CCLXXXVI.—*Salicylidene Derivatives of
d-Glucosamine.*

By JAMES COLQUHOUN IRVINE and JOHN CAMPBELL EARL.

IN the preceding paper it is shown that salicylaldehyde reacts readily with the amino-group of triacetyl bromoglucosamine to give a characteristic salicylidene derivative. The highly reactive bromine atom present in the glucosamine chain takes no part in

The method of preparation consists in dissolving the glucosamine salt in water, liberating the free base by the addition of alkali, and then agitating the solution with salicylaldehyde. The salicylidene derivative generally separates directly in the crystalline condition. The properties of five typical examples may now be summarised, as their study has opened out some interesting theoretical considerations.

	Colour.	M. p.	$[\alpha]_D$ in methyl alcohol.	Yield per cent.
A. 2-Salicylidene glucosamine	Canary-yellow	183.5°	+11.0°	99
B. 2-Salicylidene-1-methyl glucosamine	Deep yellow	120	+2.2	26
C. 2-Salicylidene-3:5:6-tri- acetyl-1-methyl glucosamine	Pale yellow	151	+75.7	80
D. 2-Salicylidene-3:5:6-tri- acetyl-1-ethyl glucosamine	Pale yellow	135	+40.7	88
E. 1-Bromo-2-salicylidene- 3:5:6-triacetyl glucosamine	Canary-yellow	118	+241.9	65—70

It is significant that with one exception the formation of these salicylidene compounds proceeded with unusual smoothness. The exception is presented by methylglucosamine, which reacted with salicylaldehyde only with difficulty, giving a 26 per cent. yield of the product. This comparative failure to participate in the general reaction cannot be due to the presence of the methyl group in view of the results obtained with the acetylated glucosides, nor can it be attributable to the absence of acetyl groups, as free glucosamine reacted with extreme ease. The abnormal behaviour of methylglucosamine is thus in agreement with the cyclic formula previously suggested for this compound.

Now, the composition of triacetyl bromoglucosamine, which is the starting point in synthetical work in this series, does not admit of a formula of the above type and the compound must

therefore possess the normal structure characteristic of reducing sugars :

It follows that the corresponding salicylidene derivative in which the reactive bromine atom is retained must also be an open chain structure :

When this compound reacts with methyl alcohol to give a "methylglucoside" there seems no reason why profound structural alteration should accompany the change, and the compound formed may be termed 2-salicylidene-3:5:6-triacetyl-1-methyl glucosamine,

The reactions sketched above have been carried out, and the final product proved to be identical with that obtained when salicylaldehyde was condensed with triacetyl methylglucosamine. In other words, no isomerism is involved if the order of introducing the methyl group and the salicylidene residue is varied. The argument leads to the conclusion that triacetyl methylglucosamine is not constituted on the betaine model, but that a change to this type occurs when the acetyl groups are eliminated. It is, of course, possible that triacetyl methylglucosamine may exist in both forms, and in the experimental part a levorotatory isomeride of this compound is described. This new variety is being further investigated, but the combined results submitted evidently afford strong support to the view formerly expressed that in methylglucosamine the alkyl group is directly attached to the nitrogen atom.

EXPERIMENTAL.

Salicylidene Glucosamine.

Ten grams of glucosamine hydrochloride (1 mol.) and 6.3 grams of sodium bicarbonate ($1\frac{1}{4}$ mols.) were dissolved in 100 c.c. of water, and 6.3 c.c. of salicylaldehyde (1 mol.) added. The mixture was stirred vigorously at the temperature of the room, and in thirty minutes the separation of crystals commenced. Stirring was continued for three and a half hours, when the product was filtered, washed with cold water, and dried in a vacuum. The yield was 13 grams (99 per cent.). After recrystallisation from

methyl alcohol, the compound melted sharply at 183.5° (Found: C = 54.92; H = 6.18. $C_{13}H_{17}O_6N$ requires C = 55.09; H = 6.05 per cent.).

Salicylidene glucosamine crystallises in bright yellow needles, insoluble in chloroform, but readily dissolved by hot methyl or ethyl alcohol. The compound was easily hydrolysed by dilute acids, giving salicylaldehyde and the corresponding salt of glucosamine.

2-Salicylidene-1-methyl Glucosamine (Salicylidene Methyl-glucosamine).

7.5 Grams of recrystallised methylglucosamine hydrochloride were dissolved in 100 c.c. of water containing 3.75 grams of sodium bicarbonate and 3.2 c.c. of salicylaldehyde. The liquid, which was stirred for two hours, soon acquired a yellow colour and deposited a clear syrup, which adhered to the sides of the vessel. Excess of chloroform was then added and the mixture was shaken repeatedly with this solvent, and after drying the extract over magnesium sulphate, it was evaporated to a small bulk. On the addition of light petroleum, the product separated in a semi-crystalline condition. Purification was effected by again dissolving in chloroform and precipitating in the manner described above, salicylidene methylglucosamine being thus obtained in bright yellow needles melting at 120° . The yield from the experiment just described was 1.7 grams (26 per cent.), and this was not improved in subsequent preparations [Found: C = 56.33; H = 6.41; OMe = 9.63. $C_{13}H_{16}O_5N(OMe)$ requires C = 56.56; H = 6.39; OMe = 10.47 per cent.]. Salicylidene methylglucosamine is readily hydrolysed by acids to regenerate methylglucosamine. On the other hand, the action of nitrous acid involves the removal of the salicylidene residue followed by the elimination of the amino- and glucosidic groups.

2-Salicylidene-3:5:6-triacetyl-1-methyl Glucosamine (Salicylidene Triacetyl Methylglucosamine).

Two distinct methods were employed in the preparation of this compound and their significance is referred to in the introduction.

Method I.—A solution of 5.3 grams of 1-bromo-2-salicylidene-3:5:6-triacetyl glucosamine in 30 c.c. of methyl alcohol was mixed with 3.2 grams of morphine, dissolved in 60 c.c. of the same solvent. When the mixture was kept at the temperature of the room for seven days, morphine hydrobromide gradually separated. The filtrate, on evaporation under diminished pressure, gave a solid residue, which was recrystallised from alcohol. Yield 50 per cent.

Method II.—8.2 Grams of recrystallised triacetyl bromoglucosamine hydrobromide were dissolved in 100 c.c. of methyl alcohol containing 1.65 c.c. of pyridine. The solution was set aside for twenty hours, filtered, and concentrated to a small bulk at 25°/90 mm. Thereafter a solution of 3.5 grams of sodium bicarbonate in 40 c.c. of water was added together with 1.95 c.c. of salicylaldehyde. Vigorous stirring occasioned the separation of the crystalline product, which, after thirty minutes, was filtered and washed with cold water. One recrystallisation from alcohol gave a pure product melting at 151—152°. Yield 80 per cent. (Found: C = 56.93; H = 6.25; OMe = 8.2. $C_{20}H_{25}O_9N$ requires C = 56.71; H = 5.95; OMe = 7.3 per cent.). The salicylidene derivative crystallises in pale yellow, prismatic needles readily soluble in hot alcohol; $[\alpha]_D$ in methyl alcohol + 75.7° for $c = 1$. The three acetyl groups in the compound are remarkably stable, but were quantitatively removed by distillation with 15 per cent. sulphuric acid. After four hours' treatment with absolute alcohol saturated with ammonia at 0°, no acetamide was formed, and 70 per cent. of the original material was recovered unaltered (Fischer, *Ber.*, 1914, **47**, 218).

Action of Nitrous Acid.—When salicylidene triacetyl methylglucosamine was suspended in water and an aqueous solution of nitrous acid (prepared from silver nitrite) gradually added with vigorous stirring, no visible reaction ensued until the temperature was raised to 50°. The solid then passed into solution with copious evolution of nitrogen and liberation of salicylaldehyde. On neutralising the solution with barium carbonate, a quantity of salicylidene triacetyl methylglucosamine was regenerated and was precipitated in the crystalline state. The filtrate was evaporated to dryness under diminished pressure and extracted with boiling alcohol. This extract contained a glucosidic syrup, which was deacetylated by boiling with acidified methyl alcohol. After neutralisation with silver carbonate and removal of the solvent, a non-crystalline syrup remained which behaved as a glucoside towards Fehling's solution, but could not be identified either as methylglucoside or methylmannoside.

2-Salicylidene-3 : 5 : 6-triacetyl-1-ethyl Glucosamine (Salicylidene Triacetyl Ethylglucosamine).

Starting from triacetyl ethylglucosamine, the usual method of preparation was employed and gave an 88 per cent. yield of the above product [Found: C = 57.51; H = 6.39; OEt = 10.14. $C_{20}H_{24}O_8N(OEt)$ requires C = 57.63; H = 6.18; OEt = 10.29 per cent.]. In every respect the compound resembled the corre-

sponding methyl derivative, m. p. 131° , $[\alpha]_D$ in methyl alcohol $+ 40.7^{\circ}$ for $c = 1$.

3 : 5 : 6-Triacetyl-1-methyl Glucosamine (Triacetyl Methylglucosamine).

For reasons given in the introduction, the preparation of this compound from triacetyl bromoglucosamine was repeated.

(a) *Using pyridine*: The method adopted was identical with that described by Irvine, McNicoll, and Hynd (*loc. cit.*), and the properties previously assigned to the product were confirmed. The specific rotation in methyl alcohol was, however, slightly higher ($+ 23.3^{\circ}$ in place of $+ 20^{\circ}$).

(b) *Using morphine*: This preparation was conducted according to the variation recommended by Irvine and Hynd (T., 1912, **101**, 1137) and the crude product was crystallised repeatedly by solution in methyl alcohol and the addition of ether. The finely divided solid was then extracted with methyl alcohol in the cold, the filtrate being concentrated and precipitated with ether. Repetition of these processes gave a small, crystalline crop which decomposed at $201-202^{\circ}$ and showed $[\alpha]_D$ in methyl alcohol $- 14.6^{\circ}$ for $c = 1.8656$ [Found: C = 39.00; H = 5.79; OMe = 8.0. $C_{12}H_{18}O_7N(OMe).HBr$ requires C = 38.99; H = 5.55; OMe = 7.75 per cent.]. No morphine aminoglucoside was present, and the compound is thus a new stereoisomeric form of triacetyl methylglucosamine hydrobromide.

CHEMICAL RESEARCH LABORATORY,

UNITED COLLEGE OF ST. SALVATOR AND ST. LEONARD,

UNIVERSITY OF ST. ANDREWS. [Received, September 19th, 1922.]