Nucleosides of D-Glucuronic Acid and of D-Glucofuranose and D-Galactofuranose[1,2]

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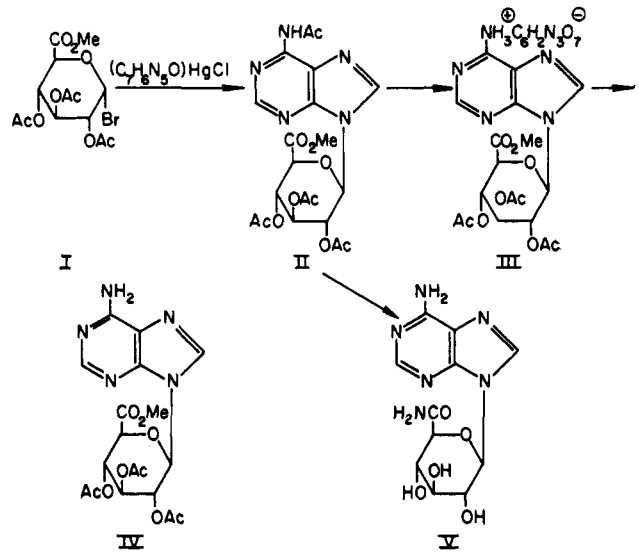
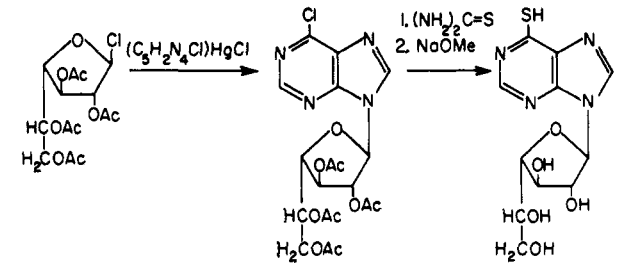
Methyl tri-*O*-acetyl-α-D-glucopyranosyluronate 1-bromide (I) was coupled with 6-acetamido-9-chloromercuripurine to give 6-acetamido-9-(methyl tri-*O*-acetyl-β-D-glucopyranosyluronate)purine (II) which on *N*-deacetylation with picric acid gave 9-(methyl tri-*O*-acetyl-β-D-glucopyranosyluronate)adenine (IV) and on complete deacetylation with methanolic ammonia gave 9-(β-D-glucuronosylamide)adenine (V). The coupling of tetra-*O*-acetyl-β-D-galacto- and -β-D-glucofuranosyl chlorides (VI and VIa) with 6-chloro-9-chloromercuripurine, followed by treatment with thiourea and deacetylation with sodium methoxide, has given the two crystalline 9-glycofuranosyl-6-mercaptopurines (VIII and VIIIa).

The utilization of D-glucuronic acid for glycoside synthesis has demonstrated the value of methyl tri-*O*-acetyl-α-D-glucopyranosyluronate 1-bromide (I) as an efficient intermediate for this purpose. The preparation of the latter by Goebel and Babers[3] made possible the syntheses of aldobiouronic acid methyl esters[4] and their acetates. Condensation of I with alcohols in the presence of silver oxide yielded the corresponding β-D-glucuronides.[3] Several methyl (aryl β-D-glucopyranosid)uronates[5] have been synthesized by the reaction of I with phenols under varying conditions.

To our knowledge, nucleosides of glycuronic acids have hitherto not been synthesized by coupling reactions. Levene and LaForge[6] obtained 5-nitro-1-(β-D-ribosyluronic acid)uracil by nitric acid oxidation of 9-β-D-ribosyluracil. In view of the significance of glycosides of D-glucuronic acid in animal metabolism,[7] it was considered of interest to attempt the synthesis of a nucleoside of this acid. Such a derivative resulted when I was coupled with 6-acetamido-9-chloromercuripurine by the method of Davoll and Lowy.[8] Crude, sirupy 6-acetamido-9-(methyl tri-*O*-acetyl-β-D-glucopyranosyluronate)purine (II) was formed in 57% yield and was purified by silicate column chromatography. The *N*-deacetylation of II with ethanolic picric acid[9] resulted in formation of the crystalline 9-(methyl tri-*O*-acetyl-β-D-glucopyranosyluronate)adenine picrate (III) and this on treatment with an ion-exchange resin produced crystalline 9-(methyl tri-*O*-acetyl-β-D-glucopyranosyluronate)adenine in 55% yield from II. The complete deacetylation of II with methanolic ammonia gave crystalline 9-(β-D-glucuronosylamide)adenine (V), the methyl ester on C-6 being ammonolized to the amide. These nucleoside derivatives probably possess the β-D configuration because of their method of synthesis from an α-D-glucopyranosyl bromide derivative.



We report also the application of ethyl tetra-*O*-acetyl-1-thio-α-D-galactofuranoside and the corresponding D-glucofuranoside to the preparation of hexofuranosyl nucleosides[10] of 6-chloropurine and 6-mercaptopurine. Ethyl tetra-*O*-acetyl-1-thio-α-D-galactofuranoside was converted to tetra-*O*-acetyl-β-D-galactofuranosyl chloride (VI)[11,12] by a modification of the procedure of Wolfrom and Groebke[12] and was then coupled with 6-chloro-9-chloromercuripurine to yield crude, sirupy 6-chloro-9-(tetra-*O*-acetyl-β-D-galactofuranosyl)purine (VII). This crude material was convertible to amorphous 9-(tetra-*O*-acetyl-β-D-galacto-



VI (VII) VIII

VI a, D-gluco configuration (VII a) VIII a

(1) Preliminary communication: Abstracts of Papers, 148th National Meeting of the American Chemical Society, Chicago, Ill., Sept. 1964, p. 24D.

(2) Supported by Grant CY-3232(C5) (The Ohio State University Research Foundation Project 759) from the National Institutes of Health, U.S. Public Health Service, Department of Health, Education, and Welfare, Bethesda, Md.

(3) W. F. Goebel and F. H. Babers, *J. Biol. Chem.*, **111**, 347 (1935).

(4) R. P. Hotchkiss and W. F. Goebel, *ibid.*, **115**, 285 (1936).

(5) G. N. Bollenback, J. W. Long, D. G. Benjamin, and J. A. Lindquist, *J. Am. Chem. Soc.*, **77**, 3310 (1955).

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(7) H. G. Bray, *Advan. Carbohydrate Chem.*, **8**, 251 (1953); R. S. Teague, *ibid.*, **9**, 185 (1954).

(8) J. Davoll and B. A. Lowy, *J. Am. Chem. Soc.*, **73**, 1650 (1951).

(9) J. R. Parikh, M. E. Wolff, and A. Burger, *ibid.*, **79**, 2778 (1957); M. L. Wolfrom, A. B. Foster, P. McWain, W. von Bebenburg, and A. Thompson, *J. Org. Chem.*, **26**, 3095 (1961).

(10) M. L. Wolfrom, P. McWain, R. Pagnucco, and A. Thompson, *ibid.*, **29**, 454 (1964).

(11) C. S. Hudson and J. M. Johnson, *J. Am. Chem. Soc.*, **38**, 1223 (1916).

(12) M. L. Wolfrom and W. Groebke, *J. Org. Chem.*, **28**, 2986 (1963).

furanosyl)-6-mercaptopurine with thiourea and to the final crystalline 9-(β-D-galactofuranosyl)-6-mercaptopurine (VIII) by deacetylation with sodium methoxide. In a similar sequence ethyl tetra-*O*-acetyl-1-thio-α-D-glucofuranoside was utilized in preparing sirupy 6-chloro-9-(tetra-*O*-acetyl-β-D-glucofuranosyl)-purine (VIIa) which was converted to amorphous 9-(tetra-*O*-acetyl-β-D-glucofuranosyl)-6-mercaptopurine and the latter was deacetylated to crystalline 9-(β-D-glucofuranosyl)-6-mercaptopurine (VIIIa).

Experimental[13]

6-Acetamido-9-(methyl tri-*O*-acetyl-β-D-glucopyranosyluronate)purine (II).—Methyl tetra-*O*-acetyl-α,β-D-glucopyranosyluronate[3,5] (10 g.) was converted to the corresponding 1-bromide[3] (I) and this was added to an azeotropically dried mixture of 11.0 g. of 6-acetamido-9-chloromercuripurine, 11.0 g. of cadmium carbonate, 4 g. of Celite,[14] and 300 ml. of toluene, followed by 1 hr. of heating under reflux and filtration of the hot mixture. The hot chloroform-soluble material was collected from the filter cake and from the residue obtained on evaporation of the filtrate. The extract was washed twice with aqueous potassium iodide, twice with water, and dried over anhydrous sodium sulfate. Evaporation under reduced pressure gave a crude, amber sirup: yield 7.5 g. The crude sirup, 1.3 g., was dissolved in chloroform and poured onto a 40 × 45 mm. column of Micro-Cel C,[15] prewet with benzene. The column was washed with benzene–ethanol (100:1) until all colored material had been removed. Elution was effected by washing with acetone. Evaporation of the acetone gave a sirup, yield 460 mg., which was crystallized from toluene. Treating with decolorizing carbon in chloroform and recrystallization from toluene by the addition of ether gave m.p. 219–219.5°; $[\alpha]^{22}D$ −5° (*c* 0.38, chloroform), $[\alpha]^{18}D$ −10.5° (*c* 0.38, methanol); absorption spectra data[13] λ_{max}^{EtOH} 269 mμ; λ_{max}^{KBr} 3.10 (NH), 5.75 (ester carbonyl), 5.88 (amide), 6.25, 6.65, 6.85 (purine ring), 7.35 (methyl hydrogen), 9.25, 9.70 (C–O–C) μ; X-ray powder diffraction data[16] 11.71 m (3), 9.21 vs (1), 8.30 vw, 7.56 w, 5.75 vw, 4.80 s (2), 4.47 vw, 4.04 w, 3.77 w, 3.51 w, 3.07 w.

Anal. Calcd. for $C_{20}H_{23}N_5O_{10}$: C, 49.82; H, 4.70; N, 14.19; CH_3CO, 34.90. Found: C, 49.07; H, 4.96; N, 13.93; CH_3CO, 30.5.

9-(Methyl tri-*O*-acetyl-β-D-glucopyranosyluronate)adenine Picrate (III).—The *N*-deacetylation of II was effected by boiling ethanolic picric acid.[9] Three grams of II, dissolved in 15 ml. of hot ethanol, was refluxedf or several minutes with 15 ml. of 10% ethanolic picric acid; a yellow crystalline product resulted on cooling. Collection on a filter and washing with cold ethanol and ether gave crude III: yield 3.0 g. (72%), m.p. 225–227° dec.

Anal. Calcd. for $C_{24}H_{24}N_8O_{16}$: C, 42.36; H, 3.56; N, 16.46. Found: C, 42.43; H, 3.89; N, 16.31.

9-(Methyl tri-*O*-acetyl-β-D-glucopyranosyluronate)adenine (IV).—Crude III, 2.8 g., was suspended in 80% aqueous acetone and stirred with Dowex 1 (CO_3^{-2}) until the solution showed no yellow color. The colorless filtrate was evaporated, and the sirupy residue was suspended in ethanol and re-evaporated to a crystalline mass; yield 1.0 g. (55%). Resuspension in hot 95% ethanol (decolorizing carbon) and crystallization by slow evaporation of the solvent under a stream of air gave IV in analytical purity: m.p. 148–151°; $[\alpha]^{18}D$ −10° (*c* 0.51, methanol); absorption spectra data[13] λ_{max}^{MeOH} 260 mμ; λ_{max}^{KBr} 3.00, 3.20 (NH, NH_2), 5.72 (ester carbonyl), 6.15, 6.30, 6.38, 6.82 (NH and purine ring), 7.35 (methyl hydrogen), 9.15, 9.45, 9.70 (C–O–C) μ; X-ray powder diffraction data[16] 8.93 m, 6.61 s (1), 5.64 w, 5.14 vw, 4.73 vw, 4.51 vw, 4.31 m (2), 3.97 m (3), 3.31 w.

Anal. Calcd. for $C_{18}H_{21}N_5O_9$: C, 47.90; H, 4.69; N, 15.51. Found: C, 47.92; H, 4.81; N, 15.18.

9-(β-D-Glucuronosylamide)adenine (V).—An amount of 170 mg. of II was suspended in 25 ml. of methanolic ammonia, nearly saturated at 0°, and allowed to stand in the refrigerator for 48 hr. The colorless solution was evaporated under reduced pressure, and the resulting sirup was evacuated (0.1 mm.) at 50–60° for several hours and at 25° for 18 hr. A mass of crystalline acetamide sublimed from the sirup leaving a solid. The residue was decolorized in hot water with carbon and filtered, and the filtrate was diluted with ethanol. Evaporation from ethanol resulted in a white crystalline deposit: yield 80 mg. (75%); m.p. 257–259° dec.; $[\alpha]^{22}D$ +20° (*c* 0.30, water); absorption spectra data[13] $\lambda_{max}^{H_2O}$ 259 mμ; λ_{max}^{KBr} 3.00 (OH–NH), 5.88 (amide), 6.10, 6.25, 6.40, 6.80 (NH_2, NH, and purine ring), 9.02, 9.30 (C–OH) μ; X-ray powder diffraction data[16] 7.80 m, 5.16 s, 4.70 m, 4.54 m, 4.24 vs (1,1,1), 3.82 vw, 3.60 vs (1,1,1), 3.46 vs (1,1,1), 3.09 m, 2.96 vw, 2.78 s, 2.67 vw, 2.59 vw, 2.52 w. The material gave a single spot on a paper chromatogram,[13] R_{Ad} 0.24.

Anal. Calcd. for $C_{11}H_{14}N_6O_5$: C, 42.55; H, 4.55; N, 27.09. Found: C, 42.57; H, 4.63; N, 26.97.

9-(β-D-Galactofuranosyl)-6-mercaptopurine (VIII).—The conditions of Wolfrom and Groebke[12] for the synthesis of tetra-*O*-acetyl-β-D-galactofuranosyl chloride were somewhat modified. Ethyl tetra-*O*-acetyl-1-thio-α-D-galactofuranoside,[10,17] 11.0 g., dissolved in 50 ml. of methylene chloride (dried over Drierite[18]), was treated with 2 g. of chlorine in 50 ml. of methylene chloride for 15 min. at 0°. The yellow solution was evaporated to a sirup and re-evaporated twice from absolute ether. The residual sirupy tetra-*O*-acetyl-β-D-galactofuranosyl chloride[12] (VI) was coupled directly with 8.87 g. of 6-chloro-9-chloromercuripurine[19] in an azeotropically dried mixture of 3 g. of Celite[14] and 200 ml. of toluene. The suspension was stirred and held at reflux temperature 0.5 hr. and filtered hot, and the chloroform-soluble material was collected from the filter cake and the filtrate. The chloroform extract was washed with aqueous potassium iodide and with water (five times), then dried over anhydrous sodium sulfate, and evaporated to a sirup; yield 11.7 g. The sirup was dissolved in ethanol and treated with decolorizing carbon, filtered, and evaporated to a glass; yield 11.6 g. An ethanol solution of the material was passed over a column of Celite[14] (480 × 30 mm.) prewet with water-saturated 1-butanol. Development with this aqueous 1-butanol gave three bands as revealed under ultraviolet light. The third band, slowest moving and most concentrated, was collected and concentrated to a glass: m.p. 55–65°; $[\alpha]^{26}D$ −6° (*c* 1.32, chloroform); absorption spectra data[13] λ_{max}^{EtOH} 264 mμ; λ_{max}^{KBr} 3.50 (C–Cl), 5.82 (CO), 6.35, 6.50, 6.70 (purine ring), 9.40–9.80 (broad C–O–C), 12.70 (C–Cl) μ. Thin layer chromatography on silica gel G with water-saturated 1-butanol developer and sulfuric acid indication revealed one major spot with two faster moving and two slower moving minor spots.

Anal. Calcd. for $C_{19}H_{21}ClN_4O_9$: C, 47.07; H, 4.37; Cl, 7.31. Found: C, 47.05; H, 4.93; Cl, 7.39.

The crude 6-chloro-9-(tetra-*O*-acetyl-β-D-galactofuranosyl)-purine (VII, 7.49 g.), in 50 ml. of absolute ethanol, was converted to the acetylated 6-mercaptonucleoside[20,21] by refluxing 2 hr. with 1.4 g. (1.2 molar equiv.) of thiourea. On cooling, the gelatinous mass was collected on a filter and washed with cold ethanol. The precipitate was resuspended in hot methanol and treated with decolorizing carbon, and the solution was evaporated to a yellow, amorphous solid; yield 4.40 g. After repeating this operation and reprecipitating the product from hot absolute ethanol, an amorphous 6-mercapto-9-(tetra-*O*-acetyl-β-D-galactofuranosyl)purine resulted: yield 1.40 g.; m.p. 178–186°; $[\alpha]^{22}D$ −36° (*c* 0.5, chloroform); absorption spectra data[13] λ_{max}^{EtOH} 323 mμ; λ_{max}^{KBr} 3.55–3.75 (–SH), 5.72 (ester carbonyl), 6.24, 6.55, 6.75

(13) The ultraviolet absorption spectra were obtained on a Perkin-Elmer recording spectrometer. The infrared spectral data were obtained with a Perkin-Elmer Infracord spectrophotometer. Structural assignments were made essentially according to H. M. Randall, N. Fuson, R. G. Fowler, and J. R. Dangl in "Infrared Determination of Organic Structures," D. Van Nostrand Co., Inc., New York, N. Y., 1949; and B. R. Baker and K. Hewson, *J. Org. Chem.*, **22**, 959 (1957). Chromatographic data were obtained on Whatman No. I paper by descending chromatograms in 1-butanol–ethanol–water (40:11:19 v./v.) with indication by ultraviolet light and by sodium metaperiodate and ammoniacal silver nitrate sprays according to L. Hough and J. K. N. Jones in "Methods in Carbohydrate Chemistry," Vol. I, R. L. Whistler and M. L. Wolfrom, Ed., Academic Press Inc., New York, N. Y., 1963, p. 28.

(14) No. 535, a product of the Johns-Manville Co., New York, N. Y.

(15) A product of the Johns-Manville Co., New York, N. Y.

(16) Interplanar spacing, Å., Cu Kα radiation. Relative intensity, estimated visually: s, strong; m, medium; w, weak; v, very. First three strongest lines numbered (1, strongest), double numbers indicate approximately equal intensities.

(17) M. L. Wolfrom, Z. Yosizawa, and B. O. Juliano, *J. Org. Chem.*, **24**, 1529 (1959).

(18) Calcium sulfate as soluble anhydrite.

(19) B. R. Baker, K. Hewson, H. J. Thomas, and J. A. Johnson, Jr., *J. Org. Chem.*, **22**, 954 (1957).

(20) H. M. Kissman and M. J. Weiss, *J. Am. Chem. Soc.*, **80**, 5559 (1958).

(21) J. A. Johnson, Jr., and H. J. Thomas, *ibid.*, **78**, 3863 (1956).

(purine ring), 7.30 (methyl hydrogen), 9.25–9.70 (broad C–O–C) μ.

Anal. Calcd. for $C_{19}H_{22}N_4O_9S$: C, 47.30; H, 4.60; S, 6.63. Found: C, 47.57; H, 4.98; S, 6.64.

Amorphous 9-(tetra-*O*-acetyl-β-D-galactofuranosyl)-6-mercaptopurine, 680 mg., was deacetylated in methanolic sodium methoxide made by adding several freshly cut pellets of sodium to the methanolic solution of the blocked nucleoside. The solution was warmed, then evaporated. The residue was redissolved in water, neutralized with glacial acetic acid, diluted with ethanol, and placed on a column (210 × 22 mm.) of Amberlite[22] IRC-50 (H^+). The material was washed from the column with 200 ml. of 50% (v./v.) aqueous ethanol. Evaporation of the eluate left a crystalline mass (VIII) which was treated with carbon in water and the colorless solution was evaporated to a sirup which was dried by codistillation with ethanol. The white crystalline solid obtained was recrystallized from warm ethanol, yielding 200 mg. (45%): m.p. 192–194°; $[\alpha]^{17}D$ −63° (*c* 0.56, water); absorption spectra data[13] $\lambda_{max}^{H_2O}$ 322 mμ; λ_{max}^{KBr} 3.0 (OH), 3.60–3.90 (broad –SH), 6.30, 6.65, 6.90 (purine ring), 9.05–9.75 (broad C–OH) μ; X-ray powder diffraction data[16] 14.85 w, 11.40 w, 9.35 w, 8.76 w, 7.34 m, 6.42 vw, 5.95 w, 5.70 vw, 5.19 s (3), 4.67 s (2), 3.67 s (1), 3.25 s, 2.84 m. Paper chromatography[13] revealed one mobile spot, R_{Ad} 0.52.

Anal. Calcd. for $C_{11}H_{14}N_4O_5S$: C, 42.04; H, 4.49; N, 17.83; S, 10.20. Found: C, 41.47; H, 4.63; N, 17.49; S, 10.70.

9-(β-D-Glucofuranosyl)-6-mercaptopurine (VIIIa).—Ethyl tetra-*O*-acetyl-1-thio-α-D-glucofuranoside[10,23] (4.47 g.) was converted to tetra-*O*-acetyl-β-D-glucofuranosyl chloride[24] (VIa) as described above for the D-galactose analog. The sirupy product was not crystallized but was used immediately in the coupling step with 6-chloro-9-chloromercuripurine as described above for the D-galactose analog except that the toluene mixture was refluxed for 4 hr. The crude product, 6-chloro-9-(tetra-*O*-acetyl-β-D-glucofuranosyl)purine (VIIa), was isolated as a sirup in the same manner with omission of the column chromatography; yield 4.70 g. (85%). Further treatment with decolorizing carbon in methanol gave a glass showing one major spot with a minor trailing spot on thin layer chromatography (silica gel G, water-saturated 1-butanol developer, sulfuric acid indicator): $[\alpha]^{26}D$ −3° (*c* 0.94, chloroform); absorption spectra data[13] λ_{max}^{EtOH} 264 mμ; λ_{max}^{KBr} 6.85 (ester carbonyl), 6.38, 6.50, 6.82 (purine ring), 7.40 (methyl hydrogen), 9.30–9.70 (broad C–O–C) μ.

An amount of 2.0 g. of the above dried, glassy product was converted to the 6-mercapto acetylated derivative with thiourea as described above for the D-galactose analog and the product was isolated in the same manner as an amorphous solid: yield 1.0 g.; m.p. 178–180°; $[\alpha]^{22}D$ −34° (*c* 0.47, chloroform); absorption spectra data[13] λ_{max}^{EtOH} 324 mμ; λ_{max}^{KBr} 3.40 (–SH), 5.80 (ester carbonyl), 6.32, 6.60, 6.85 (purine ring), 7.40 (methyl hydrogen), 9.30–9.70 (broad C–O–C) μ.

The above crude mercapto acetylated derivative (900 mg.) was deacetylated and deionized (by washing with 250 ml. of 50% aqueous ethanol) in the same manner as that described for the corresponding D-galactose derivative. The solid obtained on evaporation of the eluate was dissolved in 95% ethanol (decolorizing carbon) and evaporated to a small volume. Crystallization of VIIIa was effected by allowing the solution to stand at 0°: yield 80 mg.; m.p. 199–199.5°; $[\alpha]^{23}D$ −74° (*c* 0.47, water); absorption spectra data[13] $\lambda_{max}^{H_2O}$ 323 mμ; λ_{max}^{KBr} 3.05 (OH), 3.60–3.80 (SH), 6.32, 6.60, 6.85 (purine ring), 9.52, 9.85 (C–OH) μ; X-ray powder diffraction data[16] 10.10 vw, 8.90 w, 7.14 vw, 5.75 w, 5.39 m, 4.56 w, 4.37 w, 4.08 s (3), 3.53 s (1), 3.41 s (2), 3.16 w. The material showed one spot on paper chromatography,[13] R_{Ad} 0.58.

Anal. Calcd. for $C_{11}H_{14}N_4O_5S$: C, 42.04; H, 4.49; N, 17.83; S, 10.20. Found: C, 42.06; H, 4.49; N, 17.76; S, 10.76.

(22) A product of the Rohm and Haas Co., Philadelphia 5, Pa.

(23) W. Schneider and J. Sepp, *Ber.*, **49**, 2054 (1916); J. W. Green and E. Pacsu, *J. Am. Chem. Soc.*, **59**, 1205 (1937); M. L. Wolfrom, S. W. Waisbrot, D. I. Weisblat, and A. Thompson, *ibid.*, **66**, 2063 (1944).

(24) H. H. Schlubach, W. Rauchenberger, and H. Schultze, *Ber.*, **66**, 1248 (1933).

N-Iodohydantoins. II.[1,2] Iodinations with 1,3-Diiodo-5,5-dimethylhydantoin

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1,3-Diiodo-5,5-dimethylhydantoin, a stable reagent previously described, shows general applicability for nuclear iodination of homo- and heteroaromatic compounds activated by electron-donating substituents. It has been demonstrated, on the basis of isolation of 2-(iodoamino)-4,6-dimethylpyrimidine and 2,4-dimethyl-6-(N-iodo-N-acetylamino)pyrimidine, that the iodination of amino and acetylamino aromatic substrates occurs, at least in some cases, *via* the intermediate formation of N-iodo derivatives. Furthermore, like N-iodosuccinimide, it reacts with enol acetates derived from saturated and unsaturated ketones, affording α-iodo ketones in good yields.

The successful application of a series of N-chloro and N-bromo derivatives of the hydantoin ring as halogenating and oxidizing agents[4] led us to prepare the analogous iodo compounds. 1,3-Diiodo-5,5-dimethylhydantoin (DIH) was the most promising reagent owing to the high iodine content, the very satisfactory stability, and its economical preparation.[1] It is obtained in 74% yield by the reaction of an alkaline aqueous solution of 5,5-dimethylhydantoin with iodine monochloride, thus obviating the expensive silver derivatives commonly used as intermediates in the preparation of N-iodoamides or -imides.

It was previously shown that DIH reacts with 2-ethoxynaphthalene giving a 77% yield of 1-iodo-2-ethoxynaphthalene; similar results were obtained with several 1-iodo-5,5-disubstituted hydantoins.[1,4a] Few other data can be found in the literature dealing with nuclear iodinations by means of N-iodoamides or -imides.[5,6]

In the present work the halogenation reactions of aromatic compounds were performed in acetone, which shows excellent solvent ability for iodohydantoins[1] and is also a satisfactory solvent for the aromatic substrates.

In iodination with DIH no hydrogen iodide is formed; therefore, contrasting with reactions using molecular

(1) Part I: R. A. Corral and O. O. Orazi, *Anales asoc. quím. Arg.*, **44**, 11 (1956); *Chem. Abstr.*, **51**, 2751 (1957) (p. 2752, line 3: for "24.8 g." read "12.8 g.").

(2) Part of the Doctoral Thesis (1962) of H. E. B. is included in this work, which was supported by a research grant from the Consejo Nacional de Investigaciones Científicas y Técnicas.

(3) Fellow of Consejo Nacional de Investigaciones Científicas y Técnicas, 1960–1962, on leave from the Universidad Nacional de Córdoba, Argentina.

(4) As reference guides, see (a) R. A. Corral and O. O. Orazi, *J. Org. Chem.*, **28**, 1100 (1963); (b) O. O. Orazi and R. A. Corral, *Anales asoc. quím. Arg.*, **42**, 139 (1954); (c) R. A. Reed, *Chem. Prod.*, 299 (1960).

(5) A. Roedig, "Methoden der Organische Chemie," 5/4, Houben-Weyl, Georg Thieme Verlag, Stuttgart, 1960, p. 580.

(6) D. Lipkin, F. B. Howard, D. Nowotny, and M. Sano, *J. Biol. Chem.*, **238**, 2249 (1963).