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Fort Detrick
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The synthesis of new glycosides.

by E. Fischer.

Berichte d. D. Chem. Ges. 47: 1377-1393 (1914).

The reciprocal effect between aceto-halogen-glucose and silver compounds heretofore has been studied on a very small scale only. W. Koenigs and E. Knorr (B. 34, 957, 1901) have shown that aceto-bromo-glucose, treated with silver acetate in glacial acetic acid solution, yields pentaacetyl-glucose. On the other hand, they tried unsuccessfully to produce aceto-nitro-glucose, discovered by Colley (C. r. 76, 436, 1873), by reacting aceto-bromo-glucose with silver nitrate in aqueous-methyl alcoholic solution. Later H. Skraup and R. Kremann (M. 22, 1043, 1901) produced an aceto-nitro-glucose from aceto-chloro-glucose with silver nitrate and sodium in ethereal solution, which is isomeric with Colley's substance and changes into the latter upon recrystallization from alcohol. However, Koenigs and Knorr used methyl alcohol and silver carbonate in the conversion of aceto-bromo-glucose to tetraacetyl-β-methylglycoside. But here the silver carbonate has the primary purpose of binding hydrogen bromide; for it may be replaced by barium carbonate, as already noted by Koenigs and Knorr, and the formation of β-methyl-glycoside also takes place when a solution of aceto-bromo-glucose is allowed to stand for a longer period in absolute methyl alcohol.

Recently Helferich and I (B. 34, 957, 1901) pointed out that the silver salts of the purines may be reacted with aceto-bromo-glucose in anhydrous solvents, resulting in a useful method for the synthesis of purine-glycosides. The hope of producing other sugar derivatives in this manner has been fulfilled, as shown by the following examples.

1. Aceto-bromo-glucose and dry succinimide silver quickly react in a xylene solution on the water bath, and tetraacetyl-succinimide-glycoside is formed in good yield. Treatment with methyl alcoholic ammonia easily removes the acetyl groups, but ammonia is simultaneously deposited on the succinimide group, and the product $C_4H_7O_2N_2.C_6H_{11}O_5$ is formed, which I consider to be the glycoside of succinamide. It is difficult to choose between the two formulas

$HO.CH_2.CH(OH).CH.CH(OH).CH(OH).CH.NH.CO.CH_2.CH_2.CO.NH_2$ (with a bridge O) and

$HO.CH_2CH(OH).CH(OH).CH(OH).CH(OH).CH{:}N.CO.CH_2.CH_2.CO.NH_2$. I deem the first to be more probable.

I believe the same method will make possible the production of the corresponding derivatives of phthalimide and similar substances.

2. Aceto-bromo-glucose and thiocyanate silver yield, under the same conditions, a thiocyanate compound that may be designated as aceto-thiocyan[illegible]-glucose after its manner of development and which may be described by the

formula $C_6H_7O_5(C_2H_3O)_4.NCS$. Upon boiling, one molecule thereof is added, and the product, in all probability, is a derivative of thiourethane, in which one hydrogen of the amide is replaced by the residue of acetylated sugar: $C_6H_7O_5(C_2H_3O)_4.NH.CS.OC_2H_5$.

When the thiocyanate substance is saponified with methyl alcoholic ammonia, not only the cleavage of all acetyl groups occurs, but also the deposit of one molecule ammonia on the thiocyanate group, and the product has the composition of a thiourea of the glucose. As it is easily desulfurized by mercuric oxide in aqueous solution, the assumption is justified that the glucose residue is situated on the nitrogen and that, therefore, the substance may be designated with the formula

$$C_6H_{11}O_5.NH.CS.NH_2 \qquad \text{or}$$

$$C_6H_{11}O_5.NH.C(SH):NH.$$

3. Aceto-bromo-glucose and silver cyanate also react in xylene solution on the water bath, by the exchange of bromine and the radical of cyanic acid. Two products are formed thereby, which may be quite easily separated owing to their different solubility. One is crystalline and has the composition $C_6H_7O_5.(C_2H_3O)_4.NCO$. It combines with 1 mole of alcohol to a crystalline product, considered to be the urethane of tetraacetyl-glucose. Moreover, it easily dissolves in strong, aqueous ammonia, and upon storage of this solution for several hours, a compound of glucose with urea is formed by the separation of the 4 acetyl groups and addition of 1 mole of ammonia:

$$C_6H_{11}O_5.N_2H_3CO.$$

This compound has proved to be identical with the glucose-urea (carbamide du glucose) which N. Schoorl (R. 22, 31, 1903) produced directly from dextrose and urea, and which was extensively investigated by him. Since in this urea the glucose residue is most probably attached to nitrogen, the same should be assumed of the cyanate discussed above which, accordingly, should be considered as an isocyanate compound and is designated as such.

In addition to the crystalline isocyanate, an amorphous product is obtained which analysis shows to have approximately the same composition. Upon treatment with ammonia, it also yields an amorphous substance which again has nearly the constitution of glucose-urea. We are therefore dealing here with two products whose physical nature does not guarantee their uniformity, and which perhaps only represent mixtures of the crystalline matter mentioned above, with one isomeric substance.

Attempts to obtain glycosides of the uracils have met with far greater difficulties. As reported earlier (B. 47, 216, 1914), the silver salt of 4-methyl-uracil reacts easily with aceto-bromo-glucose in hot xylene solution, but the product is amorphous and was easily separated with reformation of methyl-uracil. Recently I have had similar experiences with uracil and cytosine. Here, too, products are formed by the effect of aceto-bromo-glucose on the silver salts, which apparently are compounds of tetraacetyl-glucose. Unfortunately their crystallization has not yet succeeded, nor have

we been able to separate the acetyl groups, as a thorough decomposition is too easily induced, accompanied by reformation of uracils.

Results were somewhat more favorable in connection with 2-thiouracil and 2-ethyl-thiouracil. The first yielded a crystalline derivative, containing twice the residue of tetraacetyl-glucose, the formation of which from the di-silver salt is not surprising. I designate the substance as 2-thiouracil-di-(tetra-acetyl-glycoside). 2-ethyl-thiouracil also yielded a crystalline derivative which, however, contains only once the residue of acetyl-glucose.

Both acetyl substances may be saponified by liquid ammonia at normal temperature, but the substances forming thereby have such inconvenient physical properties that it has not been possible so far to subject them to complete purification.

Tetraacetyl-succinimide-d-glycoside,
$C_6H_7O_5(C_2H_3O)_4.N.CO.CH_2.CH_2.CO$

26 g succinimide silver, dehydrated at 100°C and 10 mm, are heated with a solution of 50 g aceto-bromo-glucose (instead of the calculated 52 g) in 300 ccm dry xylene on a vigorously boiling water bath, accompanied by frequent shaking. The white silver salt rapidly turns into yellow bromine silver, and about 5 minutes later the reaction product fills the liquid in the form of a mash. For this reason 300 ccm dry chloroform is added about 15 minutes later, the solution is heated on the water bath for a short period and drawn off from the silver salts while still warm. Upon pouring into 5 l ligroin, a colorless, amorphous precipitate settles from the filtrate, soon becoming hard and powdery. Yield 46.8 g or 86.4% of the theory. By twofold recrystallization from 350 ccm absolute alcohol, the compound is rendered pure. The yield is thereby reduced to 31 g, however, if the mother liquor is not recovered.

Recrystallization was repeated twice for analysis. The substance, dried in the vacuum exsiccator, hardly lost any weight at 78°C and 11 mm over phosphoric anhydride.

0.1[illegible]9 g substance: 0.3545 g CO_2, 0.0910 g H_2O. — 0.2591 g substance: 7.15 ccm N (over 33% KOH): (15°, 762 mm).

$C_{18}H_{22}O_{11}N$ (429.19) Calculated: C 50.33, H 5.40, N 3.26.
Found: C 50.38, H 5.31, N 3.25.

Optical determination was accomplished in acetylene tetrachloride.

0.2999 g substance. Total weight of solution 4.8608 g, $d_4^{18} = 1.5686$, rotation in the 1 dm tube at 22° for sodium light 1.24° to the right.

Therefore, $[\alpha]_D^{18} = + 12.81°$.

0.3045 g substance (different production: Recrystallized four times from absolute alcohol and three times from a mixture of acetic ether and ligroin). Total weight of the solution 5.6907 g, d_4^{18} = 1.5711, rotation in the 1 dm tube at 22° for sodium light 1.07° to the right.

Therefore, $[\alpha]_D^{18}$ = + 12.73°.

No change in rotation occurred after storage of the solution for 24 hours.

Tetraacetyl-succinimide-glycoside sinters in the capillary tube starting at about 195°C and melts at 203-204° (corrected) to a colorless liquid. From alcohol it emanates in microscopic, long, entangled, frequently flattened needles, and from hot water in the form of concentrically fused, triangular platelets. It is poorly soluble in cold water and alcohol, much better in heated substances. It is quite difficult to dissolve in ether, much easier in benzene and very easy in chloroform, acetic ester and acetone. It does not reduce Fehling's solution and is rather easily hydrolized by hot, diluted mineral acids.

Succinamide-d-glycoside,
$NH_2.CO.CH_2.CH_2.CO.NH.C_6H_{11}O_5$.

10 g tetraacetyl-succinimide-glycoside were dissolved in 200 ccm of warm, dry methyl alcohol; the solution is saturated with gaseous ammonia under ice-cooling. The initial precipitate re-dissolved thereby. After storage in the refrigerator for 15 hours, the solution was liberated from the major portion of ammonia at 30° by vigorous evacuation. Soon copious amounts of a crystalline, white mass separated out, which was drawn off after storage on ice for 1 hour, then washed with a little methyl alcohol (5.7 g). It was twice absorbed with a trace of cold water (17 ccm); the solution was mixed with 250 ccm alcohol. Trituration was followed by instantaneous crystallization of microscopic, thin prisms, frequently in stellar formations. Yield 4.6 g or 63% of the theory in the form of an analytically pure substance, containing crystal water. The air-dry substance contained 2 moles water, removable within a short time under 0.3 mm pressure at 20°C.

0.1841 g substance (air-dry): 0.0211 g weight loss.— 0.2233 g substance (air-dry): 0.0365 g weight loss.— 0.2714 g substance (air-dry): 0.0308 g weight loss.

$C_{10}H_{18}O_7N_2 + 2\ H_2O$ (314.19). Calculated: H_2O 11.47
Found: H_2O 11.46, 11.33, 11.28, 11.35.

0.1630 g substance (anhydrous): 0.2570 g CO_2, 0.0942 g H_2O.— 0.1980 g substance (anhydrous): 16.5 ccm N (over 33% KOH) (16°, 766 mm).

$C_{10}H_{18}O_7N_2$ (278.16). Calculated: C 43.14, H 6.52, N 10.07.
Found: C 43.00, H 6.47, N 9.82.

0.2422 g anhydrous substance. Total weight of the aqueous solution 2.8649 g, d_4^{19} = 1.0262, rotation in the 1 dm tube at 19° for sodium light

1.51° to the left.

Therefore, $[\alpha]_D^{17} = -17.40°$.

0.2250 g anhydrous substance (different production): Total weight of the solution 2.9151 g, $d_4^{18} = 1.0232$, rotation in the 1 dm tube at 18° for sodium light 1.37° to the left.

Therefore, $[\alpha]_D^{18} = -17.35°$.

The rotation did not change after 20 hours.

Aqueous glycoside melts in the capillary tube at about 88-90°C to a colorless liquid, which returns to the solid state at the same temperature due to loss of water, and now has a considerably higher melting point. The anhydrous substance melts upon gradual heating at about 192°C (corrected), turns brown after a short time at this temperature, and decomposes with formation of gas. If the same anhydrous preparation is dipped into a previously heated bath of about 153°C, it melts and immediately becomes crystalline, then melts at 187-192°C (corrected). (Decomposition as above). An anydrous substance of different production did not fuse voluntarily with the higher melting mass. It sintered at 149-150°C and melted at 151.5-153° (corrected) to a viscous, colorless syrup. When the latter was inoculated with a crystal particle at the melting point, flat, oblong crystals formed a few seconds later in the form of rosettes; another fusion took place between 187 and 192° (corrected). The reason for these irregularities is still unknown.

The glycoside precipitates from aqueous-alcoholic or aqueous-acetonic solution in the form of flat, long crystals, cut off at an angle. The substance, containing crystal water, very easily dissolves in cold water, rather easily in warm methyl alcohol, less easily in ethyl alcohol, very poorly in acetone, and not at all in warm ether. It reduces Fehling's solution only after lengthy boiling, and then only gradually. It is rapidly hydrolysed by hot, diluted acids.

Aceto-gluco-thiocyanate,
$C_6H_7O_5(C_2H_3O)_4.NCS.$

20 g silver thiocyanate, 50 g aceto-bromo-glucose (1 mole) and 340 ccm dry xylene are heated for 20 minutes on a vigorously boiling water bath, accompanied by frequent shaking, causing the silver salt to turn into an egg-yellow mass. 10 g silver thiocyanate is again added, the addition is repeated after 20 minutes, the substance is heated for a like period, then drawn off from the silver salts. Upon gradual addition of 1½ l ligroin, the solution yields a weakly colored, crystalline precipitate which is allowed to stand on ice, then drawn off and washed with ligroin. Yield 39 g or 82.4% of the theory. For purposes of analysis, rapid recrystallization was effected from 200 ccm of warm alcohol, removal after thorough cooling, then washing first with cold alcohol, then with ligroin.

Recrystallization from alcohol was repeated as rapidly as possible for analytical purposes; the yield was dried at 56°C and 0.2 mm over phosphoric

anhydride.

0.1834 g substance: 0.3114 g CO_2, 0.0851 g H_2O.— 0.1676 g substance: 4.9 ccm N (over 33% KOH) (18°, 765 mm). — 0.1825 g substance: 0.1056 g $BaSO_4$.

$C_{15}H_{19}O_9NS$ (389.23). Calculated: C 46.25, H 4.92, N 3.59, S 8.24.
Found: C 46.31, H 5.19, N 3.41, S 7.95.

Optical analysis, utilizing solutions in acetylene-tetrachloride, revealed quite variable values, according to the mode of crystallization. Two samples, rapidly crystallized from alcohol, showed the following:

$[\alpha]_D^{17} = +5.66°$ and $+6.02°$ (in acetylene-tetrachloride).

The rotation decreased when these preparations were precipitated from a chloroform solution with ligroin. When the crude product was repeatedly separated from chloroform with ligroin, the rotation was negative and amounted (depending on the number of crystallizations) to $= -3.4°$ to $-8.5°$. It is doubtful that the latter represents the final value. The melting point of preparations crystallized from alcohol usually was found between 111.5 and 113°C (corrected), reaching a maximum of 114° (corrected). In the case of the levorotatory preparation, the melting point sank to about 100°C. According to these observations, either the original product is a mixture of isomers, or isomerism occurs in the process of dissolution and recrystallization. The most appropriate conclusion seems to be that we are dealing here with the two stereoisomeric derivatives of α and β -glucose. A proof cannot be offered at this time. In the conversions to thiourethane and thiourea to be discussed later, only those preparations were used which had been crystallized from alcohol.

Aceto-gluco-thiocyanate sometimes forms tetragonal, thin plates, frequently grouped concentrically, at other times fused forms without definite characteristics. It dissolves readily in acetic ether, chloroform and acetone, quite easily in benzene, rather well in cold alcohol and ether. It is poorly soluble in cold water, more easily upon heating, where it melts before dissolving. It dissolves in considerable amounts in hot ligroin and is almost insoluble in cold ligroin.

The aqueous or alcoholic solution of tetraacetyl-gluco-thiocyanate does not turn red with ferric chloride. It does not change cold Fehling's solution; upon heating, discoloration and formation of a black precipitate (of copper sulfide) take place. It melts upon heating with diluted alkali and goes into solution rather rapidly with a yellow hue. If hydrochloride is added at this time, ferric chloride evokes only a weak red tint.

Glucose-thiourea,
$C_6H_{11}O_5.N_2H_3CS$.

20 g tetraacetyl-gluco-thiocyanate are covered with 400 ccm of dry methyl alcohol which has been saturated at 0°C with dry ammonia gas, resulting in a clear, colorless solution. It is allowed to stand for 3 hours at 0°C and is then evaporated at 20°C under reduced pressure, yielding a crystalline

residue. In order to remove all ammonia, it is covered with 50 ccm methyl alcohol, again evaporated with 100 ccm absolute alcohol, thoroughly shaken, and the colorless, hard, crystalline mass is then drawn off. Yield 10.4 g or 85% of the theory. For complete purification, the product is dissolved in 40 ccm warm water and joined with 1 l alcohol, resulting in speedy crystallization, completed in 4-5 hours. The air-dry substance did not lose weight at 78° and 2 mm over phosphoric anhydride.

0.1581 g substance: 0.2061 g CO_2, 0.0847 g H_2O.— 0.1713 g substance: 17.3 ccm N (over 33% KOH) (18°, 751 mm).— 0.1570 g substance: 15.95 ccm N (over 33% KOH) (17.5°, 752 mm).— 0.1933 g substance: 0.1910 g $BaSO_4$.

$C_7H_{14}O_5N_2S$ (238.20). Calculated: C 35.26, H 5.92, N 11.76, S 13.46.
Found: C 35.55, H 6.00, N 11.57, 11.67, S 13.57.

0.2562 g substance (twice recrystallized): Total weight of the aqueous solution 2.8428 g, d_4^{20} = 1.0309, rotation in the 1 dm tube at 20° for sodium light 3.32° to the left.

Therefore, $[\alpha]_D^{20}$ = - 35.73° (for water).

0.2568 g substance (different production, once recrystallized): Total weight of the solution 2.9685 g, d_4^{20} = 1.0288, rotation in the 1 dm tube at 20° for sodium light 3.16° to the left.

Therefore, $[\alpha]_D^{20}$ = - 35.51°.

The glycoside turns brown in the capillary tube upon rapid heating to 210°C, and decomposes at 215-216° (corrected), accompanied by foaming. It precipitates from aqueous-alcoholic solution in the form of uniform, microscopic, rod-like or lancet-like crystals, from concentrated aqueous solution in the form of crude structures with many sides. It dissolves easily in cold water, very poorly in ethyl alcohol and only by traces in acetone. The aqueous solution of the glycoside shows a slow reaction in cold Fehling's solution, much faster upon moderate heating, where black copper sulfide separates. Ammoniacal silver solution is blackened instantaneously.

Perhaps the glycoside may also be obtained directly from glucose and thiourea, in aqueous solution in the presence of acids, since N Schoorl (R. 22, 63, 1903) had concluded from the change in the rotatory power that a reaction occurs under these conditions.

Desulfurization of glucose-thiourea.

As is well known, treatment with mercuric oxide in aqueous solution converts thiourea to cyanamide. Desulfurization of glucose-thiourea is accomplished under identical conditions. A product is obtained which, according to its properties, may represent a glucose-cyanamide. Unfortunately it is completely amorphous and difficult to purify, and analysis has revealed values which differ considerably from those of the formula.

2 g glucose-thiourea are dissolved in 30 ccm cold water, mixed with 0.1 g

ammonium thiocyanate. N. ;eshly precipitated, yellow mercuric oxide is added in small amounts at ~ °C. Upon trituration or shaking, the oxide soon turns dark and goes into solution. After about 2 g oxide had been used up within one hour, a sudden flocculation of mercuric sulfide took place; a small addition of oxide sufficed to desulfurize the liquid completely, easily proved by way of the spot test with ammoniacal silver solution. The precipitate was now separated by centrifugation, the poured-off liquid was purified with animal charcoal and the colorless filtrate was speedily evaporated at 20°C in the high vacuum, following addition of a trace of acetic acid. The residue represented a colorless, viscous, amorphous mass, easily soluble in water. It gradually turned hard and powdery upon trituration with alcohol. It was dried at 78°C in high vacuum for analysis.

0.1570 g substance: 0.2290 g CO_2, 0.0796 g H_2O.— 0.1570 g substance: 17.95 ccm N (over 33% KOH) (16°, 747 mm).

$C_7H_{12}O_5N_2$ (204.12). Calculated: C 41.15, H 5.93, N 13.73.
Found: C 39.78, H 5.67, N 13.13.

A strong deviation from the theory is apparent in the carbon content. In view of the amorphous nature and the difficult treatment of the preparation, I have tentatively abandoned further purification. The substance has a tendency to turn into a white compound which is very poorly soluble in water, resembling the polymerization of cyanamide. Upon heating with a little Fehling's solution, the latter is totally decolorized. If more copper solution is utilized, a dark brown liquid results. Hot ammoniacal silver solution is blackened by the substance.

Tetraacetyl-glucose-thiourethane,
$C_6H_7O_5(C_2H_3O)_4.NH.CS.OC_2H_5$.

If 15 g aceto-gluco-thiocyanate is boiled with reflux for 1 hour in 90 ccm alcohol, hard crystals separate from the weakly colored solution upon cooling. They were drawn off after standing on ice for some time, then washed with alcohol. Yield 14.7 g = 38% of the theory, of nearly pure substance.

It was twice recrystallized from alcohol and dried over phosphoric anhydride in the vacuum exsiccator for analysis. The air-dry substance lost hardly any weight in the process.

0.1947 g substance: 0.3352 g CO_2, 0.1019 g H_2O.— 0.2027 g substance: 5.3 ccm N (over 33% KOH) (16.5°, 758 mm).— 0.2082 g substance: 0.1108 g $BaSO_4$.

$C_{17}H_{25}O_{10}NS$ (435.28). Calculated: C 46.87, H 5.79, N 3.22, S 7.37.
Found: C 46.96, H 5.86, N 3.04, S 7.31.

Optical analysis was conducted with acetylene tetrachloride solution.

1. 0.3258 g substance: Total weight of the solution 5.8040 g, d_4^{21} = 1.5647, rotation in the 1 dm tube at 21° for sodium light 1.01° to the right.

Therefore, $[\alpha]_D^{21} = +11.50°$ (in acetylene tetrachloride).

2. 0.2486 g substance (different production): Total weight of the solution 4.2302 g, d_4^{21} = 1.5636, rotation in the 1 dm tube at 21° for sodium light 1.06° to the right.

Therefore, $[\alpha]_D^{21} = +11.53°$.

Mutarotation was not observed.

The substance melts exactly at 159-160°C (corrected) to a colorless liquid. It crystallizes in trapezoid, thin, at times crude forms with many sides. It is poorly soluble in hot water, easily in hot alcohol, cold acetone, acetic ester and especially chloroform, very poorly in cold ligroin. Lengthy boiling with Fehling's solution causes discoloration and the formation of a discolored precipitate. Neither mercuric oxide nor ammoniacal silver solution evokes the formation of metallic sulfide.

The acetyl substance is rather easily affected by cold baryta water as well as by alcoholic ammonia solution: A sulfurous compound is formed which dissolves easily in water, alcohol, acetone and acetic ester, and has the appearance of a colorless, totally amorphous, brittle mass. It has a bitter taste and a reducing effect.

Aceto-bromo-glucose and silver cyanate.

16.5 g dry aceto-bromo-glucose are dissolved in 80 ccm dry xylene and heated with 6 g (1 mole) finely ground, dry silver cyanate on the water bath, with frequent shaking, causing the sedimental substance to turn yellow. After about 3/4 hour, an additional 3 g of silver cyanate are admixed with further heating; this operation is repeated after ½ hour. If the solution is allowed to stand for 1 hour on the water bath, it usually becomes free of bromine. Finally the supernatant is drawn off, the silver salts are extracted with about 50 ccm acetic ester and the reunited solutions are poured in a large amount of ligroin. The main portion of the reaction product now separates in the form of white, amorphous flakes that soon fuse into resinous aggregates. Yield about 10 g.

For analysis, the product was dissolved in acetic ester and precipitated with ligroin.

0.1405 g substance (dried at 56°C and 10 mm over phosphoric anhydride): 0.2479 g CO_2, 0.0697 g H_2O.

$C_{15}H_{19}O_{10}N$ (373.16). Calculated: C 48.24, H 5.13.
Found: C 48.12, H 5.55.

The preparation, repeatedly precipitated, was dissolved in acetylene tetrachloride for optical analysis.

0.1879 g substance: Total weight of the solution 3.5329 g, d_4^{16} = 1.5649, rotation in the 1 dm tube at 16° and sodium light 1.32° to the right.

Therefore, $[\alpha]_D^{16} = + 15.86°$.

After sintering, the product turns into a colorless, foamy mass at 115-120°C, in an irregular manner. It reduces Fehling's solution upon boiling. It is very easily soluble in acetic ester, easily in benzene, warm alcohol, less easily in cold alcohol, rather poorly in ether, very poorly in cold water and ligroin. It melts and dissolves in considerable amounts upon heating with water. Cooling activates the precipitation of amorphous flakes.

The product is dissolved by shaking for two days with a six-fold quantity of 25% aqueous ammonia. Upon evaporation of the solution under low pressure, a light brown syrup is obtained which becomes solid after treatment with alcohol. The amorphous product was re-dissolved from hot alcohol and dried in the high vacuum over phosphoric anhydride for analysis.

0.1812 g substance (dried at 56° in the high vacuum over phosphoric anhydride): 0.2540 g CO_2, 0.1050 g H_2O.— 0.1716 g substance: 17.65 ccm N (16°, 743 mm).

$C_7H_{14}O_6N_2$ (222.13). Calculated: C 37.82, H 6.35, N 12.61.
Found: C 38.23, H 6.48, N 11.75.

The product was dissolved in water for optical analysis.

0.1541 g substance: Total weight of the solution 2.1419 g, d_4^{17} = 1.0236, rotation in the ½ dm tube at 17° and sodium light 1.30° to the left.

Therefore, $[\alpha]_D^{17} = - 35.30°$.

The substance is easily soluble in cold water, very poorly in cold alcohol, and melts with vigorous foaming at about 195°C, after turning brown and sintering. As already mentioned in the introduction, an evaluation of its homogeneity is not possible owing to its amorphous nature.

Tetraacetyl-glucose-isocyanate.

The mother liquor of the above amorphous acetyl substance, after standing for some time, yields needles and prisms by precipitation, usually fused in the form of stars. Yield 3 g.

They were dried over phosphoric anhydride at 57°C and 12 mm pressure. The product, dried in the exsiccator, lost very little weight.

0.1917 g substance: 0.3400 g CO_2, 0.0893 g H_2O.— 0.1471 g substance: 4.9 ccm N (over 33% KOH) (16°, 745 mm).

$C_{15}H_{19}O_{10}N$ (373.16). Calculated: C 48.24, H 5.13, N 3.75.
Found: C 48.37, H 5.21, N 3.82.

An additional 0.6 g of this crystalline product was obtained by evaporating the mother liquor under reduced pressure. The total yield, therefore, amounted to 3.6 g or 24% of the theory. Purification is accomplished by dissolving in a little warm acetic ester and mixing with ligroin until turbidity persists. Thin, macroscopic prisms crystallize upon cooling.

The product melts at 117-118°C (corrected) to a colorless liquid. It is very easily soluble in warm alcohol, benzene and acetic ester, less easily in ether and warm ligroin. It dissolves easily in aqueous ammonia. It reduces Fehling's solution rather slowly upon boiling.

Optical determination was carried out with repeatedly recrystallized preparations, dissolved in acetylene tetrachloride.

0.2203 g substance: Total weight of the solution 3.6933 g, d_4^{19} = 1.567, rotation in the 1 dm tube at 19° and sodium light 0.69° to the left.

Therefore, $[\alpha]_D^{19} = -7.38°$.

0.1848 g substance: Total weight of the solution 3.1442 g, d_4^{18} = 1.579, rotation in the 1 dm tube at 18° and sodium light 0.70° to the left.

Therefore, $[\alpha]_D^{18} = -7.54°$.

Upon boiling for 1 hour with an eight-fold amount of alcohol (in weight) on the reflux cooler, the isocyanate absorbes 1 mole of alcohol; upon evaporation of this solution under reduced pressure, a colorless syrup forms the initial residue. When dissolved in hot water, of which quite a lot is required, a colorless oil separates from it upon cooling, becoming crystalline after standing in the mother liquor for several days. This preparation shows the composition of a tetraacetyl-glucose-urethane, $C_{17}H_{25}O_{11}N$.

0.1923 g substance (dried in the vacuum exsiccator): 0.3411 g CO_2, 0.1040 g H_2O.— 0.1790 g substance: 4.9 ccm N (over 33% KOH)(16°, 747 mm).

$C_{17}H_{25}O_{11}N$ (419.21). Calculated: C 48.66, H 6.01, N 3.34.
Found: C 48.38, H 6.05, N 3.14.

However, the irregularity in the melting point and the observation to the effect that a small residue remains after solution in ether, show that the preparation was not quite pure yet. I shall therefore return to this subject later.

New production of glucose-urea.

2 g of crystalline tetraacetyl-glucose-isocyanate were dissolved in 12 ccm aqueous ammonia of 25%, stored at normal temperature for 4 hours, then evaporated at 50° and 12 mm pressure. The oily residue was dissolved in a little water and evaporated in the exsiccator. Crystallization set in after several hours, becoming complete after trituration with alcohol. Yield 0.9 g or 75% of the theory.

The preparation, precipitated from aqueous solution by alcohol, formed small prisms with pointed ends, at times in stellar fusion, melting with foam upon gradual heating to 207°C (corrected to 210°). Rapid heating caused the elevation of the melting point by 6-7°.

0.1579 g substance (dried over phosphoric anydride at 80° and 12 mm pressure): 0.2186 g CO_2, 0.0875 g H_2O.

$C_7H_{14}O_6N_2$ (222.13). Calculated: C 37.82, H 6.35.
Found: C 37.76, H 6.20.

Optical determination was executed in aqueous solution.

0.1406 g substance: Total weight of the solution 1.7878 g, d^{19} = 1.0267, rotation in the 1 dm tube at 19° and sodium light 1.89° to the left.

Therefore, $[\alpha]_D^{19} = -23.41°$.

All these observations agree sufficiently with the data given by Schoorl for glucose-urea, and since the same applies to the solubility and mode of crystallization, there should be no doubt about the identity of the two substances.

Effect of aceto-bromo-glucose
on cystosine silver.

The cystosine is best produced synthetically after Wheeler and Johnson (Am. 29, 492 ff, 1903; C 1903, I, 1310 f). For the preparation of the silver salt, the base is dissolved in a 100-fold amount of 10% aqueous ammonia by heating on the water bath, mixed with silver nitrate solution (calculated for 1 mole) and heated for some time on the vigorously boiling water bath. The escaping ammonia is matched by a like quantity of silver salt, settling in the form of colorless needles.

0.1261 g substance (dried at 130°C and 10 mm for 6 hours): 0.0624 g Ag.

$C_4H_4ON_3Ag$ (217.94). Calculated: Ag 49.50, found: Ag 49.48.

1.1 g of this rigorously dried silver salt was boiled for 20 minutes with a solution of 2 g of pure aceto-bromo-glucose in 20 ccm dry xylene, then filtered while still hot and poured in a large quantity of ligroin. A colorless, flakey precipitate, free of bromine, is obtained. Yield 1.8 g.

This product is very easily soluble in alcohol, acetic ester, chloroform, benzene, rather easily in ether and almost insoluble in ligroin. It causes fairly strong reduction of Fehling's solution upon boiling. Unfortunately attempts at crystallization have failed to date, although the conditions for synthetic experimentation have been varied extensively. Moreover, the substance is quite unstable. For instance, if it is joined with picric acid in cold, alcoholic solution, a crystallization of cystosine-picrate occurs after a long period of time. It follows that the substance very easily splits into its components.

2-thiouracil-di-(tetraacetyl-glycoside),
$C_4H_2ON_2S(C_6H_7O_5(C_2H_3O)_4)_2$.

The 2-thiouracil was produced according to Wheeler and Liddle's method (Am. 40, 547-558; C. 1909, I, 447). It was dissolved in a 100-fold quantity of hot water for the purpose of conversion to silver salt, then a quantity of silver nitrate, calculated for 2 molecules, was added with vigorous shaking in the form of a fairly concentrated, aqueous solution. The silver salt settled out in the form of a weakly yellow, amorphous, somewhat jellied precipitate, which was quite difficult to filter. It was carefully washed with water, alcohol and ether and finally dried for 6 hours at 138° and 10-15 mm.

0.3759 g substance: 0.2350 g Ag.

$C_4H_2N_2OSAg_2$ (341.87). Calculated: Ag 63.11, found: Ag 62.52.

10 g of the salt were boiled for 2 hours in the oil bath with a solution of 16 g aceto-bromo-glucose in 130 ccm dry xylene. The baked precipitate was frequently reduced to small pieces with the aid of a glass rod. A successful operation had now produced a solution free of bromine; it was filtered and poured in a lot of ligroin. A colorless, amorphous precipitate settled out at this time (20 g). Upon solution in acetone, mixture with alcohol and evaporation of the acetone, star-shaped aggregates of fine needles settled out. Yield 12 g.

The exsiccator-dried substance lost very little weight at 100°C and 1 mm pressure.

0.1488 g substance: 0.2660 g CO_2, 0.0687 g H_2O.— 0.1577 g substance: 4.70 ccm N (over 33% KOH) (18°, 750 mm).— 0.2092 g substance: 0.0569 g $BaSO_4$.

$C_{32}H_{40}O_{19}N_2S$ (788.41). Calculated: C 48.71, H 5.11, N 3.55, S 4.07.
Found: C 48.75, H 5.17, N 3.41, S 3.74.

Optical determination was made in acetylene-tetrachloride. Solution required moderate heating, but the compound remained clear after cooling.

$$[\alpha]_D^{19} = \frac{1.45^\circ \cdot 3.4355}{1.1.573 \cdot 0.2546} = +12.44^\circ$$

$$[\alpha]_D^{11.5} = + \frac{1.42.3.8437}{1.1.568.0.2766} = + 12.59°.$$

The substance melts at 230°C (corrected) to a light brown liquid, after taking a light shade a few degrees previously. It is very poorly soluble in all cold customary organic solvents, and almost insoluble in water. On the other hand, it dissolves quite readily in warm chloroform, acetone, benzene and acetylene-tetrachloride. It is noteworthy that the amorphous crude product is much more easily soluble than the crystalline substance. The latter is decomposed by warm alkalis or hot baryta water, with formation of thiouracil. It therefore decolorizes Fehling's solution. Upon shaking with liquid ammonia at a normal temperature, it dissolves and turns into an amorphous product, very easily soluble in water, requiring additional examination.

2-ethyl-thiouracil-(tetraacetyl-glycoside),
$C_6H_7ON_2S.C_6H_7O_5(C_2H_3O)_4$.

In order to convert 2-ethyl-thiouracil (Wheeler and Merriam, Am. 29, 484, 1903) into the silver salt, 3 g are dissolved in 30 ccm of hot water and a neutral ammoniacal solution of 3.3 g silver nitrate is added. Upon boiling the silver salt rapidly settles out in the form of colorless needles, which do not lose significant weight after drying in the vacuum exsiccator at 135°C under 10-15 mm pressure.

0.2430 g substance: 0.1001 g Ag.

$C_6H_7ON_2SAg$ (263.03). Calculated: Ag 41.01, found: Ag 41.19.

14 g of this silver salt is boiled for 10 minutes with a solution of 20 g aceto-bromo-glucose in 250 ccm dry xylene, then thoroughly shaken. The solution, free of bromine, is filtered and evaporated under reduced pressure. The residue solidifies in crystalline form after a few hours. It is dissolved in a 3-fold quantity of alcohol, and ligroin is admixed until turbidity appears. Upon thorough cooling, fine needles crystallize, often in the form of clusters, which are drawn off after standing for some time at 0°C. Yield 23 g.

For the purpose of analysis, the substance was twice more crystallized in the same manner and finally dried at 78°C and 10 mm over phosphoric anhydride.

0.1497 g substance: 0.2723 g CO_2, 0.0737 g H_2O.— 0.1917 g substance: 9.20 ccm N (over 33% KOH) (16°, 766 mm).— 0.1801 g substance: 0.0837 g $BaSO_4$.

$C_{20}H_{26}O_{10}N_2S$ (486.30). Calculated: C 49.35, H 5.39, N 5.76, S 6.59.
Found: C 49.61, H 5.51, N 5.65, S 6.38.

Optical determination was accomplished in acetylene-tetrachloride solution.

I. (3 times recrystallized) $[\alpha]_D^{16} = + \frac{0.32°.3.2716}{1.1.573.0.2040} = + 3.26°$.

II. (5 times recrystallized) $[\alpha]_D^{19} = \not - \frac{0.35^\circ . 3.7366}{1.1.565 . 0.2660} = \not - 3.14^\circ$.

The substance melts at 108°C (corrected); it is extremely difficult to dissolve in cold water, it melts in hot water and goes into solution in considerable quantities. It is soluble, especially upon heating, in the usual organic solvents, with the exception of ligroin. It is rather rapidly hydrolized by hot, diluted mineral acids. It reduces Fehling's solution slowly upon boiling. It is completely changed upon standing at a normal temperature for 15 hours with liquid ammonia. A mixture of acetamide and another water-soluble substance is obtained here, of which the latter might be the free glycoside. It is rather difficult to crystallize and has not been analysed heretofore for that reason.

In the experiments with glucose derivatives of succinimide, succinamide, hydrogen thiocyanate and thiourea, I have been aided by Dr. Max Bergmann, in those dealing with cyanate and glucose-urea by Dr. Max Rapaport, and in connection with the synthesis of the two thiouracil derivatives by Dr. Ernst Pfaehler. I am grateful for their industrious and skilful assistance.

The foregoing results again serve to point out the manifold ways in which aceto-halogen-glucose may be utilized in the production of glucose derivatives. In this respect the procedure is superior to other methods. For example, the synthesis of glycosides by means of catalysis with acids (discovered by me 20 years ago), yielding α as well as β forms, has been restricted to alcohols and oxyacids and has the disadvantage that the crystallization of the products becomes quite difficult in complicated cases.

Recently E. Bourquelot and M. Bridel (A. ch. (8) 29, 145, 1913) have accomplished the synthesis of alcoholic glycosides with the aid of the yeast enzyme (α-glycosidase) and emulsine (β-glycosidase), and have shown its practical feasibility in numerous examples. Although their system is simple and interesting from the biochemical point of view, the purely chemical methods surely are not rendered superfluous thereby. Contrary to the enzymic synthesis limited to the sugars of certain configurations, such as d-glucose, d-galactose, d-fructose, they apply to a large number of hexoses, pentoses, etc., as previously pointed out.

Syntheses with aceto-halogenated sugars are also applicable to phenols, thiophenols, purines and various other nitrogenous substances, and several unmistakable advantages are noted also in connection with alcohols. Acetylated glycosides, poorly soluble in water and, as a rule, easy to crystallize, form here as intermediary products. From these, the glycosides proper may usually be obtained in pure form by the separation of the acetyl groups with baryta or ammonia. For example, β-benzyl-d-glycoside (E. Fischer and B. Helferich, A. 383, 72, 1911. Cf. Bourquelot and Bridel, A. ch. (8) 28, 203, 1913) and β-glycol-d-glycoside (E. Fischer and H. Fischer, B. 43, 2528, 1910. Cf. Bourquelot and Bridel, C. r. 158, 898, 1914) were first obtained in crystalline form in this manner, and it seems to me that our preparations were purer than those later produced by biochemical methods by Bourquelot et al., at least as far as benzyl-glycoside is concerned.

Even complicated alcohols, as amylene-hydrate, menthol, borneol (E. Fischer and K. Raske, B. 42, 1465, 1909) or cyclohexanol, geraniol, cetyl alcohol, finally glycolic acid, its ester and amide (E. Fischer and B. Helferich, A. 383, 68, 1911) were thus converted to crystalline glycosides, and recently A. H. Salway (Soc. 103, 1022, 1913) has produced the glycosides of cholesterol and sitosterol in this manner.