15. *Some Analogues of Chloramphenicol.*

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2-Dichloroacetamido-propane-1 : 3-diol, -2-hydroxymethylbutanol, -2-phenylpropane-1 : 3-diol, -2-*p*-nitrophenylpropane-1 : 3-diol, -4-methylpentane-1 : 3-diol, -3-*cyclo*hexylpropane-1 : 3-diol, and -3-*cyclo*hexylpropan-1-ol have been synthesised by standard methods. The products have no significant bactericidal or virucidal activity.

Since the publications of Rebstock, Crooks, Controulis, and Bartz (*J. Amer. Chem. Soc.*, 1949, **71**, 2458) and of Controulis, Rebstock, and Crooks (*ibid.*, p. 2463) dealing with the structure and synthesis of chloramphenicol, several analogues of this antibiotic have been synthesised. The products differ from chloramphenicol mainly in replacement of the *p*-nitro-group by other groups or elements in the *para* or other positions or in replacement of the dichloroacetyl by other acyl groups. Either of these changes is sufficient, in general, to decrease the biological activity.

We have prepared some simple analogues of chloramphenicol, in some of which the phenyl group was replaced by an alkyl group or by a reduced ring. These compounds were either inactive, or had no significant activity in *vitro* against *Staph. aureus*, *B. coli*, and *Ps. pyocyanea*, and *in vivo* against influenza, mouse pneumonitis, and *B. typhi*.

2-Dichloroacetamidopropane-1 : 3-diol, 2-dichloroacetamido-2-hydroxymethylbutanol and 2-dichloroacetamido-2-phenylpropane-1 : 3-diol were readily obtained by catalytically reducing the corresponding 2-nitropropane-1 : 3-diols and heating the resulting amino-diols with methyl dichloroacetate (Controulis, *et al.*, *loc. cit.*). In addition, 2-dichloroacetamido-2-*p*-nitrophenylpropane-1 : 3-diol, a positional isomer of chloramphenicol, was prepared by a route essentially identical with that subsequently described by Ruoff and Miller (*J. Amer. Chem. Soc.*, 1950, **72**, 1417). Since its properties agree with those given by the latter authors, only those intermediates not reported by the American workers are described in the present communication.

None of these four compounds possesses an asymmetric carbon atom; two other analogues which were prepared, 2-dichloroacetamido-4-methylpentane-1 : 3-diol and 2-dichloroacetamido-3-*cyclo*hexylpropane-1 : 3-diol, possess two asymmetric carbon atoms and should exist in both the *threo*- and the *erythro*-configuration. In both cases, however, only one of the two possible racemates was ever isolated.

The preparation of 4-methyl-2-nitropentane-1 : 3-diol was first attempted by condensation of 3-methyl-1-nitrobutan-2-ol (Schmidt, Ascherl, and Mayer, *Ber.*, 1925, **58**, *B*, 2430) with aqueous formaldehyde in the presence of potassium carbonate or sodium hydroxide, following Sprang and Degering's technique (*J. Amer. Chem. Soc.*, 1942, **64**, 1735; 1943, **65**, 628). This led to an oily mixture from which the required compound could not be isolated. The required nitro-diol was eventually obtained by condensation of *iso*butaldehyde with 2-nitroethanol in the presence of methanolic sodium methoxide, whereupon the sodium salt separated in reasonably good yield. Liberation of the diol was best effected with salicylic acid in ether (Schmidt and Wilkendorf, *Ber.*, 1919, **52**, 389). It formed an oil (possibly a mixture of racemates) which failed to crystallise when kept, but which was readily reduced catalytically over Raney nickel to the corresponding base, characterised as the crystalline triacetyl derivative. Condensation with methyl dichloroacetate then yielded the required 2-dichloroacetamido-4-methylpentane-1 : 3-diol. Reduction of the nitro-diol over platinum oxide or palladium oxide in acetic acid was slow and incomplete and the product contained a large proportion of non-basic material.

Small amounts of 2-acetamido-1 : 3-diacetoxypropane and 2-dichloroacetamidopropane-1 : 3-diol were invariably isolated during the preparation of the above compounds; they probably arose from some 2-nitropropane-1 : 3-diol present in the 2-nitroethanol used.

The condensation of *cyclo*hexanaldehyde with 2-nitroethanol was similarly effected in the presence of sodium methoxide, and 3-*cyclo*hexyl-2-nitropropane-1 : 3-diol was liberated from the resulting sodium salt by acetic acid and reduced over platinum oxide. 2-Amino-3-

*cyclo*hexylpropane-1 : 3-diol was isolated as its hydrochloride and converted into the dichloroacetamide. It was possible to assign to the product the *erythro*-configuration, since it differed from the authentic *threo*-compound obtained by Dr. B. J. Heywood (unpublished observation) by complete catalytic reduction of ±-*threo*-2-nitro-3-phenylpropane-1 : 3-diol.

When the sodium salt of the 3-*cyclo*hexyl-2-nitropropane-1 : 3-diol was dissolved in cold dilute hydrochloric acid, dehydration occurred (cf. Emerson, *Chem. Reviews*, 1949, **45**, 368; Hass and Riley, *ibid.*, 1943, **32**, 410); the resulting unsaturated nitro-alcohol was reduced by either lithium aluminium hydride (Gilsdorf and Nord, *J. Org. Chem.*, 1950, **15**, 807) or catalytically over platinum oxide or Raney nickel, yielding 2-amino-3-*cyclo*hexylpropan-1-ol, which was isolated as the hydrochloride. Reaction of the base with methyl dichloroacetate then afforded the expected 2-dichloroacetamido-3-*cyclo*hexylpropan-1-ol.

An attempt to prepare 2-dichloroacetamido-2-1′-hydroxy*cyclo*hexylethanol a lower homologue of 2-dichloroacetamido-3-*cyclo*hexylpropane-1 : 3-diol was unsuccessful. Condensation of *cyclo*hexanone with nitromethane according to Frazer and Kon's method (*J.*, 1943, 604) proceeded readily and the difficulties described by Nightingale, Erickson, and Knight (*J. Org. Chem.*, 1950, **15**, 782; cf. Hass and Riley, *loc. cit.*, p. 384; Grob and Tscharner, *Helv. Chim. Acta*, 1950, **33**, 1070; Kon, *J.*, 1951, 843) were not encountered, but further condensation of 1-nitromethyl*cyclo*hexanol with aqueous formaldehyde in the presence of potassium carbonate or sodium hydroxide, or with paraformaldehyde in the presence of methanolic potassium hydroxide, could not be effected. In addition, *cyclo*hexanone failed to react with 2-nitroethanol in the presence or sodium methoxide.

The preparation of some other less closely-related dichloroacetamides was also investigated. Reduction of *cyclo*hexanone cyanohydrin over a platinum oxide catalyst in acetic acid yielded a mixture of 1-aminomethyl*cyclo*hexanol and bis*cyclo*hexylmethylamine (both of which were converted into the respective *N*-dichloroacetyl derivatives), although Goldberg and Kirchensteiner (*Helv. Chim. Acta*, 1943, **26**, 288) found that this method gave a mixture of 1-aminomethyl*cyclo*hexanol and di-(1-hydroxy*cyclo*hexylmethyl)-amine. Tchoubar (*Bull. Soc. chim.*, 1949, **16**, 160) obtained the primary amine by carrying out the reduction in the presence of carbon disulphide, hydrochloric acid, or hydrogen cyanide. Bis*cyclo*hexylmethylamine has recently been obtained by Nightingale, Erickson, and Knight (*loc. cit.*) by high pressure reduction of 1-nitromethyl*cyclo*hex-1-ene over Raney nickel.

Experimental

M. p.s are uncorrected. Activated alumina (Peter Spence type H) was used for chromatographic work.

2-*Dichloroacetamidopropane*-1 : 3-*diol*.—2-Nitropropane-1 : 3-diol (Otter, *Rec. Trav. chim.*, 1938, **57**, 13) (3·3 g.) in methanol (40 ml.) was reduced over Raney nickel at atmospheric temperature and pressure. When the uptake of hydrogen ceased (after 3 hours), the solution was filtered and evaporated, and the residue heated on the steam-bath with methyl dichloroacetate (7 g.) for 2 hours. After removal of excess of ester *in vacuo*, the residue was crystallised from acetone–benzene. Recrystallisation of the product (2·35 g.; m. p. 132—134°) from the same solvents gave 2-*dichloroacetamidopropane*-1 : 3-*diol* as glistening plates, m. p. 144—146° (Found: N, 7·1; Cl, 34·8. $C_5H_9O_3NCl_2$ requires N, 6·9; Cl, 35·2%). The 1 : 2 : 3-triacetyl derivative (see below) formed needles, m. p. 79—80°.

2-*Dichloroacetamido*-2-*hydroxymethylbutanol*.—2-Amino-2-hydroxymethylbutanol (Vanderbilt and Hass, *Ind. Eng. Chem.*, 1940, **32**, 34) (5·5 g.) and methyl dichloroacetate (14·2 g.) were heated on the steam-bath for 18 hours. After removal of excess of ester *in vacuo*, the residue was dissolved in benzene and chromatographed. Elution with benzene and benzene–chloroform, followed by crystallisation from acetone–light petroleum, gave 2-*dichloroacetamido*-2-*hydroxymethylbutanol* (1·35 g.; this does not represent the maximum yield) as prisms, m. p. 108° (Found: N, 6·0; Cl, 30·7. $C_7H_{13}O_3NCl_2$ requires N, 6·1; Cl, 30·85%).

2-*Amino*-2-*phenylpropane*-1 : 3-*diol*.—2-Nitro-2-phenylpropane-1 : 3-diol was reduced over Raney nickel in methanol at atmospheric temperature and pressure. The product (66%; m. p. 116—117°) was crystallised from ethyl acetate; it then had m. p. 117—118° (Found: C, 64 8; H, 7·8; N, 8·2. Calc. for $C_9H_{13}O_2N$: C, 64·7; H, 7·8; N, 8·4%) (Ruoff and Miller,

loc. cit., give 50% yield; m. p. 116—118·5°). The *hydrochloride* formed plates, m. p. 181—182°, from methanol–ether (Found: N, 7·0; Cl, 17·0. $C_9H_{13}O_2N$,HCl requires N, 6·9; Cl, 17·9%).

2-*Dichloroacetamido*-2-*phenylpropane*-1 : 3-*diol*.—2-Amino-2-phenylpropane-1 : 3-diol (1·3 g.) and methyl dichloroacetate (5·2 g.) were heated on the steam-bath for 4·5 hours. After removal of excess of ester, the residue was dissolved in ethyl acetate, washed free from unchanged base, evaporated, and chromatographed in benzene. Elution with benzene and ether gave 2-*dichloroacetamido*-2-*phenylpropane*-1 : 3-*diol* (0·8 g) as prisms, m. p. 105—106°, from ethyl acetate–light petroleum (Found: N, 5·1; Cl, 25·6. $C_{11}H_{13}O_3NCl_2$ requires N, 5·0; Cl, 25·5%).

2-*Acetamido*-2-p-*nitrophenylpropane*-1 : 3-*diol*.—The ethyl acetate mother-liquors from the crystallisation of 2-amino-2-*p*-nitrophenylpropane-1 : 3-diol during 1—2 weeks deposited a small quantity of 2-*acetamido*-2-p-*nitrophenylpropane*-1 : 3-*diol* as long prisms; m. p. 178° (Found: C, 51·7; H, 5·6. $C_{11}H_{14}O_5N_2$ requires C, 51·9; H, 5·6%).

4-*Methyl*-2-*nitropentane*-1 : 3-*diol*.—A solution of sodium methoxide [from sodium (5·7 g.) and dry methanol (100 ml.)] was added during 40 minutes to a stirred solution of freshly-distilled *iso*butaldehyde (18 g.) and 2-nitroethanol (22·5 g.) in dry methanol (50 ml.). The solution was cooled, and the *sodium* salt (24·4 g.; 53%) which separated was filtered off and washed with a little cold methanol and with ether. A sample was purified for analysis by precipitation of its aqueous solution with acetone (Found: N, 7·5; Na, 13·2. $C_6H_{12}O_4NNa$ requires N, 7·6; Na, 12·4%). The finely powdered sodium salt (11·3 g.) was boiled with salicylic acid (8 g.) in dry ether (150 ml.) for 2·5 hours. The solution was filtered and evaporated, and the residue dried over sulphuric acid *in vacuo*. The yield was 7·5 g. (75%).

2-*Amino*-4-*methylpentane*-1 : 3-*diol*.—The foregoing nitro-diol (7·5 g.) in methanol (100 ml.) was reduced over Raney nickel, the crude 2-amino-4-methylpentane-1 : 3-diol (4·8 g.) being obtained as an oil. A small amount of the base was dissolved in acetic anhydride–pyridine and kept overnight. Excess of reagents was removed *in vacuo* and the residue chromatographed in benzene–light petroleum. Elution with benzene and ether gave 2-*acetamido*-1 : 3-*diacetoxy*-4-*methylpentane* as plates, m. p. 100—102°, from ether–light petroleum (Found: C, 55·85; H, 8·2. $C_{12}H_{21}O_5N$ requires C, 55·6; H, 8·2%). Further elution of the column with acetone gave a small quantity of 2-*acetamido*-1 : 3-*diacetoxypropane* as needles, m. p. 79—80°, from ether (Found: C, 50·0; H, 7·1. $C_9H_{15}O_5N$ requires C, 49·8; H, 7·0%).

2-*Dichloroacetamido*-4-*methylpentane*-1 : 3-*diol*.—The base obtained by reduction of 4-methyl-2-nitropentane-1 : 3-diol (1·2 g.) was heated for 2 hours on the steam-bath with a large excess of methyl dichloroacetate. After removal of excess of ester *in vacuo*, the residue was chromatographed in benzene. Elution with benzene and ether gave 2-*dichloroacetamido*-4-*methylpentane*-1 : 3-*diol* (0·4 g.; m. p. 137°), which separated in plates, m. p. 140—141°, from acetone–light petroleum (Found: C, 39·6; H, 6·3; N, 6·3; Cl, 28·7. $C_8H_{15}O_3NCl_2$ requires C, 39·3; H, 6·2; N, 5·7; Cl, 29·1%). In a similar experiment in which the base from nitro-diol sodium salt (10·85 g.) was heated for 16 hours at 100° with methyl dichloroacetate (16·8 g.), there were obtained, after chromatography, 2-dichloroacetamido-4-methylpentane-1 : 3-diol (1·15 g.) and 2-dichloroacetamidopropane-1 : 3-diol (0·55 g.) (Found: N, 7·0; Cl, 35·1%), m. p. and mixed m. p. 142—144°.

3-cyclo*Hexyl*-2-*nitropropane*-1 : 3-*diol*.—A solution of sodium methoxide [from sodium (5 g.) and methanol (150 ml.)] was slowly added to a stirred solution of *cyclo*hexanaldehyde (Wood and Comley, *J. Soc. Chem. Ind.*, 1923, **42**, 431T; cf. Heilbron, Jones Richardson, and Sondheimer, *J.*, 1949, 737) (24·3 g.) and 2-nitroethanol (19·8 g.) in methanol (50 ml.). A transient orange colour was observed at the first addition. After 1—2 hours, the sodium salt (34 g.; 70%) was filtered off and washed with a small amount of cold methanol and with ether. For analysis a sample was precipitated from its aqueous solution with acetone (Found: N, 5·9; Na, 10·6. $C_9H_{16}O_4NNa$ requires N, 6·2; Na, 10·2%).

2-*Amino*-3-cyclo*hexylpropane*-1 : 3-*diol*.—The above sodium salt (14·6 g.) in acetic acid (200 ml.) was reduced over Adams's platinum oxide (1 g.) at atmospheric temperature and pressure. When the uptake of hydrogen ceased, the solution was filtered and treated with fresh catalyst. After 4 hours, 4 g. of catalyst had been used and the uptake was 3·15 l. (theory 5·2 l.). The solution was then filtered and evaporated *in vacuo*, and the residue dissolved in 2N-hydrochloric acid (200 ml.) and extracted thrice with ether. Evaporation of the acid solution and crystallisation of the residue from methanol–ether gave the crude hydrochloride (3·4 g.; m. p. 120—140°). By recrystallisation from methanol–ether and methanol–benzene, 2-*amino*-3-cyclo*hexylpropane*-1 : 3-*diol hydrochloride* was obtained as long prisms, m. p. 240—242° (softens 172°) (Found: C, 51·4; H, 9·9; N, 7·1. $C_9H_{19}O_2N$,HCl requires C, 51·5; H, 9·6; N, 6·7%).

2-*Dichloroacetamido*-3-cyclo*hexylpropane*-1 : 3-*diol*.—The crude base hydrochloride (3·2 g.) was dissolved in methanolic potassium hydroxide (2·46N; 6·21 ml.) and the solution evaporated to dryness. The residue was heated on the steam-bath with a large excess of methyl dichloroacetate for 3·25 hours, the solution evaporated *in vacuo*, and the residue dissolved in benzene containing a small amount of acetone and chromatographed. Elution with benzene and ether gave a trace of 2-dichloroacetamido-3-*cyclo*hexylpropan-1-ol (60 mg.), m. p. 114° (see below). Elution with ether–acetone and acetone gave 2-*dichloroacetamido*-3-cyclo*hexylpropane*-1 : 3-*diol* (1·03 g.), which separated from acetone–benzene as plates, m. p. 162—163° (Found : C, 46·5; H, 6·7. $C_{11}H_{19}O_3NCl_2$ requires C, 46·5; H, 6·7%).

2-*Amino*-3-cyclo*hexylpropan*-1-*ol*.—(*a*) A solution of the nitro-diol sodium salt (4·5 g.) in 2N-hydrochloric acid was extracted thrice with ether. The washed and dried extracts were slowly added to a stirred solution of lithium aluminium hydride (1·52 g.) in dry ether. After being refluxed for 2 hours, the solution was decomposed with water, treated with sodium hydroxide, and repeatedly extracted with chloroform and ethyl acetate. The washed, dried extracts were evaporated, the residual oil (1·5 g.) dissolved in 2N-hydrochloric acid and the solution extracted with ether and then evaporated *in vacuo*. 2-*Amino*-3-cyclo*hexylpropan*-1-*ol hydrochloride* separated from methanol on the addition of acetone and benzene as glistening plates, m. p. 195° (Found : N, 7·1; Cl, 18·2. $C_9H_{19}ON,HCl$ requires N, 7·2; Cl, 18·3%).

(*b*) The sodium salt (6·4 g.) was acidified as described above, and the product reduced over Raney nickel in ethanol at 20° and 5 atm. pressure. The basic portion of the product gave the same hydrochloride (1·1 g.), m. p. 196°.

(*c*) The nitro-alcohol from the sodium salt (17 g.) was reduced over Adams's platinum oxide in acetic acid. The basic portion of the product yielded the above hydrochloride (8·3 g.) m. p. 192—193°.

2-*Dichloroacetamido*-3-cyclo*hexylpropan*-1-*ol*.—The base hydrochloride [2·25 g. from (*c*) above] was dissolved in 0·815N-methanolic potassium hydroxide (13·45 ml.) and the solution evaporated; the residue was heated with methyl dichloroacetate (10 g.) for 2·5 hours on the steam-bath and excess of ester distilled off. The crude product was chromatographed in benzene. Elution with benzene and ether gave 2-*dichloroacetamido*-3-cyclo*hexylpropan*-1-*ol* (1·8 g.) as leaflets, m. p. 114°, from acetone–light petroleum (Found : C, 49·5; H, 7·2. $C_{11}H_{19}O_2NCl_2$ requires C, 49·6; H, 7·2%). The *acetate*, obtained by treatment of the propanol with acetic anhydride–pyridine overnight, formed long narrow prisms, m. p. 80—81°, from light petroleum (Found : C, 50·6; H, 7·0; N, 4·5. $C_{13}H_{21}O_3NCl_2$ requires C, 50·3; H, 6·8; N, 4·5%). Further elution of the column with acetone gave a trace of 2-dichloroacetamido-3-*cyclo*hexylpropane-1 : 3-diol (60 mg.), m. p. 160—162°.

Reduction of cyclo*Hexanone Cyanohydrin*.—*cyclo*Hexanone cyanohydrin (Frank, Berry, and Shotwell, *J. Amer. Chem. Soc.*, 1949, **71**, 3891) (47·5 g.) in acetic acid (150 ml.) was reduced over Adams's platinum oxide (5 g.) at atmospheric temperature and pressure. Hydrogen uptake was 17·4 l. in 36 hours. The solution was evaporated *in vacuo*, and the residue treated with 20% sodium hydroxide and extracted five times with ether (total 500 ml.). The washed and dried extracts were evaporated on the steam-bath and then distilled at 0·8—1 mm., fractions being collected at (1) <100° (11·7 g.), (2) 100—119° (3·25 g.), and (3) 120—144° (10·4 g.).

1-*Dichloroacetamidomethyl*cyclo*hexan*-1-*ol*. (*a*) Fraction (1) (2·8 g.) was dissolved in benzene (20 ml.), treated with dichloroacetyl chloride (1 ml.), and heated under reflux for 1 hour on the steam-bath. The cooled solution was diluted with ether, filtered from 1-aminomethyl*cyclo*hexanol hydrochloride, m. p. 209—210° (Goldberg and Kirchensteiner, *loc. cit.*, give m. p. 210—212°; Tchoubar, *loc. cit.*, gives m. p. 190°), washed with dilute hydrochloric acid, sodium hydrogen carbonate solution and water, and dried, concentrated, and cooled. 1-*Dichloroacetamidomethyl*cyclo*hexan*-1-*ol* (1·4 g.) crystallised from benzene–light petroleum in plates, m. p. 122—124° (Found : N, 5·85; Cl, 29·5. $C_9H_{15}O_2NCl_2$ requires N, 5·8; Cl, 29·6%).

(*b*) The same compound, m. p. and mixed m. p. 122—124°, was the only crystalline product isolated when 1-nitromethyl*cyclo*hexanol (Frazer and Kon, *loc. cit.*) in alcohol (25 ml.) and 5·8N-sodium hydroxide (1 ml.) was treated with 40% formaldehyde (7·5 ml.), and the solution kept for 6 days, neutralised with 2N-hydrochloric acid (2·9 ml.), concentrated at 25 mm. and then at 0·8 mm. (bath temp. 55°), reduced over Raney nickel in methanol and finally heated on the steam-bath with methyl dichloroacetate.

N-*Dichloroacetylbis*cyclo*hexylmethylamine*. Fraction (3) (3·55 g.) and dichloroacetyl chloride (1·5 ml.) in dry benzene (30 ml.) were heated under reflux for one hour on the steam-bath, cooled, diluted with ether, and filtered from bis*cyclo*hexylmethylamine hydrochloride (0·6 g.), m. p. 271—272° (decomp.) (Found : N, 5·7; Cl, 14·1. Calc. for $C_{14}H_{27}N,HCl$: N, 5·7; Cl,

14·5%) (Nightingale, Erickson, and Knight, *J. Org. Chem.*, 1950, **15**, 782, give m. p. 264—265°). The ethereal solution was washed with dilute hydrochloric acid, sodium hydrogen carbonate solution, and water, dried, concentrated, and treated with light petroleum, to give N-*dichloroacetylbis*cyclo*hexylmethylamine* (2·1 g.), prisms from acetone–light petroleum, m. p. 168—170° (Found : N, 4·4; Cl, 22·1. $C_{16}H_{27}ONCl_2$ requires N, 4·4; Cl, 22·2%).

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