285. *Studies in the Amino-sugars. Part I. A Case of Acyl Migration.*

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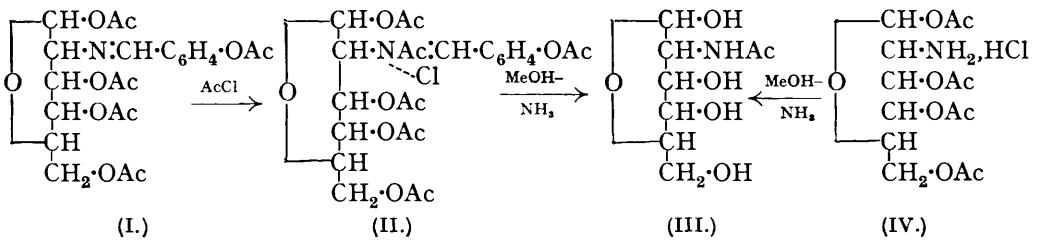
The author has attempted to apply to salicylidene glucosamine certain known additive reactions of Schiff's bases with a view to obtain products which could be broken down to *N*-acyl glucosamines and glucopeptides of glucosamine, thus providing a new synthesis of these important compounds. This aim was not realised, but the work brought to light a previously unknown migration of an acyl group from an oxygen to a nitrogen atom under the influence of methyl-alcoholic ammonia, whereby tetra-acetyl glucosamine hydrochloride is converted into *N*-acetyl glucosamine.

JAMES and JUDD (J., 1914, **105**, 1427), extending work by Hantzsch (*Ber.*, 1901, **34**, 836), found that anils react with acyl halides to yield salts which decompose readily with acid, alkali, or hot water, affording the original aldehyde, a hydrogen halide, and an aromatic amide corresponding to the original amine; *e.g.*,

$$NPh{:}CHPh + Ph{\cdot}COCl \longrightarrow Cl\ldots.\ NPh{:}CHPh \longrightarrow NHPh{\cdot}COPh + Ph{\cdot}CHO + HCl$$

Irvine and Earl (J., 1922, **121**, 2376) noted that glucosamine and salicylaldehyde readily form compounds of the Schiff's base type, and, using their salicylidene glucosamine, the author attempted unsuccessfully to add on various acyl chlorides and the hydrochlorides of various amino-acid chlorides. The failure to react was attributed to the insolubility of salicylidene glucosamine in non-hydroxylic solvents.

Following the method of Bergmann and Zervas (*Ber.*, 1931, **64**, 975) for anisylidene glucosamine, salicylidene glucosamine was therefore acetylated, producing 1 : 3 : 4 : 6-*tetra*-O-*acetyl* N-*acetylsalicylidene glucosamine* (I), which was treated in chloroform solution with acetyl chloride with a view to obtain the addition complex (II). A translucent thixotropic gel, which formed slowly, was filtered off, washed several times with chloroform, then with ether, and finally dried, giving a white amorphous powder. The resemblance of the product to a quaternary ammonium salt was easily demonstrable, and the readiness with which it gave off salicylaldehyde tended to confirm the expected constitution and also rendered recrystallisation impossible. The crude product gave inconclusive analyses, and was therefore treated at room temperature with methyl-alcoholic ammonia, affording the expected *N*-acetyl glucosamine (III) in good yield. Thus, the presence of an acetyl group, a chlorine atom, and a salicylaldehyde residue on the nitrogen atom of the hexose appeared to be confirmed.



(I.) (II.) (III.) (IV.)

Similar reactions were then carried out with propionyl, butyryl, and benzoyl chlorides, but instead of the anticipated *N*-acyl glucosamines, *N*-acetyl glucosamine was obtained as the final product in each case.

Reconsideration of the results led to the conclusion that the action of the acyl chlorides on (I) was not the formation of additive complexes of the type (II), but rather a hydrolysis of the aldehyde grouping of (I), resulting in the production of tetra-acetyl glucosamine hydrochloride (IV), the reaction probably depending ultimately on the presence of traces of water in the solvent. The absence of the additive reaction may possibly be due to steric hindrance. The ultimate production of *N*-acetyl glucosamine by treatment of (IV) with methyl-alcoholic ammonia must then involve elimination of three of the *O*-acetyl groups, accompanied by migration of the fourth to the nitrogen atom of the hexose.

Recrystallisation of the apparent complexes gave in each case a product which, in properties and analytical data, was identical with the tetra-acetyl glucosamine hydrochloride of Bergmann and Zervas (*loc. cit.*). The presence of salicylaldehyde in the crude product, despite the thorough washing with organic solvents, must be explained as due to an almost quantitative adsorption of the aldehyde on the gel-like precipitate of the hydrochloride during the process of hydrolysis.

Finally, tetra-acetyl glucosamine hydrochloride was prepared by dissolving (I) in acetone and adding to the boiling solution the theoretical quantity of concentrated hydrochloric acid. The product, which contained no salicylaldehyde, was recrystallised, treated with methyl-alcoholic ammonia and, as expected, gave *N*-acetyl glucosamine, thus confirming the postulated migration.

The existence of this migration obviously calls for caution in deducing the presence of *N*-acetyl glucosamine in any more complex substances from which this product has been isolated by a process involving the use of mild alkaline reagents at any stage.

Experimental.

Salicylidene glucosamine, m. p. 183—184°, was prepared according to Irvine and Earl's method (*loc. cit.*).

1 : 3 : 4 : 6-*Tetra*-O-*acetyl* N-*Acetylsalicylidene Glucosamine* (I).—15 G. of salicylidene glucosamine were dissolved with cooling and shaking in 100 c.c. of pyridine containing 45 c.c. of acetic anhydride and kept at room temperature for 24 hours, then poured into 250 c.c. of ice-cold water. The resultant white crystalline precipitate was filtered off after 2 hours, washed with ice-cold water, dried on a porous plate, and recrystallised from methyl alcohol, forming white needles, m. p. 132°, sparingly soluble in water, soluble in organic solvents and hot alcohols; yield 19·25 g., 81% (Found : C, 55·9; H, 6·0; N, 2·75; $CO{\cdot}CH_3$, 44·0. $C_{23}H_{27}O_{11}N$ requires C, 55·9; H, 5·5; N, 2·8; $CO{\cdot}CH_3$, 43·5%).

1 : 3 : 4 : 6-*Tetra*-O-*acetyl Glucosamine Hydrochloride* (IV).—(*a*) 10 G. of (I) were dissolved in 50 c.c. of acetone, heated to boiling, and 2 c.c. (1 mol.) of concentrated hydrochloric acid added. The product crystallised out on cooling as white needles, which were filtered off and recrystallised from 90% alcohol; yield 6·5 g., 84% (Found : C, 44·0; H, 5·95; N, 3·67; Cl, 9·25; $CO{\cdot}CH_3$, 45·0; equiv., 384. Calc. for $C_{14}H_{22}O_9NCl$: C, 43·8; H, 5·74; N, 3·66; Cl, 9·25; $CO{\cdot}CH_3$, 44·9%; equiv., 383·5). These decomposed at 230°; they were soluble in water and hot alcohols, but scarcely so in other organic solvents. The product so prepared was not contaminated with salicylaldehyde. (*b*) 10 G. of (I), dissolved in 20 c.c. of chloroform dried over potassium sulphate, were treated with 3 c.c. (2 mols.) of acetyl chloride and kept at room temperature. The translucent, gel-like product was filtered off after 2 hours, washed three times with chloroform, then with ether, and dried at room temperature. A further yield was obtained on allowing the mother-liquor to stand for 2 days; total yield 4·8 g., 57%. The crude product so obtained was a white amorphous powder which readily gave off salicylaldehyde even on keeping at room temperature. The positive results of tests for the presence of ionic halogen (*e.g.*, with silver nitrate) confirmed its saline structure. Recrystallisation from methyl alcohol removed all traces of salicylaldehyde, and gave a product identical with that prepared by method (*a*). Treatment of (I) with propionyl, butyryl, or benzoyl chlorides gave a similar result.

N-Acetyl Glucosamine (III).—6·3 G. of (IV) were dissolved in 50 c.c. of absolute methyl alcohol, saturated at 0° with dry ammonia, with cooling and shaking, and kept at room temperature for 3 hours. The ammonia and methyl alcohol were then removed by distillation under reduced pressure at room temperature, the crude product washed several times with cold alcohol

to remove acetamide, and recrystallised from hot 75% methyl alcohol plus half its volume of hot alcohol and a little ether; it formed white needles, m. p. 205°, mixed m. p. with a sample (m. p. 196°) prepared by the method of Zuckerkandl and Messiner-Klebermass (*Biochem. Z.*, 1931, **236**, 19) 200°; yield 2·3 g., 64%; $[\alpha]_D^{18°} = 64°$ (init.) $\longrightarrow$ 40·9° (in water) (Found: C, 43·45; H, 6·8; N, 6·3; $CO{\cdot}CH_3$, 19·7. Calc. for $C_8H_{15}O_6N$: C, 43·4; H, 6·8; N, 6·3; $CO{\cdot}CH_3$, 19·45%).

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