38. *The Conversion of Sucrose into Furan Compounds. Part IV. Some Aminotetrahydrofuran Derivatives.*

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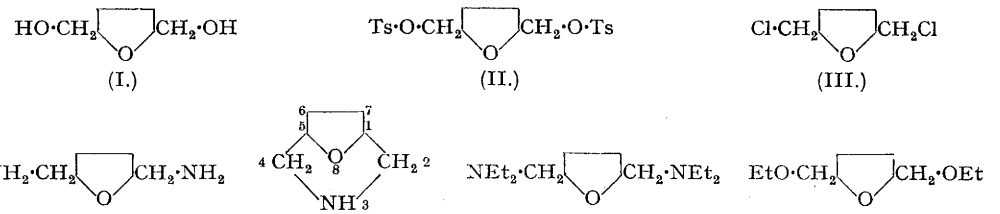
2 : 5-Bishydroxymethyltetrahydrofuran has been converted into a crystalline *di*-p-*toluenesulphonate* and also into 2 : 5-*bischloromethyltetrahydrofuran*. By means of methyl alcoholic ammonia, both of these compounds have been transformed into a secondary amine, herein

shown to be 8-*oxa*-3-*aza*bicyclo[3 : 2 : 1]*octane*. The preparation of 2 : 5-*bis*(*diethylaminomethyl*)*tetrahydrofuran* is also described.

THE reduction product of 5-hydroxymethylfurfuraldehyde, 2 : 5-bishydroxymethyltetrahydrofuran (I) obtained by Haworth, Jones, and Wiggins, (*J.*, 1945, 1), is a convenient intermediate for the preparation of various 2 : 5-disubstituted derivatives of tetrahydrofuran. Thus, by treatment with *p*-toluenesulphonyl chloride in pyridine, it was smoothly converted into the crystalline 2 : 5-*bishydroxymethyltetrahydrofuran di*-p-*toluenesulphonate* (II). Furthermore, (I) was readily chlorinated by means of thionyl chloride to give 2 : 5-*bischloromethyltetrahydrofuran* (III).

It was expected that the di-*p*-toluenesulphonate (II) would give rise to the diamine, 2 : 5-bisaminomethyltetrahydrofuran (IV), on treatment with methyl-alcoholic ammonia. The compound isolated, however, was not a diamine but a substance of empirical formula $C_6H_{11}ON$ to which the dicyclic structure (V) has been assigned. The argument in support of this is as follows. The compound was basic and very hygroscopic, and on exposure to air readily formed a crystalline *carbonate*. It was a monoacidic base, and the crystalline *hydrochloride*, *oxalate*, *picrate*, and p-*toluenesulphonate* were prepared. Treatment of the compound with nitrous acid



(Ts = *p*-Me·C_6H_4·SO_2.)

yielded a *nitrosoamine* which gave the Liebermann reaction, thus showing the nitrogen atom in the molecule to be secondary and probably involved in a ring. Treatment of the compound $C_6H_{11}ON$ with acetic anhydride in methyl alcohol gave only the crystalline acetate, and not the expected *N*-acetyl derivative, but acetylation with acetic anhydride and sodium acetate gave a liquid which was not hydrolysed readily by aqueous sodium hydroxide, showing it to be an N-*acetyl* derivative. Although the amine absorbed bromine and decolourised alkaline permanganate slowly, it was shown to be fully saturated by the fact that no catalytic hydrogenation occurred in the presence of Raney nickel.

These experiments show that in the compound $C_6H_{11}ON$ the oxygen atom must be present as part of the tetrahydrofuran ring; and the nitrogen atom, since the compound forms a nitrosoamine, must be involved in a second ring structure. The compound $C_6H_{11}ON$ must be 8-*oxa*-3-*aza*bicyclo[3 : 2 : 1]*octane* (V).

Treatment of 2 : 5-bischloromethyltetrahydrofuran (III) with methyl-alcoholic ammonia gave the same products as were formed when 2 : 5-bishydroxymethyltetrahydrofuran di-*p*-toluenesulphonate was treated in a similar way, although the yield of (V) was somewhat lower.

A diamino-derivative of tetrahydrofuran was obtained when 2 : 5-bischloromethyltetrahydrofuran was treated with a secondary amine. Thus, with diethylamine at 160° under pressure, it gave 2 : 5-*bis*(*diethylaminomethyl*)*tetrahydrofuran* (VI), a pale yellow liquid which on treatment with methyl iodide gave a crystalline *dimethiodide*. It seems probable, therefore, that a bisaminomethyl-derivative of tetrahydrofuran can be obtained only when no elimination of ammonia or amine can take place between the two side chains.

2 : 5-Bishydroxymethyltetrahydrofuran di-*p*-toluenesulphonate was difficult to hydrolyse with alkali in aqueous solution owing to its low solubility. Some hydrolysis did occur, however, when it was heated at 180° under pressure, and 2 : 5-bishydroxymethyltetrahydrofuran was isolated in small yield. Boiling with aqueous-alcoholic alkali on the other hand readily hydrolysed the compound to 2 : 5-*bisethoxymethyltetrahydrofuran* (VII).

EXPERIMENTAL.

2 : 5-*Bishydroxymethyltetrahydrofuran Di*-p-*toluenesulphonate*.—2 : 5-Bishydroxymethyltetrahydrofuran (27 g.) was dissolved in dry pyridine (250 c.c.) and cooled to 0°. A solution of *p*-toluenesulphonyl chloride in pyridine (85 g. in 100 c.c.; 2·2 mols.) was added to the cooled solution with stirring and

the mixture kept for 24 hours. It was then poured into water and the crystalline p-*toluenesulphonate* filtered off, washed with water until free from pyridine, and dried. It recrystallised from alcohol in needles, m. p. 127·5—128°. Yield, 77 g. (90%) (Found: C, 54·6; H, 5·2; S, 13·7. $C_{20}H_{24}O_7S_2$ requires C, 54·6; H, 5·4; S, 14·5%).

2 : 5-*Bischloromethyltetrahydrofuran*.—2 : 5-Bishydroxymethyltetrahydrofuran (7·6 g.) was dissolved in dry pyridine (14·5 c.c.), and anhydrous magnesium sulphate (2 g.) added. Thionyl chloride (13·6 c.c.) was added dropwise to the stirred solution cooled to 0°, and the mixture heated at 50° until evolution of sulphur dioxide had subsided; the temperature was then raised to 100° for ½ hour. The dark syrupy liquid was then poured on ice and extracted with ether. The extract was neutralised with sodium carbonate solution, washed with water, and dried ($MgSO_4$). Evaporation of the ether gave 2 : 5-*bischloromethyltetrahydrofuran* which distilled at 69° (bath temp.)/0·03 mm., 130° (bath temp.)/15 mm., as a pale yellow mobile liquid, $n_D^{15°}$ 1·4840. Yield, 5·5 g. (56%) (Found: C, 43·0; H, 5·9; Cl, 43·8. $C_6H_{10}OCl_2$ requires C, 42·6; H, 5·9; Cl, 42·1%).

8-*Oxa*-3-*aza*bicyclo[3 : 2 : 1]*octane*.—2 : 5-Bishydroxymethyltetrahydrofuran di-*p*-toluenesulphonate (50 g.) was heated with dry methyl alcohol (1 l. saturated with ammonia at 0°) under pressure at 160° for 36 hours. After evaporation of the alcohol under reduced pressure, the residue was hydrolysed with barium hydroxide solution (54 g. in 500 c.c. of water) at 100° for 1 hour in an atmosphere of nitrogen. After evaporation of the water under reduced pressure, the residue was freed from last traces of water by azeotropic distillation with benzene and thereafter the residue was extracted with boiling chloroform. Evaporation of the solvent gave a syrup (6·0 g.). From this, 8-*oxa*-3-*aza*bicyclo[3 : 2 : 1]*octane* (V) distilled as a colourless liquid (4·5 g.), b. p. 176—178°/760 mm., $n_D^{15°}$ 1·4883 [Found: N, 11·3; *M* (ebullioscopic), 115. $C_6H_{11}ON$ requires N, 12·5%; *M*, 113]. Analysis was extremely difficult owing to the ease with which the compound combines with carbon dioxide.

A second fraction, which distilled at 135—140° (bath temp.)/0·02 mm. as a colourless syrup (1·1 g.) showing $n_D^{20°}$ 1·5014, has not yet been identified.

8-Oxa-3-aza*bicyclo*[3 : 2 : 1]octane was basic to litmus and to brilliant-yellow, and was very hygroscopic. It decolourised alkaline permanganate slowly and absorbed bromine, but in spite of this, no hydrogenation occurred in the presence of Raney nickel and the substance was recovered unchanged. On exposure to air, a crystalline *carbonate* was formed. This was very deliquescent and when left exposed to the atmosphere overnight completely volatilised. It was recrystallised from dry light petroleum–dioxan and then had m. p. 24—25° but was very difficult to analyse [Found: N, 10·1; equiv. (by titration with hydrochloric acid), 158. $C_6H_{11}ON,\frac{1}{2}H_2CO_3$ requires N, 9·7%; equiv., 144]. Evaporation of the aqueous solution from the titration gave the crystalline *hydrochloride* which on recrystallisation from alcohol–ether had m. p. 197—199° (Found: C, 47·7; H, 7·5. $C_6H_{11}ON,HCl$ requires C, 48·2; H, 8·0%).

The *oxalate*, prepared from alcoholic solutions of the base (0·1 g.) and oxalic acid (0·7 g.), recrystallised from alcohol in prisms, m. p. 266—267° (Found: C, 52·8; H, 7·6; N, 9·1. $C_{14}H_{24}O_6N_2$ requires C, 53·2; H, 7·6; N, 8·9%). The *picrate* recrystallised from water in plates, m. p. 188—189° (Found: C, 42·0; H, 4·1; N, 16·0. $C_{12}H_{14}O_8N_4$ requires C, 42·1; H, 4·1; N, 16·3%). The p-*toluenesulphonate*, prepared by mixing alcoholic solutions of the base (0·1 g.) and *p*-toluenesulphonic acid (0·1 g.) and adding ether, recrystallised from alcohol–ether in plates, m. p. 204—205° (Found: C, 54·8; H, 6·4; N, 5·1. $C_{13}H_{19}O_4NS$ requires C, 54·8; H, 6·6; N, 4·9%).

The base (0·36 g.) was dissolved in glacial acetic acid (3 c.c.) and 30% potassium nitrite solution (2·5 c.c.) added. After being kept overnight, the solution was evaporated and the residue dried and extracted with ether. Evaporation of the ethereal extract gave a syrup (0·3 g.) which crystallised on refrigeration. The *nitrosoamine* recrystallised from absolute ether in plates, m. p. 39—40·5° (Found: C, 50·8; H, 6·9; N, 19·9. $C_6H_{10}O_2N_2$ requires C, 50·7; H, 7·0; N, 19·7%). The nitrosoamine on treatment with phenol and concentrated sulphuric acid gave the characteristic Liebermann reaction.

Acetylation of (V).—(*a*) The base (0·7 g.) was dissolved in dry methyl alcohol (5 c.c.) and acetic anhydride (0·31 c.c.) added. The solution was kept for 12 hours and then evaporated under reduced pressure at room temperature. A hygroscopic crystalline residue was obtained which recrystallised from ether in needles, m. p. 133—134·5. Yield, 0·2 g. (Found: C, 55·7; H, 8·5. $C_8H_{15}O_3N$ requires C, 55·5; H, 8·7%). It was the *acetate* of (V).

(*b*) The base (0·5 g.) was dissolved in acetic anhydride (5 c.c.) and fused sodium acetate (0·5 g.) added. The solution was boiled under reflux for 5 minutes and then poured into water. The acid was neutralised with sodium hydrogen carbonate and the solution extracted with chloroform. The extract was dried ($MgSO_4$) and evaporated. A syrup (0·7 g.) was obtained, which distilled at 140° (bath temp.)/0·02 mm. as a colourless liquid, $n_D^{15°}$ 1·5098; it was the N-*acetyl* derivative of (V) [Found: C, 61·4; H, 7·9; *O*-Ac (by treatment with N/10-NaOH at 60°), nil. $C_8H_{13}O_2N$ requires C, 61·9; H, 8·4%; *O*-Ac, nil].

Attempted Acetolysis of (V).—The base (0·6 g.) was boiled under reflux with acetic anhydride (6 c.c.) and zinc chloride (0·1 g.) for 2 hours. The excess of acetic anhydride was distilled off and the residual oil poured into water. The acid was neutralised with sodium hydrogen carbonate and the solution extracted with chloroform. The extract was dried ($MgSO_4$), and, on evaporation of the solvent, a syrup (0·4 g.) was obtained which distilled at 135° (bath temp.)/0·01 mm. and had $n_D^{15°}$ 1·4989; it was the *N*-acetyl derivative, obtained above (Found: N, 8·3; *O*-Ac, nil. Calc. for $C_8H_{13}O_2N$: N, 9·0%; *O*-Ac, nil.).

Treatment of 2 : 5-*Bischloromethyltetrahydrofuran with Methyl-alcoholic Ammonia*.—The compound (30 g.) was dissolved in dry methyl-alcoholic ammonia (700 c.c. saturated at 0°) and heated at 150° for 72 hours. After evaporation of the alcohol under reduced pressure, the residue was hydrolysed with a solution of barium hydroxide (62 g. in 200 c.c. of water) at 100° for 1 hour in an atmosphere of nitrogen. After evaporation of the water under reduced pressure, the residue was freed from last traces of water by distillation with benzene and the residue extracted with boiling chloroform. Evaporation of the solvent gave a syrup (4·2 g.) from which 8-oxa-3-aza*bicyclo*[3 : 2 : 1]octane distilled at 97—100°/15 mm. (nitrogen), $n_D^{20°}$ 1·4840. A *p*-toluenesulphonate was obtained, m. p. 204—205° alone or in admixture with that obtained previously.

Treatment of 2 : 5-*Bischloromethyltetrahydrofuran with Diethylamine*.—The compound (2 g.) was heated in a sealed tube with excess of diethylamine (10 c.c.) at 165° for 8 hours, during which time crystals of diethylamine hydrochloride separated. The excess of diethylamine was evaporated and the residue acidified with dilute hydrochloric acid. Some unchanged starting material separated at this stage and was removed by extraction with ether. The aqueous portion was then made alkaline and the oil which separated extracted with ether. Evaporation of the solvent after drying ($MgSO_4$) gave 2 : 5-*bis*(*diethylaminomethyl*)*tetrahydrofuran*, which distilled at 134° (bath temp.)/15 mm. as a colourless liquid showing $n_D^{18°}$ 1·4639. Yield, 1 g. (46·5%) (Found : N, 11·9. $C_{14}H_{30}ON_2$ requires N, 11·6%).

2 : 5-Bis(diethylaminomethyl)tetrahydrofuran (0·1 g.) was treated with excess methyl iodide at room temperature for one hour. On evaporation of the methyl iodide, an oil was obtained which crystallised on trituration with alcohol. The *dimethiodide* recrystallised from alcohol in clusters of needles, m. p. 187—188·5°. Yield, almost quantitative (Found : C, 36·6; H, 6·9. $C_{16}H_{36}ON_2I_2$ requires C, 36·5; H, 6·8%).

Action of Alkali on 2 : 5-*Bishydroxymethyltetrahydrofuran Di*-p-*toluenesulphonate*.—The compound (16 g.) was boiled under reflux with a solution of sodium hydroxide (3·5 g. in 500 c.c. of water) for 2 days. At the end of this time no reaction had occurred. The above mixture was then heated under pressure at 150—180° for 4 hours. Unchanged di-*p*-toluenesulphonate was filtered off (14 g.) and excess of alkali neutralised with carbon dioxide. The solution was evaporated to dryness under reduced pressure and the residue extracted with chloroform. Evaporation of the solvent gave a syrup (0·5 g.) which distilled at 140° (bath temp.)/0·08 mm. and had $n_D^{16°}$ 1·4902; it was 2 : 5-bishydroxymethyltetrahydrofuran, identified as the crystalline di-*p*-toluenesulphonate which, on recrystallisation from alcohol, had m. p. 126—127° alone or in admixture with an authentic specimen.

The compound (25 g.) was dissolved in alcohol (250 c.c.) and a solution of sodium hydroxide (5 g. in 50 c.c. of water) added. After 24 hours' boiling under reflux, the alcohol was evaporated and water (100 c.c.) added. The solution was then extracted with ether and the extract dried ($MgSO_4$). After evaporation of the solvent 2 : 5-*bisethoxymethyltetrahydrofuran* distilled at 210°/760 mm. as a colourless mobile liquid, $n_D^{19°}$ 1·4356. Yield, 4·7 g. (40%) (Found : C, 63·6; H, 10·2. $C_{10}H_{20}O_3$ requires C, 63·8; H, 10·6%).

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