[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE OHIO STATE UNIVERSITY]

The Reduction of Diazomethyl-*keto* Acetates; A New Route to Osone Derivatives[1]

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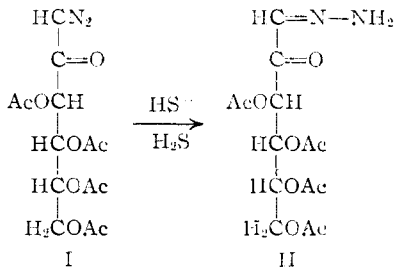
Reduction of 1-deoxy-1-diazo-*keto*-D-*galacto*-heptulose pentaacetate (III) with ammonium hydrogen sulfide or sodium dithionite yields 3,4,5,6,7-penta-*O*-acetyl-D-*galacto*-heptosone 1-hydrazone. The reaction was applied also to the synthesis of 3,4,5,6-tetra-*O*-acetyl-D-*arabino*-hexosone 1-hydrazone (II). Reduction of III with aluminum amalgam gave penta-*O*-acetyl-1-deoxy-*keto*-D-*galacto*-heptulose (IV). 3,4,5,6,7-Penta-*O*-acetyl-D-*galacto*-heptosone 1-[(2-hydroxy-1-naphthylmethylene)-hydrazone] is described.

In 1910, Forster and Zimmerli found that a diazo group may be reduced to a hydrazone with ammonium sulfide[3] and thus demonstrated the reversibility of the hydrazone–diazo systems since the oxidation of certain hydrazones had previously been shown to yield diazo compounds.[4] The actual reducing agent in this reaction system is most probably the anion HS^- since both Staudinger and co-workers[5] and ourselves found that in this reaction hydrogen sulfide will not act as a reducing agent in the absence of ammonium hydroxide (or ammonium sulfide). The HS^- anion will act as a catalyst in the presence of added hydrogen sulfide as

$$RCOCHN_2 + 2HS^- \longrightarrow RCOCH{=}N{-}NH_2 + S^- + S$$

$$H_2S + S^- \longrightarrow 2HS^-$$

Application of this reduction method to 1-deoxy-1-diazo-*keto*-D-fructose tetraacetate[6] (I) yielded the 1-hydrazone of 3,4,5,6-tetra-*O*-acetyl-D-*arabino*-hexosone (II).



I II

The reaction was extended to the synthesis of the analogous 3,4,5,6,7-penta-*O*-acetyl-D-*galacto*-heptosone by reduction of 1-deoxy-1-diazo-*keto*-D-*galacto*-heptulose pentaacetate[7] (III).

A 1-hydrazone also was obtained on reduction of 1-deoxy-1-diazo-*keto*-D-*galacto*-heptulose pentaacetate with sodium dithionite but in inferior yield to the hydrogen sulfide method. The total retention of nitrogen in this case is in contrast to the formation of amines and hydrocarbons when the *N*-nitroso group is reduced with sodium dithionite.[8]

The 4.75 μ absorption peak characteristic of diazo compounds[1,9] disappears upon reduction to the hydrazone, but the 6.1 μ absorption[9] is retained (Table I). Yates and associates[10] have shown that a band in the region 7.2–7.5 μ is also characteristic of diazomethyl ketones and we find this to be true.

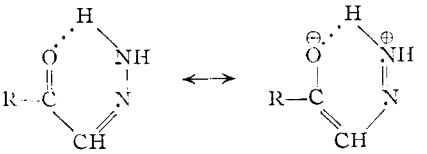
TABLE I

INFRARED SPECTRA OF DIAZO COMPOUNDS AND THEIR HYDRAZONE DERIVATIVES

Compound	Absorption band,[a] μ			Dispersing medium
Diazoacetophenone[b]	4.85	6.2	7.2	KBr
Phenylglyoxal hydrazone[c]		6.1		Nujol
Diphenyldiazomethane[d]	4.95	6.2	7.2	Petr. ether
Benzophenone hydrazone[d]		6.15		Nujol
1-Deoxy-1-diazo-*keto*-D-*galacto*-heptulose pentaacetate[e]	4.75	6.05	7.2	Nujol
3,4,5,6,7-Penta-*O*-acetyl-D-*galacto*-heptosone 1-hydrazone[f]		6.1		Nujol

[a] Infrared recording spectrophotometer, model B, Baird Associates, Inc., Cambridge, Mass. [b] W. Bradley and R. Robinson, *J. Chem. Soc.*, 1310 (1928). [c] Reference 11. [d] "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 351. [e] Reference 7. [f] This work.

Attempts to cleave the hydrazones and obtain acyclic osone acetates have thus far been unsuccessful. The α-ketohydrazone group, $-CO-CH{=}N-NH_2$, is neutral[11] rather than basic and could be considered to be the vinylog of an amide with resonance



This neutrality makes sufficient protonation for acid hydrolysis difficult under conditions sufficiently mild to retain the acetate groups intact. The other commonly used cleavage method, namely, acid-catalyzed exchange with another carbonyl compound in large excess, is further defeated by the tendency for aldehydes to yield very stable azines. In the present case this stability is en-

(1) Paper No. 18 in the series entitled "The Action of Diazomethane upon Acylic Sugar Derivatives"; previous communication, M. L. Wolfrom, D. I. Weisblat, Evan F. Evans and J. B. Miller, THIS JOURNAL, **79**, 6454 (1957).

(2) Procter and Gamble Fellow, 1955–1956; Visking Corporation Fellow, 1956–1957.

(3) M. O. Forster and A. Zimmerli, *J. Chem. Soc.*, **97**, 2150 (1910).

(4) T. Curtius and K. Thun, *J. prakt. Chem.*, [2] **44**, 161 (1891); see also W. Borsche and R. Frank, *Ann.*, **450**, 75 (1926); W. R. Bamford and T. S. Stevens, *J. Chem. Soc.*, 4735 (1952).

(5) H. Staudinger, L. Hammet and J. Siegwart, *Helv. Chim. Acta*, **4**, 228 (1921).

(6) M. L. Wolfrom, S. W. Waisbrot and R. L. Brown, THIS JOURNAL, **64**, 1701 (1942).

(7) M. L. Wolfrom, R. L. Brown and E. F. Evans, *ibid.*, **65**, 1021 (1943).

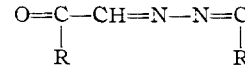
(8) C. G. Overberger, J. C. Lombardino and R. G. Hiskey, *J. Org. Chem.*, **22**, 858 (1957).

(9) M. L. Wolfrom and H. B. Wood, Jr., THIS JOURNAL, **77**, 3096 (1955).

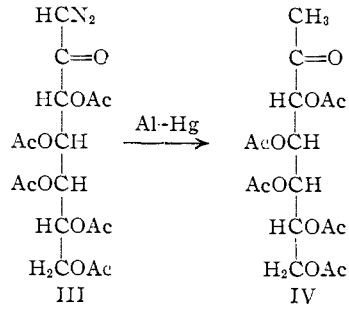
(10) P. Yates and B. L. Shapiro with N. Yoda and J. Fugger, *ibid.*, **79**, 5756 (1957).

(11) L. Wolff, *Ann.*, **394**, 23 (1912).

hanced by the free carbonyl group which further extends the conjugated system of the azine.



Staudinger and associates found that the aluminum amalgam reduction of diphenyldiazomethane gave diphenylmethylamine, whereas 9-diazofluorene gave fluorene.[12] In analogy with the latter case we find that the aluminum amalgam reduction of 1-deoxy-1-diazo-*keto*-D-*galacto*-heptulose pentaacetate gives 1-deoxy-*keto*-D-*galacto*-heptulose pentaacetate but in inferior yield to the hydriodic acid reduction method of Wolfrom and Brown.[7,13]



III IV

Experimental

3,4,5,6-Tetra-*O*-acetyl-D-*arabino*-hexosone 1-Hydrazone (II).—To a solution of 960 mg. of crude 1-deoxy-1-diazo-*keto*-D-fructose tetraacetate (I, m.p. 86.5–90.5°, recorded[6] 93–94°) in 110 ml. of ethanol was added 4 drops of ammonium sulfide solution (Mallinckrodt, analytical reagent). A stream of hydrogen sulfide was passed through the solution for 2 hr. at the approximate rate of 100 ml./min. followed by a stream of nitrogen for 1 hr. Removal of the solvent under reduced pressure at room temperature gave an orange colored, crystalline magma which was dissolved in benzene–ethanol and filtered. Carbon disulfide was added to the filtrate until crystallization began after which the solution was refrigerated overnight. Filtration followed by washing with benzene gave small, colorless crystals of 3,4,5-6-tetra-*O*-acetyl-D-*arabino*-hexosone 1-hydrazone; yield 570 mg., m.p. 155–158°. Pure material was obtained on recrystallization from benzene–ethanol (1:1 by vol.) by the addition of carbon disulfide to incipient turbidity, ethanol–petroleum ether (b.p. 30–60°), and finally ether–1,2-dimethoxyethane (2:1 by vol.) by the addition of petroleum ether; m.p. 158.5–160°, $[\alpha]^{24}D$ +76° (*c* 3.9, U.S.P.[14] $CHCl_3$).

Anal. Calcd. for $C_{14}H_{20}O_9N_2$: C, 46.67; H, 5.60; N, 7.78. Found: C, 46.82; H, 5.64; N, 7.77.

3,4,5,6,7-Penta-*O*-acetyl-D-*galacto*-heptosone 1-Hydrazone. (a) By Hydrogen Sulfide Reduction.—An amount of 840 mg. of 1-deoxy-1-diazo-*keto*-D-*galacto*-heptulose pentaacetate[7] was reduced with hydrogen sulfide as described above for the corresponding D-fructose derivative and the resultant sirup obtained on solvent removal crystallized on scratching. The product was crystallized twice from benzene–carbon disulfide; yield 740 mg., m.p. 133–136°. Pure 3,4,5,6,7-penta-*O*-acetyl-D-*galacto*-heptosone 1-hydrazone was obtained on recrystallization from benzene–petroleum ether; m.p. 137–138.5°, $[\alpha]^{23}D$ −28.5° (*c* 3.40, U.S.P. $CHCl_3$), very slightly yellow crystals.

Anal. Calcd. for $C_{17}H_{24}O_{11}N_2$: C, 47.22; H, 5.60; N, 6.48. Found: C, 47.30; H, 5.58; N, 6.41.

The reduction of more concentrated solutions appeared to enhance color formation and provided a precipitate of beautifully crystalline sulfur. Thus, 1 g. of the diazo derivative in 30 ml. of ethanol gave a precipitate of sulfur corresponding to 86% reduction and a 72% yield of brown colored, crude hydrazone, m.p. 134–135.5°. The hydrazone gave a weakly positive ninhydrin test. It was determined that: (a) in the absence of ammonium sulfide no reduction occurred in 65 min., and (b) in the presence of ammonium sulfide at ice–salt-bath temperature essentially no reduction occurred in 60 min.

(b) By Sodium Dithionite Reduction.—An aqueous ethanol solution saturated with sodium bicarbonate was prepared by mixing equal volumes of ethanol and a saturated aqueous sodium bicarbonate solution and filtering. The sodium dithionite solution was prepared by dissolving 1.01 g. of sodium dithionite in a minimum of water and then adding 20 ml. of the sodium bicarbonate solution prepared above. The sodium dithionite solution thus prepared was added to 500 mg. of 1-deoxy-1-diazo-*keto*-D-*galacto*-heptulose pentaacetate[7] dissolved in 100 ml. of the aqueous ethanolic sodium bicarbonate solution. At the end of 15 min. an excess of reducing agent remained as shown by the ability of the solution to bleach blue litmus paper. An equal volume of water was then added and the solution was extracted with four 20-ml. portions of chloroform. Solvent removal from the combined, dried chloroform extracts yielded a sirup. Dissolution twice in benzene with subsequent solvent removal gave a thick sirup which crystallized; yield 160 mg., m.p. 134–137.5°. Recrystallization from benzene–carbon disulfide gave crystals of m.p. 138–140° unchanged on admixture with material prepared in (a) above; X-ray powder diffraction patterns identical.

3,4,5,6,7-Penta-*O*-acetyl-D-*galacto*-heptosone 1-[(2-Hydroxy-1-naphthylmethylene)-hydrazone].—To a solution of 100 mg. of 3,4,5,6,7-penta-*O*-acetyl-D-*galacto*-heptosone 1-hydrazone in 30 ml. of peroxide-free ether was added 5 drops of ethanol followed by 80 mg. of 2-hydroxynaphthaldehyde. The solution was allowed to stand overnight at room temperature and was then refluxed for 1 hr. Three drops of acetic acid was added and the solution was again allowed to stand overnight at room temperature followed by refluxing for 1 hr. Removal of the solvent under reduced pressure gave a bright yellow sirup which crystallized spontaneously. This was dissolved in 5 ml. of ethyl acetate, 1 ml. of acetic acid was added and the solution was refluxed for 10 min. After standing overnight at room temperature, the solvent was removed under reduced pressure and the resultant sirup was chromatographed on a Magnesol[15]–Celite[16] (5:1 by wt.) column using one "column volume" of benzene–*t*-butyl alcohol (100:1 by vol.) as developer.

Three zones were observed: a zone at the top of the column which was discarded, a broad middle zone (bright orange-yellow), and a lower zone (bright yellow) which gave on elution 5 mg. of unidentified material. The middle zone was dissected and extracted with ethanol. Removal of the solvent under reduced pressure gave 65 mg. of bright orange crystals, m.p. 112–118°. Recrystallization from methanol, aqueous ethanol, and then methanol gave pure 3,4,5,6,7-penta-*O*-acetyl-D-*galacto*-heptosone 1-[(2-hydroxy-1-naphthylmethylene)-hydrazone], m.p. 116–119°.

Anal. Calcd. for $C_{28}H_{30}O_{12}N_2$: C, 57.33; H, 5.16; N, 4.78. Found: C, 56.98; H, 5.07; N, 4.74.

This material gave a yellow ethanolic solution which turned red on being made slightly basic. This red solution turned yellow on acidification or on being made strongly basic. The original yellow solution gave no apparent color change on acidification. The yellow solutions obtained by the action of acid or of excess base could not be converted to the red solution by a change in *p*H.

It should be noted that the above experimental work was done with the intent of cleaving the initial hydrazone. Success would have been indicated by precipitation of the highly colored and highly insoluble bis-(2-hydroxynaphthaldehyde) azine. When this failed to occur progressively more drastic conditions were employed. For this reason the above involved procedure in no way represents a recommended method for the preparation of the product actually obtained.

1-Deoxy-*keto*-D-*galacto*-heptulose Pentaacetate.—Amalgamated aluminum was prepared by covering 300 mg. of granu-

(12) H. Staudinger, A. Gaule and J. Siegwart, *Helv. Chim. Acta*, **4**, 212 (1921).

(13) M. L. Wolfrom and R. L. Brown, THIS JOURNAL, **65**, 1516 (1943).

(14) United States Pharmacopoeia; contains ethanol.

(15) Westvaco Chemical Division of Food Machinery and Chemical Corp., South Charleston, W. Va.

(16) No. 535, Johns-Manville Co., New York, N. Y.

lar aluminum with a saturated solution of mercuric chloride acidified with hydrochloric acid. After amalgamation had occurred (about 1 min.), the solvent was decanted and the amalgam was washed by decantation twice with acetone, twice with ether, and then twice with peroxide-free 1,2-dimethoxyethane.

The reduction was carried out by adding to the amalgam prepared above a solution of 1 g. of 1-deoxy-1-diazo-*keto*-D-*galacto*-heptulose pentaacetate[7] in 30 ml. of peroxide-free 1,2-dimethoxyethane. Immediate reaction occurred as evidenced by bubbling and the formation of an orange-gold color on the surface of the amalgam. One very small drop of water was added and the mixture was stirred at room temperature for 24 hr. The mixture was then filtered and the dark colored residue was washed thoroughly with chloroform. Upon removing the solvent from the combined filtrate and washings a dark sirup was obtained. Some of the color was removed by passing a chloroform solution of the sirup through a column (0.9 × 8 cm.) of Magnesol[15]–Celite[16] (5:1 by wt.) followed by 15 ml. of pure chloroform. The yellow effluent was dissolved in 10 ml. of methanol and again concentrated to a sirup. This treatment was repeated. A solution of the sirup in 10 ml. of methanol was then passed through a Darco G60[17] column (0.9 × 8 cm.) followed by 15 ml. of methanol. The colorless effluent was evaporated in a desiccator, over sulfuric acid and under reduced pressure, to a light yellow sirup. The addition of methanol to this sirup and refrigeration gave beautiful bright yellow crystals which were removed by filtration and washed with 50% (by vol.) aqueous methanol; yield 560 mg., m.p. 55–61°. Four recrystallizations from ether–petroleum ether gave crystals of m.p. 65.5–68.5° which on crystallizing from the melt then remelted at 78.5°. Recrystallization from ether–petroleum ether and seeding with the higher melting polymorph of 1-deoxy-*keto*-D-*galacto*-heptulose pentaacetate[13] gave m.p. 78–80°, $[\alpha]^{21}D$ −13.2° (*c* 1.85, U.S.P. $CHCl_3$), recorded[13] 78–79° and −14°. The X-ray powder diffraction pattern[13] of this material was identical with that of an authentic sample of the higher melting polymorph of 1-deoxy-*keto*-D-*galacto*-heptulose pentaacetate.

Silicate column chromatography of the crude reaction mixture from other preparations showed only one zone in addition to a highly colored zone at the column top. Isolation of material from this colorless zone gave 1-deoxy-*keto*-D-*galacto*-heptulose pentaacetate. Although no attempt was made to determine optimum reaction conditions it was found that without the addition of water, less of the dark residue was formed and the deoxy compound was obtained in low yield together with some starting material, the two being separable by virtue of their solubility difference in ether—the starting material being the much less soluble. Larger amounts of water added to the reaction mixture gave correspondingly larger amounts of dark colored residue and lower yields of the 1-deoxy compound.

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(17) Darco Corporation, 60 E. 42nd St., New York, N. Y.

[CONTRIBUTION FROM THE STANFORD RESEARCH INSTITUTE]

Potential Anticancer Agents.[1] I. Model Experiments for Synthesis of 2′-Deoxynucleosides by the 2,3-Episulfide Approach

BY LEON GOODMAN, ALLEN BENITEZ AND B. R. BAKER

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Cyclopentene episulfide has been prepared from cyclopentene oxide in 71% over-all yield by a three-step synthesis which should be compatible with the chemistry of nucleosides. Several other cyclopentane derivatives have been shown to be useful precursors of cyclopentene episulfide. The application of the chemistry of these cyclopentane transformations to the synthesis of 2′-deoxynucleosides is discussed.

The class of nucleosides composed of natural 2-deoxy-D-ribofuranose coupled with fraudulent bases represents a group of potential anticancer agents that should have interesting biological properties. Only one such compound, 6-azathymidine (V, base is 6-azathymine), has been synthesized—by an enzymatic route[2]—and it possessed biological activity. The enzymatic method, however, is tedious, difficult to carry out on a large scale, and has limitations in structural variation.

The first direct chemical synthesis of a nucleoside derived from D-ribofuranose, by condensation of tri-O-acetyl-D-ribofuranosyl bromide with silver theophylline,[3] was reported almost 10 years ago, but efforts to use this standard method[4,5] of coupling 3,5-di-O-acyl-2-deoxy-D-ribofuranosyl halides with heavy metal salts of pyrimidines[6,7] to form V have had no success. These failures can be attributed to the extreme acid lability of 2-deoxy-D-ribofuranose and its derivatives, in particular the 3,5-di-O-acyl-2-deoxy-D-ribofuranosyl halides. The synthesis of 2′-deoxy-D-ribopyranosyltheophylline has been accomplished by the coupling reaction of 3,4-di-O-acetyl-2-deoxy-D-ribopyranosyl chloride with silver theophylline,[8] but a mixture of α- and β-anomers was formed and, although these could be separated, it has not been possible to assign configurations to the two isomers. It can be predicted that, if a method of carrying out the coupling reaction with a 2′-deoxy-D-ribofuranosyl halide derivative could be found, similar objectionable, anomeric mixtures would be encountered.

It is clear from the above that indirect methods will have to be applied to accomplish synthesis of 2′-deoxynucleosides derived from 2-deoxy-furanose sugars. This fact was appreciated quite early by the Cambridge group.[9] These workers attempted to form the 2′-(ethylthio)-D-arabinoside (II, R =

(1) Work carried out under the auspices of the Cancer Chemotherapy National Service Center, National Cancer Institute, in collaboration with Sloan-Kettering Institute for Cancer Research.

(2) A. D. Welch, W. H. Prusoff and L. G. Lajtha, *Trans. Assoc. Am. Physicians*, **68**, 112 (1955).

(3) J. Davoll, B. Lythgoe and A. R. Todd, *J. Chem. Soc.*, 967 (1948).

(4) E. Fischer and B. Helferich, *Ber.*, **47**, 210 (1914).

(5) J. Davoll and B. A. Lowy, THIS JOURNAL, **73**, 1650 (1951).

(6) "Attempts by Lipkin and Sowden to use the Hilbert–Johnson synthesis with 3,5-di-O-benzoyl-2-deoxy-D-ribofuranosyl chloride or bromide and 2,4-diethoxypyrimidine met with no success," private communication from D. Lipkin, Washington University (St. Louis).

(7) Personal communication from Dr. J. J. Fox, Sloan-Kettering Institute, New York, N. Y.

(8) J. Davoll and B. Lythgoe, *J. Chem. Soc.*, 2526 (1949).

(9) J. Davoll, B. Lythgoe and S. Trippett, *ibid.*, 2230 (1951).