532. *Nuclear Halogen-containing Analogues of Chloramphenicol.*

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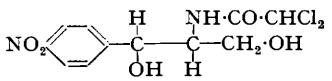
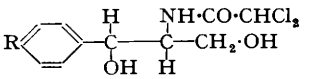
In continuation of earlier work on analogues of chloramphenicol, molecules derived from chloramphenicol by replacement of the nitro-group by fluorine and iodine have been synthesised for biological testing. In connection with this problem, 1-*p*-chloro- and 1-*p*-bromo-phenyl-2-dichloroacetamidoethanol were also prepared.

Notwithstanding the now widespread clinical use of chloramphenicol (chloromycetin), little definite is yet known about the nature of its antibiotic activity. However, its chemical constitution as an optically active form of *threo*-2-dichloroacetamido-1-*p*-nitrophenylpropane-1 : 3-diol (I) (Controulis, Rebstock, and Crooks, *J. Amer. Chem. Soc.*, 1949, **71**, 2463) strongly suggests that the versatile antibacterial and virucidal effects of that drug might be caused by biochemical



(I.)

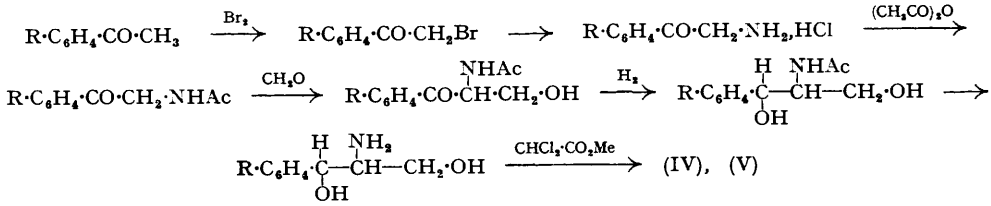


(II; R = Br.) (III; R = Cl.) (IV; R = Cl.) (V; R = I.)

competition with several important metabolites of the aromatic series which bear a more or less similar structure. A tentative, but by no means exhaustive, list of such metabolites would include *p*-aminobenzoic acid, β-phenylalanine, tyrosine, and even tryptophan, the last particularly with regard to antiviral activity. *p*-Nitrobenzoic acid and its esters are already known to antagonise *p*-aminobenzoic acid (Miller, *J. Pharmacol. Exp. Therap.*, 1941, **71**, 14); and substances such as β-hydroxyphenylalanine, *m*-fluorophenylalanine, and 3-fluorotyrosine are known to be competitive antagonists for β-phenylalanine (Beerstecher and Shive, *J. Biol. Chem.*, 1946, **164**, 53; Mitchell and Niemann, *J. Amer. Chem. Soc.*, 1947, **60**, 1232). These considerations led us to think that the antibiotic properties of chloramphenicol might not be specific, and that other substances with similar constitution might also be active. This assumption has now proved to be correct, as (±)-*threo*-2-dichloroacetamido-1-*p*-bromophenylpropane-1 : 3-diol (II) was found only about five times less active than (±)-chloramphenicol against a variety of micro-organisms including *Staphylococcus aureus*, *Escherichia coli*, and *B. paratyphosus*

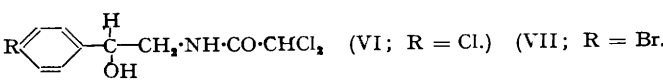
B. Owing to its relatively low toxicity in animals, this compound is now undergoing clinical trial. The activity of (±)-*threo*-2-dichloroacetamido-1-*p*-chlorophenylpropane-1 : 3-diol (III) was somewhat inferior, although of the same nature. The presence of a substituent in the *para*-position seems to be of paramount importance, since (±)-*threo*-2-dichloroacetamido-1-*m*-nitrophenylpropane-1 : 3-diol (Buu-Hoï and Khoï, *Compt. rend.*, 1949, **229**, 1343; 1950, **230**, 967) was inactive.

In view of these promising results, we have now prepared the *p*-fluoro- (IV) and *p*-iodo-analogues (V) for biological testing. The method used started from *p*-fluoro- and *p*-iodo-acetophenone, and followed the pattern of the Long–Troutman synthesis of chloramphenicol (*J. Amer. Chem. Soc.*, 1949, **71**, 2469) and of the synthesis of (II) and (III) (Buu-Hoï, Hoán, Jacquignon, and Khoï, *Compt. rend.*, 1950, **230**, 662) :



Whereas formaldehyde and acetophenone give a di(hydroxymethyl) compound (Fuson and McKewer, *J. Amer. Chem. Soc.*, 1938, **60**, 2935), only one hydroxymethyl group could be introduced in the present instances. This behaviour seems to be general to α-acetamidoacetophenones, and is reminiscent of the inertia towards substitution found of the tertiary hydrogen atom of *iso*propyl groups (cf. Ziegler *et al.*, *Annalen*, 1942, **551**, 80). It is also noteworthy that the Ponndorf–Meerwein reductions of α-acetamino-*p*-fluoro-β-hydroxy- and α-acetamino-β-hydroxy-4-iodopropiophenone led to a single secondary alcohol in each case. These reaction products are assumed to belong to the *threo*- and not to the *erythro*-series, both because of analogy with the behaviour of α-acetamido-β-hydroxy-*p*-nitropropiophenone (Long and Troutman, *loc. cit.*), and because of the antibacterial activity of (IV) and (V). Unexpectedly, the latter compound had only about one-thirtieth of the activity of (±)-chloramphenicol towards *Staph. aureus* and *E. coli*.

A striking feature of the biochemistry of chloramphenicol is that whilst 2-dichloroacetamido-2-*p*-nitrophenylpropane-1 : 3-diol (a position-isomer very close to chloramphenicol) was completely inactive (Ruoff and Miller, *J. Amer. Chem. Soc.*, 1950, **72**, 1417), suppression of the



terminal hydroxymethyl group has no such drastic effect, as (±)-2-dichloroacetamido-1-*p*-nitrophenylethanol (Buu-Hoï and Khoï, *loc. cit.*) is now found to produce complete inhibition of the growth of *Staph. aureus* and *E. coli*. at a concentration of 6×10^{-5}. This led us to describe here two analogous compounds, (±)-1-*p*-chloro- (VI) and (±)-1-*p*-bromophenyl-2-dichloroacetamidoethanol (VII). These were prepared from *p*-chloro- and *p*-bromo-acetophenone by a method similar to that already outlined in a previous paper (Buu-Hoï and Khoï, *loc. cit.*, 1950).

Experimental.

(±)-2-*Acetamido*-1-p-*chlorophenylethanol*.—A solution of α-acetamido-*p*-chloroacetophenone (Buu-Hoï, Hoán, Jacquignon, and Khoï, *loc. cit.*) (20 g.) and freshly distilled aluminium *iso*propoxide (23 g.) in anhydrous *iso*propyl alcohol (200 c.c.) was gently refluxed, and the acetone formed removed through an efficient Vigreux column. After 24 hours, no more acetone could be detected in the distillate by means of sodium hydrogen sulphite; water (20 c.c.) was then added and the mixture boiled for some minutes. The solid obtained was filtered off and extracted 3 times with small quantities of boiling *iso*propyl alcohol. The liquid from the filtration was combined with the extracts and the whole was concentrated in a vacuum. The *compound* obtained after cooling formed fine colourless microscopic needles (15 g.), m. p. 122°, from *iso*propyl alcohol (Found : C, 56·0; H, 5·6. $C_{10}H_{12}O_2NCl$ requires C, 56·2; H, 5·6%).

(±)-2-*Amino*-1-p-*chlorophenylethanol*.—The foregoing amide (10 g.) was heated for 1 hour on a water-bath with concentrated hydrochloric acid (10 g.) and water (100 c.c.). The solution obtained was chilled, and basified with ice-cooled 20% aqueous sodium hydroxide. The solid *amine* precipitated (8 g.) was collected, washed with a little ice-water, and dried in a vacuum; it formed colourless needles, m. p. 94°, from benzene (Found : C, 55·8; H, 6·0. $C_8H_{10}ONCl$ requires C, 55·9; H, 5·8%).

(±)-1-p-*Chlorophenyl*-2-*dichloroacetamidoethanol* (VI).—A mixture of the foregoing amine (5 g.) with methyl dichloroacetate (6 g.) was heated at 90° for 3 hours, and the reaction product poured into ligroin; the solid obtained on scratching (5 g.) crystallised in shiny colourless needles, m. p. 85°, from ethyl acetate or ligroin (Found : C, 42·3; H, 3·6. $C_{10}H_{10}O_2NCl_3$ requires C, 42·4; H, 3·5%).

(±)-2-*Acetamido*-1-p-*bromophenylethanol*.—A solution of α-acetamido-*p*-bromoacetophenone (Buu-Hoï, Hoán, Jacquignon, and Khoï, *loc. cit.*) (25 g.) and aluminium *iso*propoxide (31 g.) in *iso*propyl alcohol (200 c.c.) was treated as in the case of the chlorine analogue. The *product* obtained (20 g.) formed fine colourless needles, m. p. 142°, from *iso*propyl alcohol (Found : C, 46·5; H, 4·7. $C_{10}H_{12}O_2NBr$ requires C, 46·5; H, 4·65%).

(±)-2-*Amino*-1-p-*bromophenylethanol*.—This *amine* (4 g.), obtained as usual from the foregoing compound (7 g.) by means of 10% hydrochloric acid, formed colourless needles, m. p. 112°, from benzene (Found : C, 44·4; H, 4·8. $C_8H_{10}ONBr$ requires C, 44·4; H, 4·6%).

(±)-1-p-*Bromophenyl*-2-*dichloroacetamidoethanol*.—A mixture of the foregoing amine (1 g.) and methyl dichloroacetate (5 g.) was heated for 3 hours at about 90°; the *amide* obtained after treatment with ligroin crystallised in fine colourless needles, m. p. *ca.* 85°, from benzene (Found : C, 36·4; H, 3·2. $C_{10}H_{10}O_2NCl_2Br$ requires C, 36·6; H, 3·1%).

α-*Acetamido*-p-*fluoroacetophenone* [with Miss D. Lavit].—A mixture of α-bromo-*p*-fluoroacetophenone (115 g.) (cf. Lutz *et al.*, *J. Org. Chem.*, 1947, **12**, 617; Buu-Hoï, Hoán, and Jacquignon, *Rec. Trav. chim.*, 1949, **68**, 781) and hexamethylenetetramine (80 g.) in dry chlorobenzene (1 l.) was stirred at 50° for 4 hours, and kept overnight at room temperature. The hexamethylenetetramine salt of α-bromo-*p*-fluoroacetophenone (170 g.) thus obtained was filtered off, and gave after crystallisation colourless needles, m. p. about 184—185° (decomp.), from ethanol. The crude quaternary salt (165 g.) was stirred with ethanol (350 c.c.) and concentrated hydrochloric acid (300 c.c.) at room temperature for 20 hours. Concentration *in vacuo* and subsequent chilling gave a colourless crystalline magma of 4-fluorophenacylamine hydrochloride (60 g.), which was filtered off and washed with cold ethanol. To a well-stirred solution of this crude salt (50 g.) in ice-water (200 c.c.), acetic anhydride (50 g.) and then a solution of sodium acetate (74 g.) in ice-water (150 c.c.) were cautiously added. Stirring was continued for a further hour at room temperature, and the solid obtained filtered off and recrystallised in ethyl acetate. α-*Acetamido*-p-*fluoroacetophenone* (15 g.) formed shiny colourless leaflets, m. p. 155° (Found : C, 58·6; H, 5·0. $C_{10}H_{10}O_2NF$ requires C, 61·5; H, 5·1%).

α-*Acetamido*-p-*fluoro*-β-*hydroxypropiophenone*.—A mixture of α-acetamido-*p*-fluoroacetophenone (10 g.), ethanol (40 c.c.), and 30% aqueous formaldehyde (10 c.c.) was stirred with sodium hydrogen carbonate (0·5 g.) for 2 hours at 35°. The clear solution thus obtained was poured into ice-water and extracted several times with ether. The *ketone* obtained after evaporation of the ether (10 g.) crystallised in fine colourless needles, m. p. 128°, from ethyl acetate (Found : C, 58·6; H, 5·5. $C_{11}H_{12}O_3NF$ requires C, 58·7; H, 5·3%).

(±)-threo-2-*Acetamido*-1-p-*fluorophenylpropane*-1 : 3-*diol*.—A solution of the foregoing compound (9 g.) and aluminium *iso*propoxide (13 g.) in anhydrous *iso*propyl alcohol (100 c.c.) was gently refluxed for 7 hours with removal of acetone. The *amide* (5 g.) obtained after the usual treatment formed colourless needles, m. p. 144°, from ethyl acetate (Found : C, 58·0; H, 6·2. $C_{11}H_{14}O_3NF$ requires C, 58·1; H, 6·1%). There was no sign of the presence of a stereoisomer formed during this reduction.

(±)-threo-2-*Amino*-1-p-*fluorophenylpropane*-1 : 3-*diol*.—Hydrolysis of the foregoing amide by hydrochloric acid in the usual way, and basification of the reaction product, gave the free *amine*, crystallising in fine colourless prisms, m. p. 121°, from benzene (Found : C, 58·1; H, 6·4. $C_9H_{12}O_2NF$ requires C, 58·3; H, 6·4%).

(±)-threo-2-*Dichloroacetamido*-1-p-*fluorophenylpropane*-1 : 3-*diol* (IV).—This *compound*, obtained from treatment of the foregoing carefully dried amine with methyl dichloroacetate in the usual way, formed fine colourless prisms, m. p. 131—132°, from benzene (Found : C, 44·6; H, 4·3. $C_{11}H_{12}O_3NCl_2F$ requires C, 44·5; H, 4·1%).

α-*Acetamido*-p-*iodoacetophenone*.—α-Bromo-*p*-iodoacetophenone (Kimura, *Ber.*, 1934, **67**, 395) was best prepared by bromating *p*-iodoacetophenone in chloroform in daylight; 80 g. of this compound, allowed to react with hexamethylenetetramine (40 g.) in chlorobenzene (175 c.c.) at 50° in the usual way, yielded 120 g. of the quaternary *salt*, *p*-$I{\cdot}C_6H_4{\cdot}CO{\cdot}CH_2Br,N_4[CH_2]_6$, crystallising in fine colourless prisms, m. p. *ca.* 218—220° (decomp.), from ethanol, which become pink in the air (Found : N, 11·5. $C_{14}H_{18}N_4BrI$ requires N, 11·8%). *p*-Iodophenacylamine hydrochloride (98 g.) was obtained by treatment of the foregoing quaternary salt (115 g.) with hydrochloric acid (180 g.) in ethanol (200 c.c.) in the usual way. A solution of this hydrochloride (60 g.) in ice-water (150 c.c.) was acetylated by acetic anhydride (40 g.) and sodium acetate (60 g. in 100 c.c. of ice-water); after crystallisation from ethanol, the *acetyl* compound formed fine colourless needles (26 g.), m. p. 193—194° (Found : C, 39·5; H, 3·5. $C_{10}H_{10}O_2NI$ requires C, 39·6; H, 3·3%).

α-*Acetamido*-β-*hydroxy*-p-*iodopropiophenone*.—A mixture of the foregoing amide (23 g.) in ethanol (100 c.c.), 30% aqueous formaldehyde (25 c.c.), and pure sodium hydrogen carbonate (1 g.) was stirred for 2 hours at 35°; the reaction product was poured into water, and the precipitated *compound* (20 g.) recrystallised from ethyl acetate, giving colourless needles, m. p. 179° (decomp.), becoming pink in the air (Found : C, 39·5; H, 3·7. $C_{11}H_{12}O_3NI$ requires C, 39·6; H, 3·6%).

(±)-threo-2-*Acetamido*-1-p-*iodophenylpropane*-1 : 3-*diol*.—The foregoing compound (17 g.), reduced in the usual way with aluminium *iso*propoxide (2 g.) in *iso*propyl alcohol (200 c.c.), yielded the *diol* (10 g.), crystallising in colourless needles, m. p. 166°, from ethyl acetate (Found : C, 39·2; H, 4·3. $C_{11}H_{14}O_3NI$ requires C, 39·4; H, 4·2%).

(±)-threo-2-*Amino*-1-p-*iodophenylpropane*-1 : 3-*diol*.—Hydrolysis of the foregoing *acetyl* compound (4·5 g.) with hydrochloric acid in the usual way, gave on basification the free *amine* (2·5 g.), crystallising in colourless needles, m. p. 119—120°, from benzene (Found: C, 36·6, H, 4·3. $C_9H_{12}O_2NI$ requires C, 36·5; H, 4·1%).

(±)-threo-2-*Dichloroacetamido*-1-p-*iodophenylpropane*-1 : 3-*diol* (V).—This *compound* (1·5 g.), obtained from the foregoing amine (1·5 g.) and methyl dichloroacetate, formed fine colourless prisms, m. p. 103—104°, from benzene (Found: C, 32·6; H, 3·2. $C_{11}H_{12}O_3NCl_2I$ requires C, 32·7; H, 3·0%).

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