140° (20 mm.). On redistillation the first fraction gave 10 g. of material of b. p. 70–75° (20 mm.). The crude semicarbazone of this fraction melted at 150–160°. After recrystallization it melted at 163–167° as did a mixture of it and the semicarbazone of 3-methyl-3,2-heptenone obtained by the dehydration of the ketol.

The sodium hydroxide extracts were combined and extracted with ether. The aqueous portion was acidified with dilute sulfuric acid and extracted with ether. The ether solution was dried, the ether removed, and the residue distilled. The acid boiled at 136–137° (20 mm.); neut. equiv., 145. The neutral equivalent of α-ethyl-α-hexenoic acid is 142.

The Direct Condensation of *n*-Butyraldehyde with Acetone.—This was carried out according to the directions of Eccott and Linstead.[3] The crude product was fractionated, yielding the following fractions: up to 90° (21 mm.), 62 g.; 90–130° (21 mm.), 17 g.; 130–180° (18 mm.), 43 g.; residue 30 g. The first fraction was carefully redistilled through a Podbielniak column, yielding 3 fractions.[10] The semicarbazones and 2,4-dinitrophenylhydrazones of each fraction were prepared and their melting points are given in Table I.

TABLE I

	B. p., °C. (19 mm.)	Wt., g.	M. p. (°C.) of crude semicarbazone	2,4-dinitrophenylhydrazone
1	-65	3	110–120	95–100
2	65–69	29	123–133	99–110
3	69–71	11	143–148	120–122

By repeated crystallization of the crude derivative in each case, we were able to isolate a semicarbazone melting at 152°, identical with that of α-ethyl-α-hexenal. Fraction 3 was apparently almost entirely α-ethyl-α-hexenal. In order to identify the other component of fractions 1 and 2, the crude 2,4-dinitrophenylhydrazones were dissolved in alcohol, and the solution cooled, when crystals of the 2,4-dinitrophenylhydrazone of α-ethyl-α-hexenal separated. The mother liquor was evaporated to dryness and the residue dissolved in warm gasoline. When the solution was cooled a further crop of the 2,4-dinitrophenylhydrazone of α-ethyl-α-hexenal was obtained. The mother liquor was evaporated to dryness and the residue recrystallized from alcohol. This substance melted at 125–126° but was not identical with the 2,4-dinitrophenylhydrazone of α-ethyl-α-hexenal, m. p. 124–125°, as a mixture of the two melted at 100–110°.

A sample of 3,2-heptenone was prepared by dehydrating the ketol with oxalic acid, according to the method of Eccott and Linstead, and converted into the 2,4-dinitrophenylhydrazone. This substance melted at 125–126° and was identical with that obtained above.

Anal. Calcd. for $C_{13}H_{16}O_4N_3$: N, 19.2. Found: N, 18.9, 19.0.

Summary

1. An unsuccessful attempt was made to prepare *cis* and *trans* forms of 3-methyl-3,2-heptenone. An unsuccessful attempt was also made to prepare the *cis* and *trans* forms of 3,2-heptenone as described by Eccott and Linstead.

2. The 2,4-dinitrophenylhydrazones of α-ethyl-α-hexenal, 3,2-heptenone, and 3-methyl-3,2-heptenone were prepared.

3. The *p*-toluidide of α-methyl-α-hexenoic acid was prepared.

SEATTLE, WASH. RECEIVED MAY 31, 1938

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[10] Podbielniak, *Ind. Eng. Chem., Anal. Ed.*, **3**, 179 (1931).

[CONTRIBUTIONS FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY]

Researches on Nitrogenous Glucosides. IV. Some New Attempts to Synthesize Pyrimidine Glucosides

BY TREAT B. JOHNSON AND WERNER BERGMANN

The authors desire to report in this paper new data resulting from some special experiments applied in their researches on nitrogenous glucosides, which do not find their proper place in other papers to be published on this subject. The first contribution of importance from this Laboratory was made in 1930 when Hilbert and Johnson[1] synthesized successfully 3-glucosidouracil by interaction of 2,6-dimethoxypyrimidine with tetraacetylbromoglucose. The resulting acetyl derivative gave the desired nucleoside on hydrolysis. Later Hilbert[2] applied a similar reaction using 2-methoxy-6-aminopyrimidine and tetraacetylbromoglucose in order to obtain the corresponding glucoside of cytosine, but without success. It is of interest to note here that E. Fischer also failed in his attempts to prepare glucosides of both uracil and cytosine by the action of tetraacetylbromoglucose on the silver salts of these two pyrimidines.[3] Recognizing the limitations of this method of approach to practical methods of synthesizing nitrogenous glucosides, we next turned our attention to the study of techniques based on the use of sugar isocyanates and corresponding ureas as starting points. The only

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[1] Hilbert and Johnson, THIS JOURNAL, **52**, 4489 (1930).

[2] Hilbert, *ibid.*, **56**, 190 (1934).

[3] E. Fischer, *Ber.*, **47**, 1377 (1914).

sugar isocyanate derivatives recorded in the literature previous to our work were tetraacetylglucose isocyanate $C_{14}H_{19}O_9NCO$ and the corresponding isothiocyanate $C_{14}H_{19}O_9NCS$ described by E. Fischer in 1914.[3] This work of Fischer has been repeated in this Laboratory by different workers and several attempts have been made to utilize such simple sugar constructions for the preparation of nitrogenous glucosides in the hydantoin and pyrimidine series. Haring and Johnson[4] prepared Fischer's glucose isothiocyanate and showed that it adds as expected to α-amino acids or their esters, giving hydantoic acid derivatives which can be condensed smoothly to hydantoins. They prepared the first known glucoside derivatives of 2-thiohydantoin and hydantoin. Johnson and Bergmann[5] reëxamined Fischer's work on the preparation of tetraacetylglucose isocyanate $C_{14}H_{19}O_9NCO$ and its urea derivative, but failed in their attempts to synthesize pyrimidine glucosides from these simple sugar combinations.

In the experimental part of this paper is recorded the history of some interesting derivatives which have resulted from other types of reactions applied by the authors for the synthesis of new nitrogenous glucoside derivatives.

Experimental Part

Extension of Fischer's Isocyanate Work to Other Sugars.—We have found that as a rule the isocyanates of sugars are difficult to obtain in a pure form.[5] In most cases examined only amorphous products have been obtained in our researches. That these amorphous products sometimes contain considerable amounts of the desired isocyanate derivative can be demonstrated easily by their conversion into the corresponding ureas by the action of strong ammonia solution. The yields, however, are generally too low for service in practical synthesis.

1-Arabinose-isocyanate ⟶ 1-Arabinose-urea.—Triacetobromoarabinose was refluxed in dry xylene with twice the theoretical amount of anhydrous silver cyanate for several hours. After filtration and dilution of the xylene with petroleum ether an oil separated which solidified to a resin-like substance and from which no crystalline material could be obtained. The crude reaction product finally was suspended in concentrated ammonia solution when it dissolved immediately. The acetyl groups of the glucoside were removed by this treatment, and by application of a method of purification described in our previous paper we succeeded in isolating a beautiful crystalline urea derivative of 1-arabinose melting at 192°. It showed an optical rotation of α^{25}_D +51.9° (0.1197 g. in 3.0686 g. of water gave d + 2.02°). This substance proved to be identical with 1-arabinose urea which has been described previously by Helferich.[6]

Xylose-isocyanate ⟶ sym-Dixylose-urea.—Triacetobromoxylose was refluxed as usual with silver cyanate in xylene for several hours. The amorphous reaction product which was obtained after filtration and addition of petroleum ether was treated with concentrated aqueous ammonia in the usual way. From the reaction mixture we separated a substance which crystallized in fine needles. It showed no sharp melting point, turning brown at 230° and charring at 250°. It gave an optical rotation of α^{25}_D −20.5° (0.112 g. in 3.07 g. water gave d − 748°). The substance was identified as *sym*-dixyloseurea previously described by Helferich.[6]

Anal. Calcd. for $C_{11}H_{20}O_9N_2$: C, 40.73; H, 6.22. Found: C, 40.91; H, 6.39.

Heptaacetyllactose-isothiocyanate, $C_{12}H_{14}O_3(OCOCH_3)_7$-NCS.—As a rule it has been the authors' experience that the isothiocyanate derivatives of sugars are easier to obtain in a pure crystalline condition than the corresponding isocyanates. Seven grams of heptaacetylbromolactose was refluxed with 5 g. of silver thiocyanate in xylene for ten minutes. After addition of petroleum ether to the filtered solution crystals of the isothiocyanate began to separate. After purification by crystallization from chloroform and petroleum ether the isothiocyanate was obtained in the form of large prismatic crystals. It melted at 169–170°.

Anal. Calcd. for $C_{27}H_{35}O_{17}NS$: C, 47.82; H, 5.20. Found: C, 47.89; H, 5.39.

Heptaacetyllactose-ethylthiourethan, $C_{29}H_{41}O_{18}NS$.—This was prepared by refluxing the above isothiocyanate derivative in absolute ethyl alcohol. It crystallizes from hot alcohol in the form of needles melting at 119°. Like many other thiourethans it contains water of crystallization.

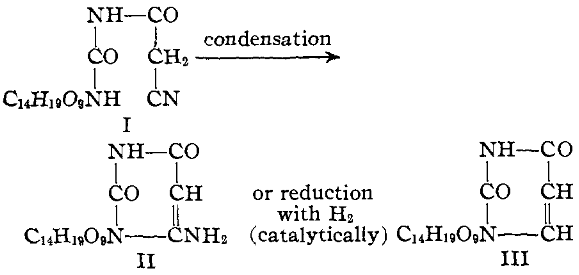
Anal. Calcd. for $C_{29}H_{41}O_{18}NS$: C, 46.94; H, 5.85. Found: C, 47.10; H, 5.81.

Heptaacetyllactosethioureido-ethyl acetate, $C_{31}H_{44}O_{19}N_2S$.—One one-hundredth mole of the above isothiocyanate and 0.015 mole of ethyl glycine hydrochloride were refluxed in chloroform, containing a few drops of pyridine, for two hours. The excess of solvent was then expelled *in vacuo*, water added to the residue and the condensation product extracted with ether. After drying the ether solution, petroleum ether was added, when crystals of the reaction product separated. It deposited in the form of octahedra melting at 100°.

Anal. Calcd. for $C_{31}H_{44}O_{19}N_2S$: C, 47.68; H, 5.68. Found: C, 47.61; H, 5.73.

Attempts to Prepare Pyrimidine Glucosides in the Barbituric Acid Series.—The following proposed synthesis of a glucosido-uracil was studied:

A. Tetraacetylglucose-urea + cyanacetic acid



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(4) Haring and Johnson, THIS JOURNAL, 55, 395 (1933).

(5) Johnson and Bergmann, *ibid.*, 54, 2360 (1932).

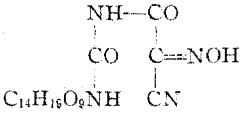
(6) Helferich, *Ber.*, 59, 69 (1926).

Four grams of tetraacetylglucose-urea, 1 g. of cyanoacetic acid and 2 cc. of acetic anhydride were heated at 100° for ten minutes. On adding water to the cooled solution a crystalline substance separated. After crystallizing several times from dilute alcohol it melted constant at 135°.

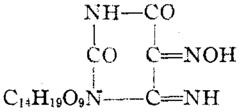
Anal. Calcd. for $C_{18}H_{23}O_{11}N_3$: C, 47.15; H, 5.27; N, 9.17. Found: C, 47.16; H, 5.24; N, 9.12.

Theoretically this substance could be either an acyclic or a cyclic compound (I or II). In order to determine its constitution molecular proportions of the compound and sodium nitrite were warmed in water for several minutes. The solution became yellow in color and on acidifying with acetic acid prismatic, plate-like crystals separated. After recrystallization from boiling water they melted at 179–180°. That we are dealing here with a nitroso derivative of the acyclic compound I as represented by formula IV is supported by the yellow color, and, furthermore, by the fact that cyanoacetic acid itself and sodium nitrite interact in a similar manner.

Anal. Calcd. for $C_{18}H_{22}O_{12}N_4$: C, 44.34; H, 4.75; N, 11.50. Found: C, 44.42; H, 4.74; N, 11.18.



IV



V

If the reaction product resulting from condensation with cyanoacetic acid is to be represented by the cyclic structure II, it should react with ammonia with removal of the acetyl groups and with formation of the stable cyclic glucoside. We found, however, that such treatment yielded smoothly glucose urea, leading to the conclusion that formula I and not II represents the correct constitution of the original condensation product.

Anal. Calcd. for glucose urea: C, 37.82; H, 6.35. For $C_{10}H_{15}O_7N_3$ (from II): C, 41.53; H, 5.22. Found: C, 37.93; H, 6.40; N, 12.36.

Under no conditions did we succeed in converting the ureide I into the pyrimidine II by the action of alkali. We also attempted to effect ring closure of the ureide I by means of catalytic hydrogenation as previously applied successfully by Rupe,[7] and later by Johnson and Bergmann[8] for the preparation of uracil and thymine, respectively. We obtained no evidence of the formation of a uracil-glucoside derivative. An attempt finally was made to condense tetraacetylglucose-urea with malonic acid to obtain a barbituric acid glucoside derivative. Twelve grams of acetic anhydride, 10 g. of acetylglucose-urea and 2.7 g. of malonic acid were heated at 100° for thirty minutes. We obtained a deep orange colored solution. Dilution with water led to the precipitation of a crystalline substance from which we succeeded in separating a product that crystallized from methyl alcohol without coloration after treatment with norite. It melted at 206–207°. The results of analysis indicated that we were not dealing with a barbituric acid derivative, but with the acyclic compound *di-(tetraacetylglucose)-ureide of malonic acid*, $C_{14}H_{19}O_9NHCONHCOCH_2CONHCONHC_{14}H_{19}O_9$.

Anal. Calcd. for $C_{33}H_{44}O_{22}N_4$: C, 46.68; H, 5.23; N, 6.60. Found: C, 46.51; H, 5.34; N, 6.86.

When this diureide was allowed to interact with alcoholic ammonia at ordinary temperature, glucose urea was formed.

Summary

1. Methods have been described for preparing 1-arabinose-urea,. *sym*-dixylose-urea and heptaacetyllactose isothiocyanate and derivatives.

2. Condensation of cyanoacetic acid with tetraacetylglucose-urea leads to the formation of the ureide $C_{14}H_{19}O_9NHCONHCOCH_2CN$. Attempts to condense this to a pyrimidine construction were unsuccessful.

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[7] Rupe, *Helv. Chim. Acta*, **8**, 850 (1925).

[8] Johnson and Bergmann, THIS JOURNAL, **55**, 1733 (1933).

NEW HAVEN, CONN. RECEIVED APRIL 4, 1938

[CONTRIBUTION FROM THE BUREAU OF CHEMISTRY AND SOILS, U. S. DEPARTMENT OF AGRICULTURE]

Fixation of Active Nitrogen by Organic Compounds

BY LOUIS B. HOWARD[1] AND GUIDO E. HILBERT

The most promising of various possible methods for directly introducing some form of elementary nitrogen into organic substances is the one utilizing active nitrogen[2] which consists essentially of atomic nitrogen. General experience has shown that molecular nitrogen is inert toward organic compounds and no catalyst has yet been discovered which will activate nitrogen to the extent that it will interact with organic materials. In this connection, it is noteworthy that practically all of many assumed reactions between nitrogen and organic molecules proceed with an increase in free energy.[3] In contrast to the ordinary form of nitrogen, atomic nitrogen, in view of its high reactivity, trivalent-like structure, $\left(\mathrm{N}\!\lessdot\right)$, and relatively long life, would be expected to interact

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[1] Now in the Bureau of Entomology and Plant Quarantine, Whittier, California.

[2] For a recent review see Sponer, "Molekülspektren und ihre anwendung auf chemische Probleme," II Text, Verlag von Julius Springer, Berlin, 1936, p. 458, and also Kneser, *Ergeb. exakt. Naturw.*, **8**, 229 (1929).

[3] We are grateful to Dr. R. Wiebe and Dr. R. T. Milner for having made many of these calculations.