by partial crystallization of the ester. At the end of 20 min., the gas flow was stopped, the reaction flask was chilled in an ice bath, and 200 ml. of saturated sodium bicarbonate solution was added with stirring, followed by addition of enough solid sodium bicarbonate to bring the *p*H to 8 to "Alkacid" paper. The precipitated esters were filtered by suction, washed on the filter with cold water until the washings were neutral, and dried. No further purification was needed to prepare the esters for rearrangement. The yields were 92–96% for methyl phthalimidoacetate, m.p. 111–112°, and 96% for methyl DL-α-phthalimidopropionate, m.p. 66–67°.

Small portions of each ester were recrystallized from methanol-ligroin (1:1). The purified methyl phthalimidoacetate melted at 114–115° (corrected).

Anal. Calcd. for $C_{11}H_9NO_4$: C, 60.27; H, 4.14; N, 6.39. Found: C, 60.58; H, 4.27; N, 6.51.

The purified methyl DL-α-phthalimidopropionate melted at 66–67° (corrected).

Anal. Calcd. for $C_{12}H_{11}NO_4$: C, 61.80; H, 4.75; N, 6.01. Found: C, 61.75; H, 4.94; N, 6.05.[7]

3-Carbomethoxy-1,2,3,4-tetrahydroisoquinoline-1,4-dione (I). To a 1-l. three-neck, round-bottom flask, fitted with a mercury-seal stirrer and a Friedrichs condenser equipped with a drying tube containing calcium oxide were added 21.9 g. (0.10 mole) of methyl phthalimidoacetate, 21.6 g. of sodium methoxide, and 200 ml. of absolute methanol. Stirring and heating were initiated and the mixture became dark yellow. In about 15 min. a yellow precipitate began to form. At the end of 1 hr. the heating was stopped, the mixture was cooled to room temperature, and 100 ml. of 6*N* hydrochloric acid was added with stirring and cooling. The grayish precipitate was filtered by suction and washed on the filter with 0.1*N* hydrochloric acid until the washings were colorless, then with distilled water until the washings were neutral. The resulting mass was extracted with 500 ml. of boiling water, and the mixture was filtered through a funnel with a hot water jacket. The dried residue weighed 13.8 g. (63%) and melted at 219–220° (corrected). The reported melting point[1] is 221–222°.

1,2,3,4-Tetrahydroisoquinoline-1,4-dione (II). In a 200-ml. round-bottom flask were placed 2.2 g. (0.01 mole) of I and 20 ml. of 57% hydriodic acid. This mixture was refluxed for 1 hr., forming a clear, yellow solution which solidified on cooling to room temperature, as the result of crystallization of the hydriodide of II.[8] To this solid mass was added 100 ml. of water, and the mixture was heated to boiling, then immediately cooled, filtered, and washed on the filter with water until the washings were neutral. The resulting pale yellow powder weighed 1.5 g. (94%). It did not melt below 300°, in agreement with previous findings.[1,8]

3-Methyl-1,2,3,4-tetrahydroiosquinoline-1,4-dione (III) was prepared by a method similar to that used for I starting with 23.3 g. of methyl DL-α-phthalimidopropionate, 21.6 g. of sodium methoxide, and 200 ml. of absolute methanol. The mixture was refluxed with stirring for 3 hr., at the end of which it was deep red and contained a yellow precipitate. Addition of 100 ml. of 6*N* hydrochloric acid caused a vigorous effervescence. When the effervescence had subsided, the mixture was boiled until gas evolution ceased, and then allowed to stand overnight at room temperature. The mixture was filtered by suction and the precipitate was washed on the filter with water until the washings were neutral, leaving a residue of 7.6 g. (43%) of golden yellow crystals, m.p. 238–239.5° (corrected). The reported[1] melting point for III is 240°.

Ultraviolet absorption spectra. All absorption spectra were measured with a Cary recording spectrophotometer, using 1-cm. cells. The concentrations of the solutions were 10^{-4} to 10^{-3} molar, in 95% ethanol for neutral solutions, in 0.08–0.09*N* sodium hydroxide for basic solutions, and in 0.08–0.09*N* hydrochloric acid for acidic solutions.

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(7) Analyses by Mr. Don Ries.

(8) G. Vanags and V. Vitols, *Zhur. Obshcheĭ Khim.*, **24**, 1953 (1955); *Chem. Abstr.*, **50**, 8644c (1956).

Potential Cytostatic Carbohydrate Derivatives. I. *N*-Mustard Urethans[1]

THOMAS F. NOGRADY

Received January 13, 1961

Carbohydrates as biological carriers for nitrogen mustards were first used by Vargha *et al.*[2,3] and more recently by Reist, Spencer, and Baker.[4] These workers prepared *N*-mustard derivatives with a basic nitrogen. On the other hand, Bergel *et al.*[5] prepared *N*-mustard urethans of serine and threonine, compounds of low toxicity, of which the serine derivative was found to be very active on Walker rat sarcoma. These authors reported also the experiments of Bushby, who investigated the lower alkylurethans of *N*-mustard, and found that only the ethylurethan is active.

During our investigation of *N*-mustard derivatives of monosaccharides, we also prepared urethans of carbohydrates. By reaction of D-galactose with phosgene in dry acetone, 1,2:3,4-diisopropyliden-6-*O*-chloroformyl-D-galactopyranose (I) can be obtained.[6] When this reacted with *N*-bis(β-chloroethyl)amine in dry ether, a second molecule of the amine acting as acid acceptor, *N*-bis(β-chloroeth-

(1) This investigation was supported by the U. S. Department of Health, Education and Welfare, National Institutes of Health (Research Grant No. 2260), and by the National Cancer Institute of Canada.

(2) L. Vargha, L. Toldy, Ö. Feher, and S. Lendvai, *J. Chem. Soc.*, 805 (1957).

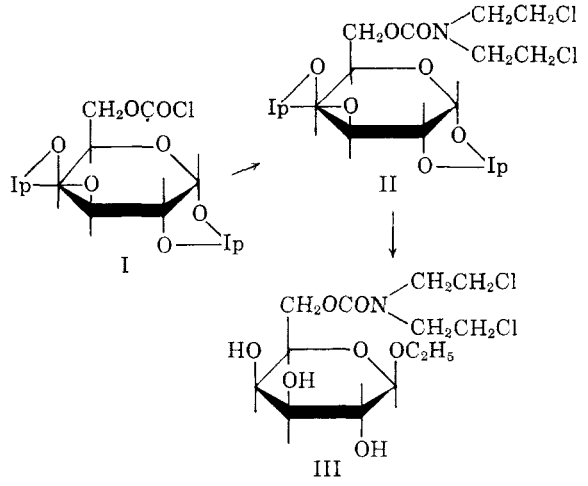
(3) L. Vargha, Ö. Feher, and B. R. Baker, *J. Am. Chem. Soc.*, **82**, 2025 (1960).

(4) E. Reist, R. R. Spencer, and B. R. Baker, *J. Am. Chem. Soc.*, **82**, 2025 (1960).

(5) F. Bergel and R. Wade, *J. Chem. Soc.*, 941 (1959).

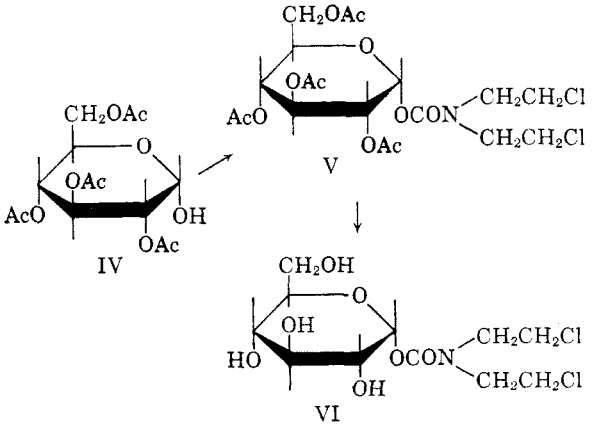
(6) W. N. Haworth, C. R. Porter, and A. C. Waine, *Rec. trav. chim.*, **57**, 541 (1938).

yl) - 1,2:3,4 - diisopropylidene - 6 - D - galactopyranosyl carbaminate (II) is obtained.



The isopropyl groups are best removed by ethanolic hydrochloric acid, with the simultaneous formation of the ethylglycoside (III), a crystalline substance. The reducing sugar could only be obtained as a sirup.

To prepare the glucose-1-urethan, we had to choose another method, since the 2,3,4,6-tetraacetylglucose forms a bistetraacetylglucose carbonate with phosgene.[7] 2,3,4,6-Tetraacetylglucose (IV) was therefore treated with *N*-chloroformylbis(β - chloroethyl)amine[8] in pyridine solution, and the *N*-bis(β-chloroethyl)-2,3,4,6-tetraacetyl-1-D-glucopyranosyl carbaminate (V) was obtained. It could be deacetylated with ethanolic hydrochloric acid, or by a large excess (ten moles) of diazomethane[9] to VI. A yellowish oil was obtained, but it did not crystallize.



Attempts to obtain the mannose-1-urethan and the glucose - 3 - urethan from 2,3:5,6 - diisopropylidene-D-mannofuranose and 1,2:5,6-diisopropylidene-D-glucofuranose, respectively, by the same method, failed. Even under drastic conditions, only starting material could be recovered.

The cancerostatic screening[10] revealed that compound III is active at 2 mg./day/mouse s.c. for fourteen days, producing a 40% inhibition of a mammary adenocarcinoma. Compound V at a dose level of 5 mg./day/mouse for fourteen days produced a 22% inhibition of the same tumor, both with a 0/20 mortality.

EXPERIMENTAL[11]

N-Bis(β-chloroethyl)-1,2:3,4-di-O-isopropylidene-6-D-galactopyranosylcarbaminate (II). Diisopropylidene-6-chloroformylgalactopyranose,[6] (31.3 g.) dissolved in 300 ml. of dry ether, and 29 g. of freshly prepared bis(β-chloroethyl)amine in 200 ml. of ether were mixed with chilling to prevent boiling of the solvent. After standing for 3 hr. at room temperature, the precipitated amine hydrochloride was filtered off, washed with ether (13.7 g., 77%), and the combined ethereal solutions were evaporated under reduced pressure. The remaining colorless crystalline substance was recrystallized from 120 ml. of *n*-heptane or 75 ml. of methanol, yielding 30.9 g. (71.8%) of product, m.p. 117–118°, $[\alpha]_D^{20}$ −34.5° (*c*, 2 chloroform).

Anal. Calcd. for $C_{17}H_{27}Cl_2NO_7$: C, 47.67; H, 6.36; N, 3.27. Found: C, 47.8; H, 6.6; N, 3.27.

Infrared maxima (cm.$^{-1}$): 1690 (C:O), 1280, 1250, 1205, 1160, 1102 (C—O and C—N).

Ethyl-N-bis(β-chloroethyl)-α-D-6-galactopyranosylcarbaminate (III), A 20-g. sample of II and 40 ml. of 21% ethanolic hydrochloric acid were stirred at room temperature until solution was complete (2.5 hr.). The red solution was evaporated under reduced pressure, the resulting red sirup dissolved in 40 ml. of water and was chilled. The separated crystals were filtered, washed with ice water, and dried, yielding 10.6 g. (60.8%) of tan crystals. Recrystallized from water or chloroform-petroleum ether (b. 30–60°) (1:1) it melts at 100–101°, $[\alpha]_D^{20}$ +92.5° (*c*, 2 chloroform).

Anal. Calcd. for $C_{13}H_{23}Cl_2NO_7$: C, 41.50; H, 6.16; N, 3.71. Found: C, 41.3; H, 6.3; N, 3.61.

Infrared maxima (cm.$^{-1}$): 3620 (free OH), 3300 (broad, H-bonded OH), 1686 (C:O), 1250, 1215, 1143 (C—O and C—N).

N-Bis(β-chloroethyl)-2,3,4,6-tetraacetyl-D-1-glucopyranosylcarbaminate (V). A 1.74-g. sample of 2,3,4,6-tetraacetylglucose was dissolved in 1 ml. of dry pyridine and 1.02 g. of *N*-chloroformylbis(β-chloroethyl)amine[8] added. The mixture stood at room temperature, and next day the yellow, sometimes semicrystalline solution was distributed between ethyl acetate and water, the organic phase washed with water, dried, and evaporated under reduced pressure. The remaining crystals were recrystallized from 2.5 ml. of methanol, yielding 1.07 g. (41%) of colorless crystals, m.p. 145–147° $[\alpha]_D^{20}$ −4.5° (*c*, 2 chloroform).

Anal. Calcd. for $C_{19}H_{27}Cl_2NO_{11}$: C, 44.20; H, 5.22; N, 2.71. Found: C, 44.1; H, 5.5; N, 2.77.

Infrared maxima (cm.$^{-1}$): 1747 (C:O ester), 1720 (C:O urethan), 1230 (C—N) 1062 (C—O).

(7) D. D. Reynolds and W. O. Kenyon, *J. Am. Chem. Soc.*, **64**, 1110 (1942).

(8) A. F. Childs, L. J. Goldsworthy, G. F. Harding, F. E. King, A. W. Nineham, W. L. Norris, S. G. P. Plant, B. Seldon, and A. L. L. Tompsett, *J. Chem. Soc.*, 2174 (1948).

(9) H. Bredereck, R. Sieber, and L. Kamphenkel, *Chem. Ber.*, **89**, 1169 (1956).

(10) The testing was done by Dr. R. Herne of Ayerst, McKenna and Harrison Ltd. (Montreal), and detailed data will be published elsewhere. We thank Dr. Herne for permission to publish his findings.

(11) All melting points are uncorrected and were determined in capillaries. The infrared spectra were taken in Nujol by Dr. C. Sandorffy and his staff, at the Département de Chimie, Université de Montreal.

N-Bis(β-chloroethyl)-D-1-glucopyranosylcarbaminate (VI). A 1.0-g. sample of V was dissolved in 50 ml. of chloroform, and 6 ml. of 16% ethanolic hydrochloric acid added (approximately 0.5*N* final hydrochloric acid concentration). After 2 days at room temperature it was evaporated and dried over solid sodium hydroxide. 0.66 g. (100%) of a colorless or slightly yellow, water soluble sirup resulted $[\alpha]_D^{20}$ +79.0° (*c*, 2 methanol).

We attempted chromatography on alumina (neutral, Brockman Grade I) but the urethan was split. After chromatography on silica gel, it could be recovered unchanged, but failed to crystallize.

Anal. Calcd. for $C_{11}H_{19}Cl_2NO_7$: N, 4.02. Found: N, 3.89.

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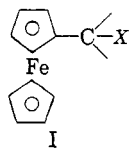
Communications TO THE EDITOR

α-Haloferrocenes. The Synthesis of Ferrocenylacetylene[1]

Sir:

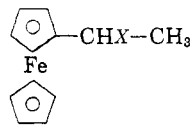
Thus far there has been no instance of the successful isolation and characterization of an α-haloferrocene (I), although several unsuccessful at-



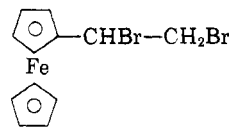
I

tempts to prepare such compounds have been reported.[2] Such compounds should be highly reactive as well as hydrolytically and perhaps even thermally unstable.[2]

We are hereby reporting the successful preparation of α-chloro- and α-bromoethylferrocene (II) as well as α,β-dibromoethylferrocene (III).



X = Cl, Br
II



III

The α-chloroethylferrocene (II. *X* = Cl) was prepared by adding dry hydrogen chloride to vinylferrocene[3] in pentane at −78°. A yellow solid was obtained (94% yield) which, after crystallization from anhydrous ether at −78° melted at 66–68° (dec. above 75°). The infrared spectrum of this material showed a C—Cl band at 14.3–14.4 μ, a CH_3—C compression at 7.3 μ, and ferrocene bands at 9, 10, and 12.2 μ.[4] (*Anal.* Calcd. for $C_{12}H_{13}FeCl$: C, 57.9; H, 5.23; Cl, 14.27. Found: C, 57.3; H, 5.52; Cl, 14.57.)

When this halide was treated at −78° with an ethereal slurry of sodium azide, an 89% yield of an amber liquid (n_D^{20} = 1.6116) was obtained, with infrared bands at 4.80 μ (—N_3) and 9, 10, and 12.2 μ. (lit. value[5] n_D^{20} = 1.6110). (*Anal.* Calcd. for $C_{12}H_{13}FeN_3$: C, 56.5; H, 5.14; Fe, 21.89; N, 16.47. Found: C, 56.3; H, 5.13; Fe, 22.08; N, 16.63.)

The α-chloroethylferrocene was also obtained in 95% yield by treating an ethereal solution of α-hydroxyethylferrocene containing activated alumina with anhydrous hydrogen chloride at −78°. The product thus obtained melted at 66–68°. This melting point was undepressed by a sample of the material prepared directly from vinylferrocene. Both samples had superimposable infrared spectra and formed identical azides.[5]

α-Bromoethylferrocene (II. *X* = Br) formed (93% yield) in a manner similar to the α-chloro compound by adding anhydrous hydrogen bromide to vinylferrocene in pentane at −78° (m.p. 48–50° dec.). The infrared spectrum of this material showed methyl group adsorption at 6.9 and 7.3 μ and bands at 9, 10, and 12.2 μ. (*Anal.* Calcd. for $C_{12}H_{13}FeBr$: C, 49.19; H, 4.47; Br, 27.27; Fe, 19.04. Found: C, 48.76; H, 4.42; Br, 26.92; Fe, 18.92.)

This bromide reacted almost instantaneously with aqueous sodium carbonate producing α-hydroxyethylferrocene[3] (m.p. 78–79°).

(1) This research was supported by the United States Air Force through the Air Force Office of Scientific Research of the Air Research and Development Command under contract No. A.F. 49(638)-297. Reproduction in whole or in part is permitted for any purpose of the United States Government.

(2) C. R. Hauser and J. K. Lindsay, *J. Org. Chem.*, **22**, 1246 (1957); K. Schlögl, *Monatsh*, **81**, 601 (1957); P. L. Pauson, *Quart. Revs.*, **9**, 391 (1955).

(3) F. Arimoto and A. Haven, Jr., *J. Am. Chem. Soc.*, **77**, 6295 (1955).

(4) An NMR spectrum of this compound showed a doublet signal at τ = 8.19 which is strong evidence for a formulation having a methyl group adjacent to a carbon atom bonded to only one hydrogen. In addition, the complete absence of peaks with τ values greater than 10 supports a formulation *without* a metal to hydrogen bond. [See T. J. Curphey, J. O. Santer, M. Rosenblum, and J. H. Richards, *J. Am. Chem. Soc.*, **82**, 5249 (1960)].

(5) The properties of this material agreed well with those reported by G. R. Buell, E. McEwen, and J. Kleinberg, *Tetrahedron Letters*, **5**, **16** (1959).