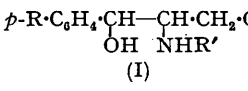
*Analogues of Chloramphenicol. Part III.**

By David D. Evans, Douglas S. Morris, Sylvia D. Smith, and David J. Tivey.

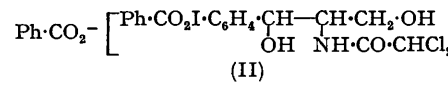
[Reprint Order No. 4895.]

The nitro-group of chloramphenicol has been replaced by trimethylammonium, iodoxyl, iodoso-, and benzyl groups. The *threo*-configuration of the known iodo-analogue of chloramphenicol has been confirmed.

The nitro-group of chloramphenicol has been replaced by strongly *meta*-directing groups, namely, trimethylammonium and iodoxyl, in the expectation that antibacterial activity might be retained. D-(−)-*threo*-2-Acetamido-1-*p*-nitrophenylpropane-1 : 3-diol was catalytically hydrogenated to the corresponding *p*-amino-compound (I; R = NH_2, R′ = Ac). Hydrogenation was continued in the presence of formaldehyde, to give the dimethylamino-compound, which was converted by standard methods into the hydrochloride of the quaternary chloride (I; R = NMe_3}Cl, R′ = H). The base (I; R = NMe_3}Cl, R′ = H) itself, obtained from the hydrochloride by treatment with the predetermined amount of alkali, was not obtained crystalline and was converted into the analogue of chloramphenicol (I; R = NMe_3}Cl, R′ = $CHCl_2$·CO) by means of methyl dichloroacetate.



(I)



(II)

The dimethylamino-compound (I; R = NMe_2, R′ = H) was prepared from the acetamido-compound by hydrolysis with dilute sulphuric acid (more efficacious than hydrochloric acid or sodium hydroxide), but attempts to convert it into a dichloroacetyl derivative gave tars (cf. attempts by Van der Meer, Kofman, and Veldstra, *Rec. Trav. chim.*, 1953, **72**, 286, to prepare a pyridyl analogue).

The iodo-analogue (I; R = I, R′ = $CHCl_2$·CO), prepared by Bambas, Troutman, and Long (*J. Amer. Chem. Soc.*, 1950, **72**, 4445) and regarded in virtue of its mode of preparation as having a *threo*-configuration, has been catalytically dehalogenated to (±)-*threo*-2-acetamido-1-phenylpropane-1 : 3-diol (Controulis, Rebstock, and Crooks, *J. Amer. Chem. Soc.*, 1949, **71**, 2463; Fodor, Kiss, and Sallay, *J.*, 1951, 1858). The iodo-analogue now of proven *threo*-configuration has been converted into the iodoxyl (I; R = IO_2, R′ = $CHCl_2$·CO) and the dibenzoyliodoso-analogue (II) by the action of perbenzoic acid.

The *p*-benzyl analogue (I; R = Ph·CH_2, R′ = $CHCl_2$·CO) has been prepared in both *threo*- and *erythro*-forms by the general method of Long and Troutman (*J. Amer. Chem. Soc.*, 1949, **71**, 2473).

The identity of *p*-benzylphenacyl bromide was established by the preparation of a pyridinium bromide and conversion of the latter into *p*-benzylbenzoic acid, thereby indicating that during bromination of *p*-benzylacetophenone no attack occurred on the bridge methylene group. Acetamido-*p*-benzylacetophenone reacted readily with formaldehyde, one or two hydroxymethyl groups being readily introduced. 2-Acetamido-1-*p*-benzylphenylpropane-1 : 3-diol was readily obtained in both the *threo*- and the *erythro*-form by catalytic reduction or Meerwein–Pondorff reduction of the corresponding ketone. The diol obtained in preponderance by the Meerwein reduction was regarded by analogy with other reductions in this field as having the *threo*-configuration.

Antibacterial tests on the dichloroacetyl compounds described above will be reported elsewhere.

Experimental

Acetylation of D-(−)-threo-2-*Amino*-1-p-*nitrophenylpropane*-1 : 3-*diol*.—Acetic anhydride (46 c.c.) was added to a thick slurry of D-(−)-*threo*-2-amino-1-*p*-nitrophenylpropane-1 : 3-diol (75 g.), sodium acetate (45 g.), and crushed ice. The mixture was vigorously shaken for 60 min.,

* Part II, preceding paper.

then extracted thoroughly with ethyl acetate, and the ethyl acetate extracts were washed to neutrality, dried, and evaporated. The residue was crystallised twice from ethyl acetate, to give the *N*-acetyl derivative (61 g.), m. p. 125—127°, in agreement with Rebstock, Crooks, Controulis, and Bartz (*J. Amer. Chem. Soc.*, 1949, **71**, 2458).

D-(−)-threo-2-*Acetamido*-1-p-*dimethylaminophenylpropane*-1 : 3-*diol*.—The foregoing acetyl derivative (71 g.) was hydrogenated in ethanol (250 c.c.) in presence of palladised charcoal (3·2 g.; 10% of PdO). After hydrogenation equivalent to the reduction of the nitro-group, aqueous formaldehyde (65 c.c. of 40%) was added and hydrogenation continued to completion. The residue (64 g.) obtained by removal of the catalyst and solvent crystallised from ethyl acetate, giving the *dimethylamino*-compound (44 g.) as plates, m. p. 136—139·5°, $[\alpha]_D^{20}$ −20·1° (*c* 1·05 in 96% ethanol) (Found: C, 61·5; H, 8·15; N, 11·2. $C_{13}H_{20}O_3N_2$ requires C, 61·9; H, 8·0; N, 11·1%).

The racemic *compound*, obtained similarly, formed pale yellow crystals, m. p. 159·5—160·5°, from methanol (Found: C, 61·4; H, 7·9; N, 11·3%).

p-[D(−)-threo-2-*Amino*-1 : 3-*dihydroxypropyl*]*phenyltrimethylammonium Derivatives*.—The solution of the dimethylamino-compound in ethanol obtained, after removal of the catalyst as in the preceding hydrogenation, from D-(−)-*threo*-2-acetamido-1-*p*-nitrophenylpropane-1 : 3-diol (30 g.) was made up to 600 c.c. A portion (100 c.c.) of this solution was evaporated to dryness and the residue set aside for 2 days with a mixture of chloroform (20 c.c.), ethanol (2 c.c.), and methyl sulphate (10 c.c.). Treatment with acetone gave an insoluble red oil, which was dissolved in water (15 c.c.), treated with barium chloride (5 g.) and concentrated hydrochloric acid (15 c.c.), and warmed on the steam-bath for 45 min. Barium sulphate was filtered off, the filtrate evaporated to dryness *in vacuo*, and the residue thrice extracted with hot absolute alcohol. The *chloride hydrochloride* precipitated by acetone crystallised from hot ethanol as hygroscopic needles, m. p. 237° (after drying *in vacuo*), $[\alpha]_D^{20}$ −28·7° (*c* 1·16 in 96% ethanol) (Found: N, 9·4; Cl, 23·7. $C_{12}H_{22}O_2N_2Cl_2$ requires N, 9·4; Cl, 23·9%).

This salt (2·97 g.) in water (4 c.c.) was neutralised with N-sodium hydroxide (10 c.c.). The residue obtained by evaporation *in vacuo* was extracted with absolute alcohol to yield a pale yellow gum. The latter was refluxed in methanol (5 c.c.) with methyl dichloroacetate (5 c.c.) for 3 hr. and finally evaporated to dryness to give a hygroscopic gum. Treatment in ethanol with charcoal and evaporation gave a deliquescent foam, and crystallisation thereof from absolute alcohol gave small needles, m. p. 115—120°, $[\alpha]_D^{20}$ +21·7° (*c* 1·07 in H_2O), of the N-*dichloroacetamide chloride* (Found: N, 7·5; total Cl, 27·8; Cl^-, 9·3. $C_{14}H_{21}O_3N_2Cl_3$ requires N, 7·5; total Cl, 28·6; Cl^-, 9·6%).

D-(−)-threo-2-*Amino*-1-p-*dimethylaminophenylpropane*-1 : 3-*diol*.—The acetyl derivative (17 g.) was refluxed with 2N-sulphuric acid (100 c.c.) for 2 hr. and distilled with steam. After treatment with charcoal, the solution was treated with an excess of barium carbonate, filtered hot, and evaporated with the ethanolic washings to dryness *in vacuo*. The *base* crystallised from chloroform or *iso*propanol and after high-vacuum sublimation was a white solid, m. p. 143—145°, $[\alpha]_D^{20}$ −24·5° (*c* 0·54 in 96% ethanol) (Found: C, 62·6; H, 8·5; N, 13·1. $C_{11}H_{18}O_2N_2$ requires C, 62·8; H, 8·6; N, 13·3%).

p-(DL-threo-2-*Acetamido*-1 : 3-*dihydroxypropyl*)*phenyltrimethylammonium Chloride Hydrochloride*.—The racemic dimethylamino-compound (4·0 g.), methanol (11·5 c.c.), and methyl iodide (20 c.c.) were heated on the steam-bath for 15 min. and evaporated to dryness *in vacuo*, to give a solid foam. This (3·7 g.) with the addition of 18% hydrochloric acid (20 c.c.) was evaporated on the steam-bath to a gum. After several weeks, the gum gave the crystalline *chloride hydrochloride*, m. p. 165—167°, on trituration with ethanol, and was finally purified by recrystallisation from ethanol–acetone as short needles, m. p. 235—237° (Found: C, 48·5; H, 7·5; N, 9·4. $C_{12}H_{22}O_2N_2Cl_2$ requires C, 48·3; H, 7·15; N, 10·4%).

Hydrogenation of the Iodo-analogue of Chloramphenicol to DL-threo-2-*Acetamido*-1-*phenylpropane*-1 : 3-*diol*.—The iodo-analogue (2·02 g.) was hydrogenated in ethanol (100 c.c.) containing 5N-sodium hydroxide (4 c.c.) and 5% palladised strontium carbonate (0·5 g.). The residue obtained by removal of the catalyst and solvent was dissolved in water and shaken with a few drops acetic anhydride and sodium acetate solution. Extraction of the aqueous mixture with ethyl acetate gave a residue which crystallised from ethyl acetate as needles, m. p. 132—133°, undepressed by admixture with authentic (±)-*threo*-2-acetamido-1-phenylpropane-1 : 3-diol.

DL-threo-2-*Dichloroacetamido*-1-p-*iodoxyphenylpropane*-1 : 3-*diol*.—The iodo-analogue (2 g.), dissolved in dimethylformamide (2 c.c.), was treated with a chloroformic solution of perbenzoic acid (132 c.c. containing 0·0378 g./c.c.) and set aside for 48 hr. The *iodoxyl* compound (1·1 g.)

was obtained as a white crystalline solid, m. p. 105° (decomp.) (Found : C, 29·5; H, 3·1; N, 2·9; Halogen, 43·2%; equiv., 106. $C_{11}H_{12}O_5NCl_2I$ requires C, 30·2; H, 2·8; N, 3·2; Halogen, 45·4%; equiv., 109).

DL-threo-1-p-*Dibenzoyliodosophenyl*-2-*dichloroacetamidopropane*-1 : 3-*diol*.—The iodo-analogue (4·5 g.) in dimethylformamide (2 c.c.) was treated with a chloroformic solution of perbenzoic acid (250 c.c. containing 0·00876 g./c.c.) and set aside in the refrigerator for 16 hr. The *iodoso*-derivative was obtained as plates, m. p. 156—157° (Found : C, 45·8; H, 3·5; N, 2·3%; equiv., 318. $C_{25}H_{22}O_7NICl_2$ requires C, 46·5; H, 3·4; N, 2·2%; equiv., 323).

p-*Benzylacetophenone*.—Acetyl chloride (360 c.c.) was slowly added to a stirred solution of diphenylmethane (1 kg.) in carbon disulphide (730 c.c.) and finely ground aluminium chloride (610 g.), at <0°. Stirring was continued for 2 hr. during which room temperature was attained. The solution was poured on crushed ice and concentrated hydrochloric acid, the carbon disulphide layer was washed to neutrality, dried, and evaporated, and the residue was distilled to give *p*-benzylacetophenone, b. p. 188—190°/5 mm. (needles), m. p. 39° [from light petroleum (b. p. 40—60°)] (cf. Duval, *Compt. rend.*, 1908, **146**, 341).

p-*Benzylphenacyl Bromide*.—*p*-Benzylacetophenone (21 g.), in chloroform (100 c.c.), was treated at −10° to 0° dropwise with bromine (17 g.). The solution was washed to neutrality with sodium carbonate solution and water, dried (Na_2SO_4), and evaporated to an oil (29·2 g.) which from light petroleum (b. p. 40—60°) and then methanol gave the *phenacyl bromide* as needles, m. p. 47·5—49·5° (Found : Br, 26·3. $C_{15}H_{13}OBr$ requires Br, 27·6%).

p-*Benzylphenacylpyridinium Bromide*.—*p*-Benzylphenacyl bromide (14·5 g.) and dry pyridine (5·0 c.c.) were mixed and warmed for 5 min. on the steam-bath. The pyridinium bromide formed hygroscopic needles, m. p. 72—83°, from ethanol (Found : C, 62·8; H, 5·1; N, 3·8; Br, 20·25. $C_{20}H_{18}ONBr,H_2O$ requires C, 62·2; H, 5·2; N, 3·6; Br, 20·7%). When it (3·68 g.) was warmed for 12 min. on the steam-bath with 10% sodium hydroxide solution (14 c.c.), methanol (84 c.c.), and water (280 c.c.) it yielded, on acidification, *p*-benzylbenzoic acid, m. p. 156—157°.

p-*Benzylphenacylamine Hydrochloride*.—*p*-Benzylphenacyl bromide (11 g.) in chlorobenzene (20 c.c.) was treated with hexamethylenetetramine (6 g.) in dry chlorobenzene (100 c.c.) at 40° and set aside overnight. The quaternary *salt* crystallised from acetone as needles, m. p. 95—105° (Found : N, 13·6; Br, 19·0. $C_{21}H_{25}ON_4Br$ requires N, 13·1; Br, 18·6%). It could not be prepared in chloroform.

The salt (12·9 g.) was warmed to 40° with ethanol (30 c.c.) and concentrated hydrochloric acid (15 c.c.), then set aside overnight. The *amino-ketone hydrochloride* was purified by crystallisation first from water and, finally, from dilute hydrochloric acid, to give plates, m. p. 194—195° (Found : C, 69·0; H, 6·5; Cl, 13·3. $C_{15}H_{16}ONCl$ requires C, 68·8; H, 6·2; Cl, 13·5%).

The hydrochloride (5·3 g.) was shaken with sodium acetate (4·1 g.), acetic anhydride (3 c.c.), and ice-water (40 c.c.) for 3 hr. The *acetamido-ketone*, m. p. 113·5—114·5°, was obtained as plates from acetone (Found : C, 76·2; H, 6·3; N, 5·3. $C_{17}H_{17}ON$ requires C, 76·3; H, 6·4; N, 5·2%). It was also prepared in *ca.* 25% yield without isolation of the intermediate.

α-*Acetamido*-p-*benzyl*-β-*hydroxypropiophenone*.—The pH of a mixture of 40% aqueous formaldehyde (2 c.c.), the acetamido-ketone (5·3 g.), and ethanol (15 c.c.) was adjusted to 9·0 by 2N-sodium hydroxide; after 3 min. a clear solution was obtained, and after a further 5 min. the mixture was diluted with water (27 c.c.). An oil was precipitated, extracted with ethyl acetate, washed to neturality, dried, and recovered by evaporation. The β-*hydroxypropiophenone* formed needles (80%), m. p. 118°, from ethyl acetate (Found : C, 72·6; H, 6·5; N, 5·0. $C_{18}H_{19}O_3N$ requires C, 72·7; H, 6·4; N, 4·7%). It was found that the usual time (1—3 hr.) for this reaction resulted in the formation of α-*acetamido*-p-*benzyl*-β-*hydroxy*-α-*hydroxymethyl*-*propiophenone* in good yield as needles, m. p. 161—163°, from ethyl acetate (Found : C, 69·4; H, 6·2; N, 4·3. $C_{19}H_{21}O_4N$ requires C, 69·7; H, 6·5; N, 4·3%).

threo- *and* erythro-2-*Acetamido*-1-p-*benzylphenylpropane*-1 : 3-*diol*.—(*a*) The β-hydroxypropiophenone (3·5 g.) was distilled with *iso*propanol (200 c.c.) and aluminium *iso*propoxide (4 g.) until no further acetone was detected in the distillate. On working up in the usual manner, two *propanediols* were obtained by crystallisation from ethyl acetate. The first (2·0 g.) (short needles), m. p. 119—120°, was regarded as the *threo*-form (Found : 71·4; H, 7·15; N, 4·6. $C_{18}H_{21}O_3N$ requires C, 72·2; H, 7·10; N, 4·7%). The second (0·1 g.) (rhombs), m. p. 167—168°, was regarded as the *erythro*-form (Found : C, 72·1; H, 7·4; N, 5·0%).

(*b*) Hydrogenation of the propiophenone (5·95 g.) in methanol in presence of Raney nickel gave, on fractional crystallisation from methanol, the *erythro*-form (1·6 g.), m. p. 166—168°,

and the *threo*-form (0·84 g.), m. p. 117°. Neither of these gave a depression in m. p. when mixed with the corresponding diol obtained as in (*a*).

Hydrolyses of the Acetamido-diols and Dichloroacetylation of the Bases obtained.—The *erythro*-acetamido-diol (1·5 g.), m. p. 168°, was refluxed for 2½ hr. with 2N-sulphuric acid (15 c.c.). DL-erythro-2-*Amino*-1-p-*benzylphenylpropane*-1 : 3-*diol sulphate* (1·1 g.), plates, m. p. 230—234°, was isolated on cooling and crystallised from dilute sulphuric acid (Found: C, 63·1; H, 6·7; N, 4·4. $C_{16}H_{19}O_2N,\frac{1}{2}H_2SO_4$ requires C, 62·7; H, 6·6; N, 4·6%). The free *base* was obtained, by treatment of the sulphate with sodium hydroxide solution followed by extraction with ethyl acetate and crystallisation from ether, as needles, m. p. 110—114° (Found: N, 5·5. $C_{16}H_{19}O_2N$ requires N, 5·4%). The base (1 g.) was converted into the dichloroacetyl derivative by an excess of methyl dichloroacetate in methanol on the steam-bath (90 min.); after cooling, a crystalline product was isolated by filtration and washed with ether. The solid, dissolved in ethyl acetate, was washed to neutrality with dilute hydrochloric acid and finally with water. The *dichloracetamido*-derivative crystallised from ethyl acetate as plates, m. p. 140—140·5° (Found: C, 58·7; H, 4·9; N, 4·1. $C_{18}H_{19}O_3NCl_2$ requires C, 58·7; H, 5·2; N, 3·8; Cl, 9·3%). The threo-*dichloracetamido*-derivative, obtained in a similar manner but without isolation of the sulphate or base, crystallised from water as needles, m. p. 110° (Found: C, 58·8; H, 5·34; N, 2·8; Cl, 18·7%).

The authors are indebted to Dr. R. E. Bowman for many helpful discussions and to Drs. Schlingman and Galbraith for carrying out antibacterial tests.

RESEARCH DEPT., MESSRS. PARKE, DAVIS & CO., LTD.,
STAINES ROAD, HOUNSLOW, MIDDX. [*Received, December 16th*, 1953.]