CLX.—*The Mechanism of Tautomeric Interchange and the Effect of Structure on Mobility and Equilibrium. Part IV. Further Evidence relating to the Mechanism of Acid Catalysis in the Mutarotation of Nitrogen Derivatives of Tetra-acetylglucose.*

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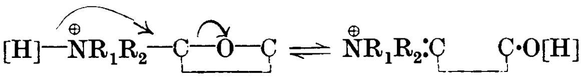
IN Part II (J., 1928, 1583) two types of catalyst for the mutarotation of certain nitrogen derivatives of sugars were recognised: (i) those which attack the ionising proton directly, and (ii) those which facilitate its liberation indirectly, this class including strong acids. Since tetra-acetylglucosidylmethylanilide, in which the mobile hydrogen of the tautomeric system $[H]{-}NR{-}C{-}O{-}C \rightleftharpoons NR{=}C \quad C{\cdot}O[H]$ has been replaced by a methyl group, could not be induced to exhibit mutarotation even in the presence of considerable concentrations of hydrochloric acid, it was concluded that for such weak bases the attack of the catalyst involves, not actual co-ordination of the acid proton, but merely the augmentation, by an electrostatic mechanism, of the positive field in the region of the electrons binding the original (mobile) hydrogen atom. It was considered possible, however (*loc. cit.*, p. 1586), that in the case of derivatives of very strong bases such actual co-ordination of the catalyst proton might occur. The resulting salt might thus have acquired the necessary mobile hydrogen and exhibit mutarotation consequent on the equilibration of the kationic system.



$$[H]{-}\overset{\oplus}{N}R_1R_2{-}C{-}O{-}C \rightleftharpoons \overset{\oplus}{N}R_1R_2{:}C \quad C{\cdot}O[H]$$

α- and β-forms.

In order to test this possibility various tetra-acetylglucosidyl derivatives of the type required have been prepared by the action of tetra-acetylglucosidyl bromide on strong secondary bases, which include various *p*-substituted benzylmethylamines, dimethyl- and diethyl-amines and piperidine. The hydrochlorides of these sugar derivatives have been isolated in a crystalline condition, and their solutions in absolute or 90% alcohol do in fact exhibit a change in rotation in accordance with the kinetics of unimolecular reaction. This change, however, does not appear to be due to the inter conversion of the α- and β-forms, but to slow fission of the derivative into the parent tetra-acetylglucose and the hydrochloride of the secondary base. A similar phenomenon is observed when the free sugar derivatives are examined in ethyl acetate solution in the presence of a little hydrochloric acid as a catalyst, and in these cases slow crystallisation of the base hydrochloride from the solution occurs in the polarimeter tube. On the basis of these negative results it seems probable, therefore, that for mutarotation, dependent on simple isomeric change, to be possible, the original sugar derivative itself (as distinct from its kation) must contain a separable hydrogen atom as was originally postulated by Baker, Ingold, and Thorpe (J., 1924, **125**, 268).

EXPERIMENTAL.

Preparation of p-*Substituted Benzylmethylamines.*—A mixture of 21 g. of the appropriate *p*-substituted benzyl bromide, 40 c.c. of 33% aqueous methylamine solution, and 200 c.c. of alcohol was warmed at 30—40° for 1 hour. Most of the alcohol was then distilled off, the residue was poured into dilute sodium hydroxide solution and shaken with ether, and the bases were extracted from the ethereal solution by dilute hydrochloric acid, recovered by means of ether from the basified extract, dried over anhydrous potassium carbonate, and, after removal of the ether, fractionated under reduced pressure; the monobenzylmethylamine distilled first (yield, 6—7 g.) and then, at a much higher temperature, the dibenzylmethylamine, which was not generally further purified. The secondary bases were purified and characterised in the form of their hydrobromides.

p-Methylbenzylmethylamine has b. p. 84°/6 mm. The *hydrobromide* separates from alcohol–ligroin in glistening plates, m. p. 166° (Found : Br, 36·9. $C_9H_{13}N,HBr$ requires Br, 37·0%).

p-Chlorobenzylmethylamine has b. p. 101°/5 mm. The *hydrobromide* crystallises from absolute alcohol in feathery clusters of thin square plates, m. p. 196° (Found : Br, 34·0. $C_8H_{10}NCl,HBr$ requires Br, 33·8%).

p-Cyanobenzylmethylamine has b. p. 143°/6 mm. The *hydrobromide* crystallises from absolute alcohol in clusters of fine needles, m. p. 209—210° (Found : Br, 35·3. $C_9H_{10}N_2,HBr$ requires Br, 35·3%).

Di(*p*-methylbenzyl)methylamine has b. p. about 180°/6 mm., and di(*p*-chlorobenzyl)methylamine b. p. about 200°/5 mm.

Di(*p*-cyanobenzyl)methylamine is left as a semi-solid residue after distillation of the *p*-cyanobenzylmethylamine. It crystallises from ligroin (b. p. 40—60°) in clusters of thin plates, m. p. 65°. The *hydrochloride*, crystallised from alcohol, has m. p. 250° (decomp.) (Found : Cl, 12·5. $C_{17}H_{15}N_3,HCl$ requires Cl, 11·9%).

Preparation of Tetra-acetylglucosidyl Derivatives of Various Secondary Bases.—Tetra-acetylglucosidyl bromide * (1 mol.) and the substituted benzylmethylamine (2 mols.) were gently warmed in ethereal solution until most of the ether had evaporated; the mixture was then left at the ordinary temperature for several hours. Separation of the hydrobromide of the base began almost immediately. The product was diluted with dry ether, the hydrobromide filtered off and washed with dry ether, the filtrate and washings extracted with 5% hydrochloric acid to remove any unchanged base, and the residue from the dried ethereal extract left to crystallise. The product from the *p*-cyano-derivative, which would not crystallise well, was converted into its hydrochloride by the action of hydrogen chloride in dry ether, and regenerated by the action of sodium carbonate solution. In the other cases the hydrochlorides were similarly prepared from the purified tetra-acetylglucosidylbenzylmethylamides.

The *benzylmethylamide*, crystallised from ether–ligroin, has m. p. 125° (Found : C, 58·5; H, 6·6. $C_{22}H_{29}O_9N$ requires C, 58·5; H, 6·5%). The *hydrochloride*, after crystallisation from a concentrated solution in ether–ligroin, has m. p. 80° (Found : Cl, 7·3. $C_{22}H_{29}O_9N,HCl$ requires Cl, 7·3%).

The p-*methylbenzylmethylamide* crystallises from ligroin (b. p. 60—80°), containing a little ether, in rosette clusters of fine needles, m. p. 99—100° (Found : C, 59·4; H, 6·5. $C_{23}H_{31}O_9N$ requires C, 59·3; H, 6·7%). The *hydrochloride* crystallises with difficulty from a concentrated solution in alcohol–ligroin (b. p. 60—80°); m. p. 175° (decomp.) (Found : Cl, 7·0. $C_{23}H_{31}O_9N,HCl$ requires Cl, 7·1%).

The p-*chlorobenzylmethylamide*, crystallised from ether–ligroin, has m. p. 104—105° (Found : C, 54·0; H, 5·7. $C_{22}H_{28}O_9NCl$ requires C, 54·3; H, 5·8%). The *hydrochloride* crystallises from alcohol–ligroin in clusters of fine needles, m. p. 137° (decomp.) (Found : ionisable Cl, 6·9. $C_{22}H_{28}O_9NCl,HCl$ requires ionisable Cl, 7·0%).

The p-*cyanobenzylmethylamide* crystallises from ether-ligroin in clumps of fine needles, m. p. 85—86° (Found : C, 57·7; H, 6·0. $C_{23}H_{28}O_9N_2$ requires C, 57·8; H, 5·9%). The *hydrochloride*, crystallised from hot alcohol, has m. p. 146° (decomp.) (Found : Cl, 7·1. $C_{23}H_{28}O_9N_2,HCl$ requires Cl, 6·9%).

Condensation of tetra-acetylglucosidyl bromide with piperidine yields two different products according to the experimental con-

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* Tetra-acetylglucosidyl bromide (β-acetobromoglucose) is best purified by crystallisation from anhydrous ether. It may then be stored indefinitely over phosphoric oxide and a little potassium hydroxide in a vacuum.

ditions. (1) When 30 g. of tetra-acetylglucosidyl bromide are added to 50 c.c. of piperidine so that practically the whole dissolves before any considerable amount of action sets in, and the mixture is kept at 0—10°, a sudden vigorous reaction with much evolution of heat begins after a short period. At this stage a large volume of ether is rapidly added, the separated piperidine hydrobromide filtered off, and the product worked up as before. Addition of ligroin to the dried concentrated ethereal extract induces crystallisation (especially after seeding). The separated crystals (4·5 g.) are recrystallised from methyl alcohol–ligroin and then from ether containing a little methyl alcohol. The *piperidide* A was thus obtained in long thin prisms, m. p. 123° without decomposition. Decomposition slowly occurs in the fused substance (Found : C, 54·9; H, 7·1. $C_{19}H_{29}O_9N$ requires C, 54·9; H, 7·0%). The *hydrochloride* of this form crystallises from alcohol–ligroin in clusters of slender prisms, m. p. 126° (Found : Cl, 7·5. $C_{19}H_{29}O_9N,HCl$ requires Cl, 7·8%).

(2) When the tetra-acetylglucosidyl bromide is added slowly in 0·5 g. portions to the piperidine diluted with half its volume of ether, and the reaction mixture is kept cool in ice, separation of piperidine hydrobromide occurs slowly without rise in temperature. After the addition is completed the mixture is left in ice for 1 hour and then at the ordinary temperature for 3 hours. Since the form obtained under these conditions is much less soluble in ether, it is filtered off, mixed with piperidine hydrobromide, after dilution of the reaction mixture with dry ether. After removal of the piperidine hydrobromide with water the *piperidide* B crystallises from methyl alcohol–ligroin or ethyl acetate–ligroin in fine needles, m. p. 136° (decomp.) with previous slight darkening (Found : C, 54·9; H, 7·1%). A mixture of the two forms softens and darkens at 120—123°, but fusion (with decomposition) is not complete until 136°. The *hydrochloride* of the second form is unstable. Rapid crystallisation from the smallest possible volume of alcohol–ligroin yields large prisms, m. p. 130—131° (decomp.) (Found : Cl, 8·7%), but slower crystallisation yields a much more soluble product obtained only as a crystalline powder, m. p. 126—127° (Found : Cl, 12·4. The deacetylated derivative $C_{11}H_{21}O_5N,HCl$ requires Cl, 12·5%).

The Diethylamide.—Tetra-acetylglucosidyl bromide (10 g.) was added in small portions to 10 g. of anhydrous diethylamine at 30—40°. The reaction mixture was kept at the ordinary temperature until separation of the diethylamine hydrobromide was complete. The crude diethylamide was isolated in the usual manner as a yellow viscous gum which, since it could not be induced to crystallise, was converted directly into its hydrochloride by the action of hydrogen chloride in dry ether. The sticky solid *hydrochloride*, after being washed with ether and crystallised from ethyl acetate containing a little methyl alcohol, had m. p. 152—153° (Found: Cl, 8·3. $C_{18}H_{29}O_9N,HCl$ requires Cl, 8·1%). The yield was very small.

The *dimethylamide hydrochloride*, obtained similarly, had m. p. 159—160° (decomp.) (Found: Cl, 8·7. $C_{16}H_{25}O_9N,HCl$ requires Cl, 8·6%).

Fission of the Hydrochlorides of Tetra-acetylglucosidyldiaryl(alkyl)-amines.—(a) *In* 90% *alcohol at* 24·5°. Since examination of the residue after the change in rotation shows that fission has occurred, only summaries of the polarimetric results are recorded. The experimental details are the same as those recorded in previous parts of this series (*loc. cit.*).

Benzylmethylamide. Strength of solution, 1·196 g./100 c.c. Mean value of unimolecular *k* (6 observations), 6·5 hrs.$^{-1}$ (maximum, 6·8; minimum, 6·1). The residue obtained by evaporation of the solution in a vacuum at the ordinary temperature was triturated several times with dry ether to remove any tetra-acetyl glucose produced by hydrolysis. The insoluble residue without purification had m. p. 178—180° and contained Cl, 23·1 (Calc. for $C_7H_7\cdot NHMe,HCl$: Cl, 22·5%).

p-*Chlorobenzylmethylamide.* Strength of solution, 0·726 g./100 c.c. Mean value of *k* (6 observations), 5·8 hrs.$^{-1}$ (maximum, 6·0; minimum, 5·4).

p-*Cyanobenzylmethylamide.* Strength of solution, 0·650 g./100 c.c. Mean value of *k* (9 observations), 2·46 hrs.$^{-1}$ (maximum, 2·98; minimum, 2·20). The residue obtained as previously described contained Cl, 20·9 (Calc. for $CN\cdot C_7H_6\cdot NHMe,HCl$: Cl, 19·4%).

p-*Methylbenzylmethylamide.* Strength of solution, 0·714 g./100 c.c. Mean value of *k* (6 observations), 13·3 hrs.$^{-1}$ (maximum, 14·1; minimum, 12·6).

Piperidide (A, m. p. 126°). Strength of solution, 0·836 g./100 c.c. Mean value of *k*, 12·8 hrs.$^{-1}$ (maximum, 14·3; minimum, 11·3).

Interconversion of the two forms could not be accomplished.

Dimethylamide. Strength of solution, 0·773 g./100 c.c. Fission is extremely rapid. Mean value of *k* (3 observations), approximately 32 hrs.$^{-1}$.

(b) *In absolute alcohol at* 24·5°. *Dimethylamide.* A solution containing 0·362 g./100 c.c. (this being the limit of its solubility) changed in rotation from $[\alpha]_{5461} - 15\cdot1°$ to $[\alpha]_{5461} + 95°$ in 26 hours. The residue, worked up as previously described, contained Cl, 30·0 (Calc. for $C_{16}H_{25}O_9N,HCl$: Cl, 8·6. Calc. for $NHMe_2,HCl$: Cl, 43·5%), showing that fission was almost complete.

Benzylmethylamide. A solution containing 0·802 g./100 c.c.

changed from $[\alpha]_{5461}$ $-$ 4·4° to $[\alpha]_{5461}$ $+$ 29·4° in 24 hours (final value, 54°). The residue after removal of the ether-soluble portion contained Cl, 23·9 (Calc. for C_7H_7·NHMe,HCl: Cl, 22·5%).

Mutarotation of Tetra-acetylglucosidyldiaryl(alkyl)amides in Ethyl Acetate containing Hydrochloric Acid at 24·5°.—Benzylmethylamide. A solution containing 0·902 g. of the amide and 0·687 g. of 22·5 wt.% hydrochloric acid (2 mols.) in 100 c.c. of dry acid-free ethyl acetate changed in rotation from $[\alpha]_{5461}$ $-$ 13·3° to $+$ 27·1° in 128 hours, whence the mean value of k is 0·036 hr.$^{-1}$. The residue, freed from the ether-soluble portion, contained Cl, 17·8 (Calc. for C_7H_7·NHMe,HCl: Cl, 22·5%), hence a large amount of fission had occurred.

p-*Chlorobenzylmethylamide.* A solution containing 0·971 g. of the amide and 0·683 g. of 22·5 wt.% hydrochloric acid (2 mols.) in 100 c.c. of ethyl acetate changed from $[\alpha]_{5461}$ $-$ 10·8° to $+$ 21·6° in 120 hours, whence the mean value of k is 0·052 hr.$^{-1}$. Some *p*-chlorobenzylmethylamine hydrochloride, m. p. 198—200° (Found: ionisable Cl, 18·2. Calc.: ionisable Cl, 18·5%), separated in the polarimeter tube.

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