scale preparation of 4-methyl- and 4-methoxy-acetophenone presented no difficulty, but that of 3 : 4-dichloroacetophenone according to the method described in the literature (Roberts and Turner, *J.*, 1927, 1855) gave extremely low yields, and another method was devised. Into a well-stirred mixture of *o*-dichlorobenzene (400 c.c.) and powdered aluminium chloride (300 g.) kept at 80°, acetic anhydride (150 g.) was dropped during 1 hour. Stirring was continued for 3 more hours, during which the temperature was raised to 120°. After 6 hours at room temperature, the semi-solid reaction mixture was treated with ice and hydrochloric acid, and the ketone thus obtained (128 g.) purified by vacuum-distillation; after recrystallisation from ligroin, it had m. p. 76°.

ω-Acetamido-4-methylacetophenone.—The hexamethylenetetramine salt of ω-bromo-4-methylacetophenone (170 g.) was prepared from ω-bromo-4-methylacetophenone (130 g.) (Kunckell, *Ber.*, 1897, **30**, 577) and hexamethylenetetramine (94 g.) in chlorobenzene (200 c.c.) in the usual way, and formed colourless microcrystals, m. p. 188° (decomp.). Hydrolysis by means of hydrochloric acid (250 c.c.) in ethanol (400 c.c.) gave α-amino-4-methylacetophenone hydrochloride (86 g.), m. p. 220° (decomp.);

Ryan (Ber., 1898, **31**, 2133) gave m. p. 206° for a product prepared by another method. To a well-stirred solution of this salt (120 g.) in ice-water (550 g.), acetic anhydride (150 g.) and then a solution of sodium acetate (175 g.) in ice-water (100 g.) were cautiously added. After 1 more hour's stirring, the solid *ω-acetamido-4-methylacetophenone* was filtered off and recrystallised from ethyl acetate, giving fine colourless prisms, m. p. 132° (Found : N, 7·2. $C_{11}H_{13}O_2N$ requires N, 7·3%).

α-Acetamido-β-hydroxy-p-*methylpropiophenone*.—A mixture of the foregoing amide (19 g.), ethanol (70 c.c.), and 30% aqueous formaldehyde (40 c.c.) was stirred with pure sodium hydrogen carbonate (1 g.; prepared *in situ* from sodium carbonate and carbon dioxide) for 2 hours at 35°. The solution thus obtained was concentrated *in vacuo* and thoroughly extracted with ethyl acetate. The *ketone* obtained after evaporation of the solvent (16 g.) crystallised from ethyl acetate in fine colourless needles, m. p. 121°, very soluble in ethanol (Found : C, 65·0; H, 6·8. $C_{12}H_{15}O_3N$ requires C, 65·1; H, 6·7%).

DL-threo-2-*Acetamido*-1-p-*tolylpropane*-1 : 3-*diol*.—A solution of the foregoing compound (15 g.) and aluminium *iso*propoxide (21 g.) in anhydrous *iso*propyl alcohol (170 c.c.) was gently heated for 12 hours with removal of acetone; water (20 c.c.) was then added and the mixture boiled for some minutes. The solid formed was filtered off and thoroughly extracted with boiling *iso*propyl alcohol; the filtrate was combined with the extracts, and the whole concentrated *in vacuo*. The *diol* (7 g.) formed, from ethyl acetate or methanol, colourless lustrous leaflets, m. p. 150° (Found : C, 64·3; H, 7·7. $C_{12}H_{17}O_3N$ requires C, 64·5; H, 7·7%). No isomer could be detected in the mother-liquors.

DL-threo-2-*Amino*-1-p-*tolylpropane*-1 : 3-*diol*.—The foregoing amide (2 g.) was hydrolysed by 10% hydrochloric acid (33 c.c.) at 95° for 2 hours; after basification of the cooled mixture by means of sodium hydroxide, the precipitated *amine* was recrystallised from benzene, giving fine colourless prisms (1 g.), m. p. 90° (Found : N, 7·4. $C_{10}H_{15}O_2N$ requires N, 7·7%).

DL-threo-2-*Dichloroacetamido*-1-p-*tolylpropane*-1 : 3-*diol* (II).—This *amide*, obtained from the foregoing amine (2 g.; dried *in vacuo*) by 2 hours' refluxing with freshly distilled ethyl dichloroacetate (5 c.c.) and precipitation with ligroin, formed from benzene fine colourless leaflets, m. p. 106° (Found : C, 49·4; H, 5·2. $C_{12}H_{15}O_3NCl_2$ requires C, 49·3; H, 5·2%)

ω-Acetamido-p-*methoxyacetophenone*.—ω-Bromo-*p*-methoxyacetophenone (95 g.) was prepared in good yield by dropping a solution of bromine in acetic acid into a well-cooled solution of *p*-methoxyacetophenone in acetic acid; Kunckell and Scheven (*Ber.*, 1898, **31**, 173) made this compound by the Friedel–Crafts reaction between anisole and bromoacetyl bromide, and Boeseken, Hansen, and Bertram (*Rec. Trav. chim.*, 1916, **35**, 311) made it by passing bromine vapour in *p*-methoxyacetophenone dissolved in acetic acid. It gave with hexamethylenetetramine (68 g.) an *adduct* which was precipitated from chlorobenzene (100 c.c.) as a colourless microcrystalline powder (135 g.), m. p. 222°. This yielded on hydrolysis with hydrochloric acid (170 c.c.) in methanol (200 c.c.) ω-amino-*p*-methoxyacetophenone hydrochloride (66 g.) which was treated with 70 g. of acetic anhydride. *ω-Acetamido*-p-*methoxyacetophenone* (43 g.) formed, from ethyl acetate, lustrous colourless leaflets, m. p. 117° (Found : N, 6·5. $C_{11}H_{13}O_3N$ requires N, 6·7%).

α-Acetamido-β-hydroxy-p-*methoxypropiophenone*.—Prepared from the foregoing amide (21 g.), aqueous formaldehyde (40 c.c.), and sodium hydrogen carbonate (1 g.) in ethanol (70 c.c.), this *ketone* formed, from ethyl acetate, shiny colourless needles (10 g.), m. p. 158° (Found : C, 61·0; H, 6·4. $C_{12}H_{15}O_4N$ requires C, 60·8; H, 6·3%).

DL-threo-2-*Acetamido*-1-p-*methoxyphenylpropane*-1 : 3-*diol*.—Obtained from the foregoing ketone (9 g.), aluminium *iso*propoxide (10 g.), and *iso*propyl alcohol (60 c.c.) in the usual way, this *diol* crystallised from water in large colourless prisms (7 g.), m. p. 123° (Found : C, 60·5; H, 7·3. $C_{12}H_{17}O_4N$ requires C, 60·2; H, 7·1%).

DL-threo-2-*Amino*-1-p-*methoxyphenylpropane*-1 : 3-*diol*.—Hydrolysis of the foregoing amide (6 g.) with 20% hydrochloric acid (60 c.c.) gave, after basification, the free *amine* (3 g.), crystallising in lustrous colourless leaflets, m. p. 102°, from ethyl acetate (Found : N, 6·8. $C_{10}H_{15}O_3N$ requires N, 7·1%).

DL-threo-2-*Dichloroacetamido*-1-p-*methoxyphenylpropane*-1 : 3-*diol* (III).—This *compound* (1·5 g.), obtained from the foregoing amine (2 g.) and methyl dichloroacetate (3 g.), formed fine lustrous colourless leaflets, m. p. 91°, from benzene (Found : C, 47·3; H, 5·0. $C_{12}H_{15}O_4NCl_2$ requires C, 46·8; H, 4·8%).

ω-Bromo-3 : 4-*dichloroacetophenone*.—This compound has apparently been prepared by Lutz *et al.* (*J. Org. Chem.*, 1947, **12**, 617), but was not described. To a solution of 3 : 4-dichloroacetophenone (50 g.) in acetic acid (100 c.c.) containing 48% hydrobromic acid (1 c.c.), bromine (43 g. in 50 c.c. of acetic acid) was added dropwise during 2 hours. The precipitate obtained on decomposition of the reaction mixture with cracked ice crystallised from ethanol in fine shiny colourless needles (70 g.), m. p. 63°. The hexamethylenetetramine *adduct* (92 g.) obtained from the bromo-ketone (70 g.) and hexamethylenetetramine (41 g.) in chlorobenzene (100 c.c.) was obtained from this solvent as a colourless microcrystalline powder, m. p. 225° (decomp.) (Found : N, 13·3. $C_{14}H_{17}ON_4BrCl_2$ requires N, 13·7%).

ω-Acetamido-3 : 4-*dichloroacetophenone*.—The foregoing adduct (90 g.) was stirred with hydrochloric acid (200 c.c.) in methanol (150 c.c.) for 12 hours at room temperature, giving *ω-amino*-3 : 4-*dichloroacetophenone hydrochloride* in the form of fine colourless needles (50 g.), decomp. >300°; usual treatment of this salt (48 g.) with acetic anhydride (60 g.) and sodium acetate (50 g.) gave the *amide* which crystallised from ethyl acetate in long shiny colourless needles (45 g.), m. p. 137° (Found : N, 5·5. $C_{10}H_9O_2NCl_2$ requires N, 5·7%).

α-Acetamido-3 : 4-*dichloro-β-hydroxypropiophenone*.—Obtained from the foregoing substance (43 g.), aqueous formaldehyde (32 c.c.), and sodium hydrogen carbonate (2 g.) in ethanol (200 c.c.), this *compound* formed, from ethyl acetate and methanol, fine shiny colourless prisms (12 g.), m. p. 158° (Found : C, 47·9; H, 3·9; N, 4·7. $C_{11}H_{11}O_3NCl_2$ requires C, 47·8; H, 4·0; N, 5·0%).

DL-threo-2-*Acetamido*-1-(3 : 4-*dichlorophenyl*)*propane*-1 : 3-*diol*.—The reduction of the foregoing ketone (6 g.) with aluminium *iso*propoxide (5 g.) in *iso*propyl alcohol (30 c.c.) yielded a single *alcohol* crystallising from methanol in lustrous colourless leaflets (5 g.), m. p. 169° (Found : C, 47·5; H, 4·6. $C_{11}H_{13}O_3NCl_2$ requires C, 47·4; H, 4·6%).

DL-threo-2-*Amino*-1-(3 : 4-*dichlorophenyl*)*propane*-1 : 3-*diol* formed shiny colourless leaflets, m. p. 130°, from benzene (Found : N, 5·9. $C_9H_{11}O_2NCl_2$ requires N, 5·9%).

DL-threo-2-*Dichloroacetamido*-1-(3 : 4-*dichlorophenyl*)*propane*-1 : 3-*diol* (IV).—A mixture of the foregoing amine (1 g.) and methyl dichloroacetate (2 g.) was kept at 80° for 3 hours; the precipitate (1 g.) obtained on treatment with light petroleum crystallised from benzene in colourless leaflets, m. p. 91° (Found : C, 38·2; H, 3·5. $C_{11}H_{11}O_3NCl_4$ requires C, 38·0; H, 3·2%).

Note : It should be mentioned that the use of freshly distilled methyl dichloroacetate is indispensable in chloramphenicol studies, as this reagent rapidly becomes acid when kept, and then yields with amines mixtures of the required dichloroacetamides with amine dichloroacetates. This might perhaps account for the difficulties encountered by Long and Troutman (*J. Amer. Chem. Soc.*, 1950, **72**, 4299) in obtaining pure DL-*threo*-2-dichloroacetamido-1-*m*-nitrophenylpropane-1 : 3-diol.

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