*Analogues of Chloramphenicol. Part II.**

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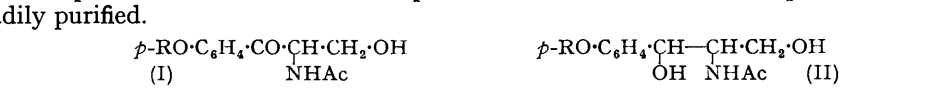
THE *p*-hydroxy-analogue of chloramphenicol has been prepared from *p*-benzyloxyacetophenone, and an abnormal Meerwein reduction product has been investigated. The analogue obtained gives a known methyl ether having the *threo*-configuration. A 3 : 5-di-iodo-derivative has been prepared.

ATTEMPTS made to replace the nitro-group of chloramphenicol by hydroxyl, by means of reduction and diazotisation were unsuccessful, and recourse was taken to an adaptation of Long and Troutman's general method (*J. Amer. Chem. Soc.*, 1949, **71**, 2437), starting from *p*-hydroxyacetophenone. This ketone was not obtained by us in the yields claimed by Irvine and Robinson for their method (*J.*, 1927, 2091) or adaptations of this and earlier methods. It was readily and consistently prepared, however, by Fries rearrangement of phenyl acetate (B.I.O.S. Final Report 766, p. 93). *p*-Benzoyloxyacetophenone was prepared by the usual Schotten–Baumann technique and was converted into α-acetamido-*p*-benzoyloxyacetophenone without isolation of the intermediate products in pure states (cf. Corrigan, Longeman, and Moore, *J. Amer. Chem. Soc.*, 1945, **67**, 1894). The acetamido-ketone (I; R = Bz) was prepared by the standard hydroxymethylation technique (Long and Troutman, *loc. cit.*) and reduced by the Meerwein–Pondorff method or by catalytic hydrogenation to (II; R = Bz). Owing to transesterification in the Meerwein–Pondorff reduction, the yields were low and repeated crystallisation was essential. The hydrogenation product which differed in m. p. from the Meerwein reduction product was more readily purified.



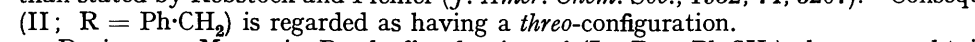
(I) (II)

Hydrolysis of (II; R = Bz) by dilute hydrochloric acid gave a 2-amino-*p*-benzoyloxy-compound, m. p. 145—146°; an isomeric base, m. p. 184°, was similarly obtained on use of dilute sulphuric acid. Low yields of these compounds, however, precluded further investigation.

Attention was then turned to *p*-benzyloxyacetophenone and satisfactory techniques were devised for the preparation of (II; R = $Ph{\cdot}CH_2$). The reduction was carried out by the Meerwein–Pondorff method or by sodium borohydride, but hydrogenation in presence of Raney nickel caused debenzylation as the primary reaction and complete reduction afforded an intractable gum. The Meerwein–Pondorff reduction product was hydrolysed with dilute sulphuric acid to give a crystalline sulphate from which the free 2-amino-*p*-benzyloxy-compound was readily obtained in a pure condition. Catalytic hydrogenation in ethanol in the presence of palladised strontium carbonate then gave the phenolic amine which with or without isolation was converted into the required analogue of chloramphenicol by the action of methyl dichloroacetate.

The 3 : 5-di-iodo-derivative was prepared by the action of aqueous sodium iodide and iodine solution in presence of sodium hydrogen carbonate. Methylation of (II; R = H) gave a methyl ether melting 5° higher than stated by Buu-Hoi (*J.*, 1951, 255) and 14° lower than stated by Rebstock and Pfeiffer (*J. Amer. Chem. Soc.*, 1952, **74**, 3207). Consequently (II; R = $Ph{\cdot}CH_2$) is regarded as having a *threo*-configuration.

During one Meerwein–Pondorff reduction of (I; R = $Ph{\cdot}CH_2$) there was obtained a compound $C_{18}H_{17}O_3N$, which corresponds to the loss of one molecule of water from the starting material. The ultra-violet spectrum of this compound had an intense maximum



(III) (IV)

at 285 mμ, indicative of a phenyl ketone, and this taken in conjunction with its mode of formation and the uptake of three mols. of hydrogen on catalytic hydrogenation is most readily accommodated by structure (IV). This was confirmed by treatment of the di-

* Part I, preceding paper.

acetate (III) with boiling quinoline, elimination of acetic acid occurring to give the Meerwein–Pondorff reduction product in high yield. The formation of compounds of type (IV) from β-hydroxypropiophenones by the action of acetic anhydride and pyridine has been observed by Huebner, Diassi, and Scholz (*J. Org. Chem.*, 1953, **18**, 21); no such products have previously been recorded as arising during Meerwein–Pondorff reduction.

Experimental

p-*Hydroxyacetophenone*.—Phenyl acetate (1 kg.) was heated, with stirring, in a 4-l. beaker. Finely ground aluminium chloride (1·1 kg.) was added portionwise, the temperature being kept at 90—95°. Benzene was added to control frothing and the reaction was complete in 2—3 hr., giving a clear melt. Decomposition was effected with ice and concentrated hydrochloric acid as usual. The product was distilled with steam to remove the *ortho*-isomeride. The distillate and residue were worked up separately to give *p*- (370 g.), m. p. 108°, and *o*-hydroxyacetophenone (258 g.), b. p. 98°/6 mm. The former was purified by crystallisation from boiling water or by vacuum-distillation.

α-*Acetamido*-p-*benzoyloxyacetophenone*.—The hexamine salt (95 g.) of *p*-benzoyloxy-ω-iodoacetophenone (prepared by Corrigan's method, *J. Amer. Chem. Soc.*, 1945, **67**, 1894) was hydrolysed by stirring it with ethanol (500 c.c.) and concentrated hydrochloric acid (250 c.c.) for 16 hr. The crude amino-ketone hydrochloride obtained by filtration was stirred for 30 min. with an excess of sodium acetate solution and acetic anhydride in ice-water. The *acetamidoketone* was obtained as needles (22 g.), m. p. 167—168°, from ethyl acetate (Found : C, 68·9; H, 5·0; N, 4·8. $C_{17}H_{15}O_4N$ requires C, 68·7; H, 5·1; N, 4·7%).

2-*Acetamido*-1-p-*benzoyloxyphenylethanol*.—The foregoing acetamido-ketone (2·97 g.) was hydrogenated in ethanol in presence of Raney nickel, to yield the *alcohol* as needles, m. p. 146—148° (from ethyl acetate) (Found : C, 68·1; H, 5·7; N, 5·2. $C_{17}H_{17}O_4N$ requires C, 68·2; H, 5·7; N, 4·7%).

α-*Acetamido*-p-*benzoyloxy*-β-*hydroxypropiophenone*.—The above acetamido-ketone (15 g.) in ethanol (100 c.c.) was stirred with aqueous formaldehyde (10 c.c.; 38%) and sodium hydrogen carbonate (1·0 g.) at 40—45° for 1 hr. The solution was treated with charcoal, filtered, and partly evaporated. On cooling, the *hydroxy-ketone* was obtained as plates (10 g.) (from ethyl acetate), m. p. 168° (Found : C, 66·6; H, 5·4; N, 4·4. $C_{18}H_{17}O_5N$ requires C, 66·1; H, 5·2; N, 4·3%).

Reductions of α-*Acetamido*-p-*benzoyloxy*-β-*hydroxypropiophenone*.—(a) *Meerwein–Pondorff reduction*. The preceding ketone (5 g.) was slowly distilled with a solution of aluminium *iso*propoxide (5 g.) in dry *iso*propanol (50 c.c.). When no acetone was present in the distillate, the residue was decomposed by boiling with water for 10 min. and filtered. Evaporation of the filtrate gave a residue which readily crystallised from ethyl acetate, to give a crude *aminodiol* (3·3 g.), m. p. 138° (Found : C, 65·65; H, 5·6; N, 4·6. $C_{18}H_{19}O_5N$ requires C, 65·7; H, 5·8; N, 4·3%). Further crystallisations from ethyl acetate raised the m. p. to 147—148° (Found : C, 65·1; H, 5·9; N, 4·5%). Repeated crystallisations gradually raised the m. p. to 162° (Found : C, 65·1; H, 5·65%).

(b) *Catalytic hydrogenation*. The preceding propiophenone (12·3 g.) was hydrogenated in ethanol in presence of Raney nickel. Repeated crystallisation from ethyl acetate gave an *acetamido-diol* (5·6 g.), m. p. 177° (the mother liquors on evaporation gave only intractable gums) (Found : C, 65·5; H, 5·55; N, 4·35%).

Acid Hydrolysis of 2-*Acetamido*-1-p-*benzoyloxyphenylpropane*-1 : 3-*diol obtained by Hydrogenation*.—(*a*) Hot concentrated hydrochloric acid caused extensive decomposition. (*b*) The acetamido-diol (1·7 g.), 2N-hydrochloric acid (12·7 ml.), and ethanol (10 ml.) was heated for 90 min. on the steam-bath. The mixture was cooled, diluted with water (50 ml.), and made alkaline with sodium hydroxide solution. 2-*Amino*-1-p-*benzoyloxyphenylpropane*-1 : 3-*diol* (0·94 g.), m. p. 134—135°, was obtained and crystallised first from aqueous ethanol to m. p. 141—142° and finally from ethanol and ethyl acetate as plates, m. p. 145—146° (Found : C, 66·7; H, 5·9; N, 4·9. $C_{16}H_{17}O_4N$ requires C, 66·9; H, 6·0; N, 4·9%). (*c*) The acetamido-diol (4·85 g.) was refluxed for 2 hr. with 2N-sulphuric acid (5 c.c.). On cooling, a crystalline compound, m. p. 225°, was obtained. When washed with hot ethanol and recrystallised from water, 2-*amino*-1-p-*benzoyloxyphenylpropane*-1 : 3-*diol sulphate* was obtained as plates, m. p. 246° (Found : C, 53·7; H, 5·65; N, 4·5; S, 4·8. $C_{16}H_{17}O_4N,\frac{1}{2}H_2SO_4,H_2O$ requires C, 5·42; H, 5·65; N, 4·0; S, 4·55%).

Another *form* of 2-*amino*-1-p-*benzoyloxyphenylpropane*-1 : 3-*diol* was obtained by treatment of the sulphate with sodium hydrogen carbonate solution. When crystallised from methanol and ethyl acetate needles were obtained, having m. p. 184° (Found : C, 67·1; H, 5·5; N, 4·6%).

p-*Benzyloxyacetophenone*.—Prepared according to Priestly and Moness (*J. Org. Chem.*, 1940, **5**, 355) in almost quantitative yield, this had m. p. 93°.

ω-*Acetamido*-p-*benzyloxyacetophenone*.—The foregoing ketone (113 g.) in chloroform (200 c.c.) and sodium-dried ether (500 c.c.) was treated dropwise with bromine (25·8 c.c.) at 10°. Bromination of slightly impure ketone was more rapid than that of pure ketone; bromination in presence of suspended calcium carbonate was extremely slow. It was necessary in some cases to warm the solution at the start of bromination and to expose the solution to ultra-violet light. Once the reaction was initiated, bromination was very rapid and cooling was essential. The solution obtained was added with stirring to hexamethylenetetramine (200 g.) in chloroform (1500 c.c.), and stirring continued for 2 hr. The damp white precipitate of hexamethylene addition product obtained by filtration was hydrolysed by stirring with ethanol (1 l.) and concentrated hydrochloric acid (500 c.c.) overnight. The crude α-amino-ketone hydrochloride obtained by filtration was acetylated in presence of ice and ice-water (1 l.) with sodium acetate (164 g.) and acetic anhydride (103 c.c.) by stirring for 2 hr. ω-*Acetamido*-p-*benzyloxyacetophenone* was obtained by crystallisation of the product from methanol as needles (75 g.), m. p. 138° (Found : C, 71·55; H, 5·8; N, 5·05. $C_{17}H_{17}O_3N$ requires C, 72·1; H, 6·05; N, 4·9%); $\lambda_{max.}$ 281 mμ (ε 16,130).

ω-*Acetamido*-p-*hydroxyacetophenone*.—The foregoing benzyl ether was hydrogenolysed in the presence of palladised strontium carbonate, to give the *phenol* as prisms, m. p. 179—180° (from ethyl acetate) (Found : C, 62·2; H, 5·7; N, 8·65. $C_{10}H_{11}O_3N$ requires C, 62·2; H, 5·7; N, 7·25%), $\lambda_{max.}$ 285 mμ (ε 15,350).

α-*Acetamido*-p-*benzyloxy*-β-*hydroxypropiophenone*.—The foregoing ketone (75 g.) was stirred at 45° for 1½ hr. with aqueous formaldehyde (50 c.c.; 38%) and sodium hydrogen carbonate (5 g.). The hot solution was treated with charcoal, filtered, and on cooling yielded the *ketone* (62 g.) as plates, m. p. 147—148° (Found : C, 68·8; H, 6·0; N, 5·3. $C_{18}H_{19}O_4N$ requires C, 69·0; H, 6·1; N, 4·5%).

α-*Acetamido*-p-*hydroxy*-β-*hydroxypropiophenone*.—The foregoing benzyl ether was hydrogenolysed in alcohol in the presence of Raney nickel or palladised strontium carbonate, to give the *ketone* as needles (from ethyl acetate), m. p. 178—179° (Found : C, 59·4; H, 6·0; N, 5·75. $C_{11}H_{13}O_4N$ requires C, 59·2; H, 5·9; N, 6·3%).

DL-threo-2-*Acetamido*-1-p-*benzyloxyphenylpropane*-1 : 3-*diol*.—(*a*) A mixture of dry *iso*propanol (100 c.c.), aluminium *iso*propoxide (3 g.), and α-acetamido-*p*-benzyloxy-β-hydroxypropiophenone (3 g.) was slowly distilled for 1½ hr. until no acetone was detectable in the distillate. The residue was heated on the steam-bath for 10 min. with the addition of water (10 c.c.), then filtered, and the solid was extracted with hot methanol. The combined extracts, on evaporation and repeated crystallisation from ethyl acetate, gave the *diol* as short needles, m. p. 169—170° (Found : C, 69·0; H, 7·0; N, 4·6. $C_{18}H_{21}O_4N$ requires C, 68·55; H, 6·7; N, 4·4%).

In one such experiment another *compound* was obtained as needles, m. p. 137—138° (Found : C, 73·1; H, 5·9; N, 4·8. $C_{18}H_{17}O_3N$ requires C, 73·2; H, 5·8; N, 4·7%), $\lambda_{max.}$ 222 and 285 mμ (ε 19,220, 14,510).

(*b*) The propiophenone (3·13 g.) in ethanol (80 c.c.) was stirred at room temperature for 10 min. with a solution of sodium borohydride (0·2 g.) in ethanol (20 c.c.). The mixture was diluted with water (20 c.c.), acidified with glacial acetic acid, and evaporated to dryness. The product was repeatedly crystallised from ethyl acetate and was identical with the diol obtained as in (*a*).

DL-threo-2-*Acetamido*-1-p-*hydroxyphenylpropane*-1 : 3-*diol*.—Debenzylation of the foregoing diol in alcohol was carried out in the presence of palladised strontium carbonate. The *phenol* was obtained as needles, m. p. 175° (decomp.), by crystallisation from ethyl acetate or dioxan (Found : C, 57·9; H, 6·5; N, 5·6. $C_{11}H_{15}O_4N$ requires C, 58·7; H, 6·7; N, 6·2%). The phenol (1 g.) was methylated by refluxing ethyl methyl ketone (150 c.c.), absolute alcohol (50 c.c.), anhydrous potassium carbonate (2 g.), and methyl iodide (5 c.c.) for 6 hr. The methyl ether, m. p. 128°, was obtained on crystallisation from water (Found : C, 59·55; H, 7·2; N, 6·0. Calc. for $C_{12}H_{17}O_4N$: C, 60·2; H, 7·2; N, 5·85%).

DL-threo-2-*Acetamido*-1-(4-*hydroxy*-3 : 5-*di*-*iodophenyl*)*propane*-1 : 3-*diol*.—The foregoing acetamido-compound (0·14 g.) in saturated sodium hydrogen carbonate solution (10 c.c.) was

treated dropwise with an aqueous solution (1·3 c.c. of 1·9N) of iodine and sodium iodide. After 30 min. the solution was filtered and acidified with dilute sulphuric acid. The precipitated solid was crystallised from aqueous ethanol to give the *di-iodo*-compound, m. p. 186° (decomp.) (Found: C, 28·3; H, 2·8; N, 2·8; I, 52·5. $C_{11}H_{13}O_4NI_2$ requires C, 27·7; H, 2·75; N, 2·9; I, 52·8%).

DL-threo-2-*Amino*-1-p-*benzoyloxypropane*-1 : 3-*diol*.—The acetyl derivative (1·5 g.) was heated under reflux for 30 min. with N-sulphuric acid (25 c.c.). On cooling, a *sulphate* (1·25 g.), m. p. 229—230° (decomp.), was obtained as plates (Found: C, 56·65; H, 6·55; N, 4·8; S, 5·4. $C_{16}H_{19}O_3N,\frac{1}{2}H_2SO_4,H_2O$ requires C, 56·5; H, 6·5; N, 4·1; S, 4·7%). When this was made alkaline with hot sodium hydrogen carbonate solution, the free *base* (0·6 g.) was obtained, forming plates, m. p. 126—127°, from water (Found: C, 69·6; H, 6·9; N, 4·95. $C_{16}H_{19}O_3N$ requires C, 70·3; H, 7·0; N, 5·1%).

DL-threo-2-*Amino*-1-p-*hydroxyphenylpropane*-1 : 3-*diol*.—The foregoing base (1·6 g.) was debenzylated by hydrogenation in alcohol in presence of palladised strontium carbonate, to give a gum which was dissolved in methanol and ethyl acetate and set aside in the refrigerator for one week. The *phenolic base* was obtained as needles (0·6 g.), m. p. 138° (Found: C, 58·1; H, 6·6; N, 7·7. $C_9H_{13}O_3N$ requires C, 59·0; H, 7·15; N, 7·65%).

DL-threo-2-*Dichloroacetamido*-1-p-*hydroxyphenylpropane*-1 : 3-*diol*.—The phenolic base (0·1 g.) obtained as in the preceding paragraph was refluxed with methyl dichloroacetate (2 c.c.) and methanol (5 c.c.) for 20 min. Evaporation and repeated trituration with light petroleum gave an oil, which was taken up in cold water and extracted twice with ethyl acetate. From the ethyl acetate extract the *dichloroacetamide* was obtained as needles, m. p. 122—124°, by evaporation and treatment of the residue with light petroleum (Found: C, 45·3; H, 4·7; N, 4·3; Cl, 22·1. $C_{11}H_{13}O_4NCl_2$ requires C, 44·9; H, 4·8; N, 4·8; Cl, 24·1%).

DL-threo-2-*Dichloroacetamido*-1-(4-*hydroxy*-3 : 5-*di-iodophenyl*)*propane*-1 : 3-*diol*.—The foregoing dichloroacetamido-compound was iodinated in the same manner as the acetamido-compound; the *product* crystallised from aqueous alcohol as a monohydrate, m. p. 165° (decomp.), a pale buff microcrystalline powder (Found: N, 2·5; Halogen, 57·6. $C_{11}H_{11}O_4NCl_2I_2,H_2O$ requires N, 2·5; Halogen, 57·6%).

α-*Acetamido*-β-*acetoxy*-p-*benzyloxypropiophenone*.—α-Acetamido-*p*-benzyloxy-β-hydroxypropiophenone (1 g.) in dry pyridine (6 c.c.) and acetic anhydride (0·4 c.c.) was left for 48 hr. The mixture was diluted with water, and the *diacetyl* derivative crystallised from ethanol as needles, m. p. 132° (Found: C, 66·5; H, 5·9; N, 4·1. $C_{19}H_{21}O_5N$ requires C, 66·5; H, 6·2; N, 4·1%), $\lambda_{max.}$ 282 mμ (ε 16,200).

α-*Acetamido*-p-*benzyloxyacrylophenone*.—The foregoing diacetate (0·4 g.) and quinoline (3 c.c.) were boiled for 3 min. and then poured into water. Crystallisation from methanol afforded the ketone as needles, m. p. 138°, alone or on admixture with the abnormal Meerwein–Pondorff reduction product described above.

This ketone (1·0 g.) absorbed 3 mols. of hydrogen in ethanol in presence of palladised strontium carbonate, giving 2-*acetamido*-1-p-*hydroxyphenylpropan*-1-*ol*, prisms, m. p. 194—195° (from water) (Found: C, 63·0; H, 7·3; N, 6·5. $C_{11}H_{15}O_3N$ requires C, 63·1; H, 7·2; N, 6·7%).

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