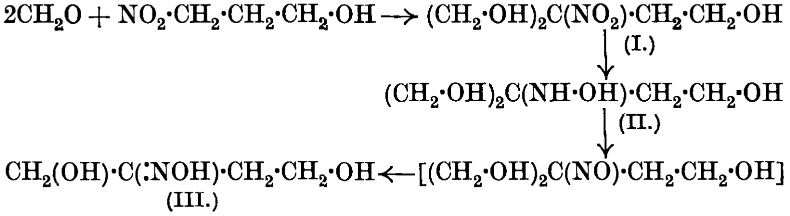
95. *Experiments on the Synthesis of Polyhydroxylic Compounds.*

By William Charlton and James Kenner.

It has been shown that Piloty and Ruff's classical synthesis of the oxime of dihydroxyacetone is dependent on a general reaction of nitroso-compounds (Earl, Ellsworth, Jones, and Kenner, J., 1928, 2697). It was therefore decided to explore the possibility that the reaction might furnish a general method of synthesising α-hydroxy-ketones, which might then be applied to the synthesis of poly-hydroxylic compounds related to the carbohydrates. The prospect was the more attractive since the ultimate product with a normal carbon chain would be generated from another containing two hydroxymethyl groups attached to the same carbon atom, such as occur in apiose (Vongerichten, *Ber.*, 1906, **39**, 235; Schmidt, *Annalen*, 1930, **483**, 115), and it might ultimately be of importance to know the configurational relationships between the two series.

As a preliminary, 2-*nitro*-2-*hydroxymethylbutan*-1:4-*diol* (I) was prepared by condensation of formaldehyde with 3-nitropropan-1-ol, and characterised by its *triacetyl* and crystalline *tribenzoyl* derivatives :



$$\begin{tikzcd}[column sep=small]
2CH_2O + NO_2\cdot CH_2\cdot CH_2\cdot CH_2\cdot OH \arrow[r] & (CH_2\cdot OH)_2C(NO_2)\cdot CH_2\cdot CH_2\cdot OH \arrow[d, "\text{(I.)}"] \\
 & (CH_2\cdot OH)_2C(NH\cdot OH)\cdot CH_2\cdot CH_2\cdot OH \arrow[d, "\text{(II.)}"] \\
\underset{\text{(III.)}}{CH_2(OH)\cdot C(:NOH)\cdot CH_2\cdot CH_2\cdot OH} & {[(CH_2\cdot OH)_2C(NO)\cdot CH_2\cdot CH_2\cdot OH]} \arrow[l]
\end{tikzcd}$$

Reduction of the hydroxymethyl derivative by Piloty and Ruff's procedure with sodium amalgam yielded a gummy product, with reducing properties. Although it was not found possible to isolate the desired hydroxylamine (II), this had evidently been formed, since the product obtained after oxidation with mercuric oxide readily yielded the osazone (IV) when treated with phenylhydrazine acetate. We concluded, therefore, that the oxime (III) had been formed in the normal manner. Further, the hydroxymethyl derivative (I) in presence of sodium ethoxide yielded the sodium salt of 3-*nitrobutane*-1 : 4-*diol* (V), from which the same osazone (IV) could be obtained after treatment with hydrochloric acid either alone or in presence of stannous chloride :

$$\begin{tikzcd}
\mathrm{CH_2(OH)\cdot C(:NO_2Na)\cdot CH_2\cdot CH_2\cdot OH} \arrow[r] \arrow[d, "\text{(V.)}"'] & \mathrm{CH_2(OH)\cdot CO\cdot CH_2\cdot CH_2\cdot OH} \arrow[d, "\text{(VI.)}"] \\
\underset{\text{(VII.)}}{\mathrm{CH_2(OH)\cdot C(:NOH)\cdot CH_2\cdot CH_2\cdot OH}} \arrow[r] & \underset{\text{(IV.)}}{\mathrm{CH(:N\cdot NHPh)\cdot C(:N\cdot NHPh)\cdot CH_2\cdot CH_2\cdot OH}}
\end{tikzcd}$$

Again, however, no success attended the attempts to isolate the ketone (VI) or its oxime (VII), which these experiments were designed to generate.

The moderate measure of success thus indicated was not maintained when our experiments were extended to the synthesis of more highly hydroxylated compounds. Thus, ethoxyacetaldehyde was converted into 3-*nitro*-1-*ethoxypropan*-2-*ol* (VIII), but, owing to the reversibility of this reaction (compare Jones and Kenner, J., 1930, 919), the aldehyde was regenerated when the attempt was made to condense the propanol with formaldehyde. The only definite product isolated from the reaction was, therefore, " nitro*iso*butylglycerol " (IX), which was obtained in its higher-melting form (compare Kleinfeller, *Ber.*, 1929, **62**, 1584) :

$$\begin{tikzcd}
\mathrm{EtO\cdot CH_2\cdot CHO + MeNO_2} \arrow[r, shift left] \arrow[r, leftarrow, shift right] \arrow[dr] & \mathrm{EtO\cdot CH_2\cdot CH(OH)\cdot CH_2\cdot NO_2}\ \text{(VIII.)} \\
 & \mathrm{NO_2\cdot C(CH_2\cdot OH)_3}\ \text{(IX.)}
\end{tikzcd}$$

Similar results attended experiments with 1-nitropropan-2-ol (X) and β-nitrolactic acid (XI) :

$$\text{(X.)}\ \mathrm{Me\cdot CH(OH)\cdot CH_2\cdot NO_2} \qquad \mathrm{NO_2\cdot CH_2\cdot CH(OH)\cdot CO_2H}\ \text{(XI.)}$$

The work of Maas (*Rec. trav. chim.*, 1899, **17**, 386; compare Wilkendorf and Trenel, *Ber.*, 1924, **57**, 306) indicates that the reversibility in question is diminished by chlorination of the nitro-compound, but we have not pursued this line of attack because Schmidt and Ascherl have shown that the process of reduction which would ultimately be necessary for our purpose also involves the replacement of a hydroxyl group (*Ber.*, 1925, **58**, 356), *e.g.* :

$$\mathrm{Me\cdot CH(OH)\cdot CCl(NO_2)\cdot CH(OH)Me} \longrightarrow \mathrm{Me\cdot CH(OH)\cdot CO\cdot CH_2Me}$$

EXPERIMENTAL.

2-*Nitro-2-hydroxymethylbutane*-1 : 4-*diol*.—A solution of 1-nitropropan-2-ol (Henry, *Rec. trav. chim.*, 1897, **16**, 193, 213), b. p. 123—128°/22 mm., in an equal weight of water was treated with the calculated amount of sieved paraform, freshly prepared by evaporating formaldehyde solution (compare Descudé, *Bull. Soc. chim.*, 1902, **27**, 867). A little solid potassium carbonate having been added, reaction set in when the mixture was warmed to 30°, and the paraform rapidly dissolved. After the resulting solution had been kept for some days in a vacuum over concentrated sulphuric acid, the *butanediol* crystallised and was purified, after draining on porous earthenware, by recrystallisation from a mixture of chloroform (4 volumes) and ethyl acetate (6 volumes). Small prisms, m. p. 59—61°, were thus obtained in 50% yield (Found: C, 36·2; H, 6·9; N, 8·4. $C_5H_{11}O_5N$ requires C, 36·4; H, 6·7; N, 8·5%). The same product resulted when formalin solution was used in place of paraform, but the subsequent process of concentration was only successful in small-scale experiments. The condensation with paraform was also very successful in boiling ethyl acetate solution in presence of a few drops of 40% sodium hydroxide solution. The gummy product remaining, after evaporation of the solvent under reduced pressure, readily crystallised.

The *tribenzoate* resulted when the nitro-compound was heated with benzoyl chloride and quinoline for 2½ hours at 100°. It crystallised from alcohol in fine needles, m. p. 145—147° (Found: C, 65·7; H, 5·3; N, 2·8. $C_{26}H_{23}O_8N$ requires C, 65·3; H, 4·9; N, 2·9%). The *triacetate* was prepared by boiling the nitro-compound with excess of acetic anhydride for 15 minutes. It could not be crystallised, but boiled at 210°/20 mm. (Found: N, 4·8. $C_{11}H_{17}O_8N$ requires N, 4·8%).

2-*Nitrobutane*-1 : 4-*diol*.—(a) A solution of 2-nitro-2-hydroxymethylbutane-1 : 4-diol (10 g.) in absolute alcohol (30 c.c.) was gradually treated with a solution of sodium (1·4 g.) in absolute alcohol (35 c.c.). Immediately crystalline salt commenced to separate, the liquor was decanted from the gummy material first precipitated. By crystallising the latter from methyl alcohol a quantity of *sodium* salt (1·9 g.) (Found: Na, 14·8%) was recovered, but the main portion (6 g.) was obtained from the decanted liquors, washed with alcohol and ether, and dried in a vacuum over sulphuric acid (Found: Na, 14·4. $C_4H_8O_4NNa$ requires Na, 14·6%).

The crude syrup obtained in the preparation of the original nitro-compound was also submitted to the process just described, and with very fair success when the volume of alcohol employed was restricted to the minimum.

(b) The following process represents a combination of the preparation of the nitro-compound with its subsequent decomposition (compare Schmidt and Wilkendorf, *Ber.*, 1919, **52**, 389): A solution of nitropropane (10 g.) in methyl alcohol (10 c.c.) was successively treated in a reflux apparatus with paraform (9 g.) and a few drops of sodium hydroxide solution (40%). Solution having been achieved by warming, the mixture was cooled and treated with a solution of sodium (3 g.) in methyl alcohol (40 c.c.). The sodium salt (10 g.) was collected and purified as before (Found: Na, 14·7%).

When a solution of the salt was coupled with benzenediazonium chloride (1 mol.), formaldehyde was eliminated, but, as in other cases (compare Jones and Kenner, *loc. cit.*), the resulting *ω-nitro-α-hydroxypropaldehydephenylhydrazone* was only isolated in the solid condition by precipitation from its solution in sodium hydroxide solution. After crystallisation from methyl alcohol, it melted at 103—104° (Found: N, 20·1. $C_9H_{11}O_3N_3$ requires N, 20·1%).

2-*Chloro*-2-*nitrobutane*-1 : 4-*diol* was prepared by passing chlorine into a suspension of the sodium salt (4·5 g.) in absolute ether (25 c.c.) until the colour of the solution indicated the presence of free chlorine. The solid, remaining after evaporation of the ethereal solution under reduced pressure, crystallised from equal volumes of ethyl acetate and chloroform in prisms, m. p. 62—66° (Found: N, 8·2. $C_4H_8O_4NCl$ requires N, 8·3%).

The free nitrobutanediol could not be obtained in the solid condition or separated from salicylic acid when the latter was employed to decompose the sodium salt (compare Schmidt and Wilkendorf, *loc. cit.*).

1 : 4-*Dihydroxybutan*-2-*onephenylosazone*.—(a) A solution of the above sodium salt (8 g.) in water (45 c.c.) was slowly run into hydrochloric acid (*d* 1·17; 20 c.c.), cooled by a freezing mixture. The solution, having been nearly neutralised with sodium carbonate, was neutralised with barium carbonate and evaporated under reduced pressure. A strongly reducing syrup (4 g.) was isolated by extraction with boiling ethyl acetate, but no crystalline semicarbazone, oxime, or benzoyl derivative could be prepared from it. However, an osazone was prepared as a black oil, and obtained in the solid condition by treatment with methyl alcohol and ligroin. It melted at 93° and did not appreciably depress the melting point of the pure material prepared by the following procedure.

(b) A solution of the sodium salt (22 g.) in water (80 c.c.) was gradually added to a cooled agitated solution of stannous chloride (35 g.) in hydrochloric acid (*d* 1·17; 190 c.c.) (compare von Braun and Kruber, *Ber.*, 1912, **45**, 396). After $\frac{3}{4}$ hour, the solution was rendered just alkaline with sodium hydroxide solution, and evaporated to dryness under reduced pressure. The residue, dried by addition of alcohol and removal of this by distillation, yielded a strongly reducing syrup (8 g.) when extracted by hot ethyl acetate. When this was heated with phenylhydrazine acetate, a dark red oily *osazone* was obtained which crystallised from its solution in benzene. By washing with aqueous methyl alcohol and light petroleum, and crystallisation from ether–light petroleum, minute yellow needles were obtained, m. p. 99—101° (Found: C, 68·1; H, 6·6; N, 20·0. $C_{16}H_{18}ON_4$ requires C, 68·1; H, 6·4; N, 19·9%).

(c) *Reduction of the hydroxymethyl compound* (compare Piloty and Ruff, *Ber.*, 1897, **30**, 1656). A solution of 2-nitro-2-hydroxymethylbutane-1 : 4-diol (4 g.) in water (120 c.c.) containing crystallised aluminium sulphate (18 g.) was agitated and treated gradually at 0° with 2½% sodium amalgam. Aluminium hydroxide was filtered off, and the filtrate evaporated to dryness under reduced pressure; the residue was extracted three times with absolute alcohol (in all, 200 c.c.) and the combined extracts were evaporated to dryness in a vacuum, a little inorganic matter being thereby removed. The hydroxylamine derivative was recovered as a clear brownish-yellow uncrystallisable gum, with strongly reducing properties. Attempts to prepare a crystalline oxalate by using a solution of oxalic acid (anhydrous) in absolute ether failed.

Some of the gum was dissolved in absolute alcohol and heated at 60° for 2 hours with excess of freshly prepared yellow mercuric oxide. This underwent reduction, and the filtered solution was evaporated under reduced pressure, the resulting gum being extracted with ethyl acetate to remove mercury compounds. The recovered oxime could not be crystallised, but readily yielded the osazone on treatment with phenylhydrazine acetate. The osazone was purified as already described: m. p. 95—96°; mixed m. p. with previous preparation (98—99°), 95—97°.

3-*Nitro*-1-*ethoxypropan*-2-*ol*.—Ethoxyacetal (20 g.), b. p. 162—166°, was hydrolysed by boiling with water (60 g.) and one drop of concentrated sulphuric acid for 10 minutes. The solution, after neutralisation with barium carbonate, was treated with nitromethane (7 g.) and potassium carbonate (0·5 g.). After 12 hours, the condensation product was isolated by extraction with ether. The *nitroethoxypropanol* (9 g.) boiled at 128°/20 mm. (Found: C, 40·2; H, 7·6. $C_5H_{11}O_4N$ requires C, 40·2; H, 7·4%). When it was treated with formalin solution or with paraform under conditions similar to those applied to 1-nitropropan-2-ol, nitro*iso*butylglycerol, m. p. 167° (identified by comparison with an authentic specimen), and the sodium salt of 2-nitropropane-1 : 3-diol were respectively obtained. The latter was characterised by conversion into 2-chloro-2-nitropropane-1 : 3-diol, m. p. 120—123°, and comparison of this with an authentic specimen (compare Schmidt and Wilkendorf, *Ber.*, 1922, **55**, 316).

Acetaldehyde was evolved and detected by Simon's reaction (*Compt. rend.*, 1897, **125**, 1105) when 1-nitropropan-2-ol, b. p. 105°/25 mm. (Henry, *Bull. Acad. roy. Belg.*, 1903, **29**, 837) (10·5 g.) and formalin solution (50 c.c.) were treated with potassium carbonate (0·2 g.) at 20—25°. By concentration at the ordinary temperature over phosphoric oxide in a vacuum, nitro*iso*butylglycerol, m. p. 155—160°, was obtained; from the liquor a further quantity, m. p. 168°, was isolated after evaporation under reduced pressure.

The nitro*iso*butylglycerol isolated from different experiments showed varying melting points, *e.g.*, 153—167° (Found: C, 31·9; H, 6·3. Calc. for $C_4H_9O_5N$: C, 31·8; H, 6·0%); 153—163° (C, 31·8; H, 6·3%); 140—154° (C, 31·8; H, 6·4%), but the analyses demonstrated the purity of each sample. As Kleinfeller showed (*loc. cit.*), two modifications, melting respectively at 180° and 157°, exist. In our experiments, the melting point never exceeded 174°, and this sample after some time melted at 163° (C, 31·8; H, 6·1%).

The sensitivity of the nitropropanol to formaldehyde was exhibited by adding one drop of the latter to a mixture of the nitro-compound with Simon's reagent; the characteristic blue colour immediately developed.

β-Nitrolactic acid (Hill and Black, *Amer. Chem. J.*, 1904, **32**, 231), m. p. 76—78°, was similarly decomposed when treated with paraform and potassium carbonate. Glyoxylic acid was detected by the red colour developed with indole solution, and by the violet tryptophan coloration, whilst nitro*iso*butylglycerol, m. p. 168—170°, was also isolated and identified. Subsequently β-nitrolactic acid alone was shown also to exhibit the above colour reaction for glyoxylic acid, after having been neutralised with potassium carbonate solution.

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