Haloacetamido Analogues of 2-Amino-2-deoxy-D-glucose and 2-Amino-2-deoxy-D-galactose. Syntheses and Effects on the Friend Murine Erythroleukemia[1]

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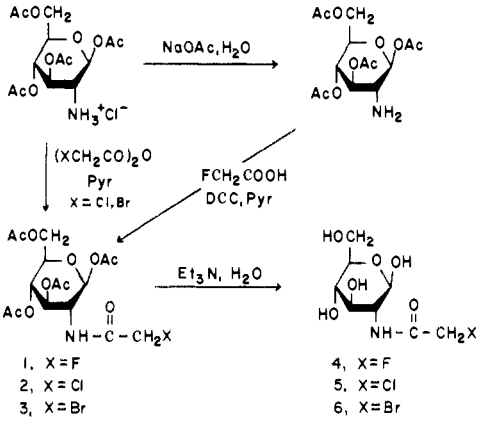
2-Deoxy-2-(haloacetamido)-D-glucose and 2-deoxy-2-(haloacetamido)-D-galactose (fluoro, chloro, and bromo) were prepared by de-O-acetylation of the appropriate 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-(haloacetamido)-β-D-hexose with triethylamine. The 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-(chloroacetamido)- and 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-(bromoacetamido)-β-D-hexoses were produced by condensation of a haloacetyl anhydride with 1,3,4,6-tetra-*O*-acetyl-2-amino-2-deoxy-β-D-hexose hydrochloride in pyridine. The hydrochlorides were converted to free bases for condensation with fluoroacetic acid in the presence of dicyclohexylcarbodiimide to produce 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-(fluoroacetamido)-β-D-hexoses. The chloroacetamido and bromoacetamido derivatives were from 3- to 12-fold more toxic on a molar basis to BDF_1 mice when administered as lipophilic tetra-*O*-acetates than as the free sugars; no significant difference existed between the glucose and galactose forms. The fluoroacetamido analogue of the glucose series was fivefold more toxic than the comparable fluoroacetamido derivative of the galactose series; no difference existed in the toxicities of the free sugars and the tetra-*O*-acetates with either of the fluoroacetamide-containing hexoses. Cytotoxicity against log-phase cultured Friend erythroleukemia cells was greatest with the tetra-O-acetylated bromoacetamido derivatives in both the gluco and galacto series, these agents being three- to fourfold more cytotoxic than tetra-O-acetylated chloroacetamido derivatives and 20-fold more cytotoxic than tetra-O-acetylated fluoroacetamido sugars. The *N*-chloroacetamido derivative in the glucose series was 50-fold more cytotoxic as the tetra-*O*-acetate than as the free nonacetylated sugar. These results support the concept that tetra-O-acetylated derivatives of the chloroacetamido and bromoacetamido carbohydrate analogues function as lipophilic alkylating agents and lose biological activity when converted to hydrophilic free hydroxyl forms, whereas the fluoroacetamido derivatives exert their effects as the de-O-acetylated form.

Alteration of the surface membrane of neoplastic cells by chemotherapeutic agents can be expected to produce changes in critical biological functions that are dependent upon membrane structural features; thus, immunogenicity, transport, cellular division, intercellular recognition, interaction with extracellular control molecules, and differential gene expression are processes that could be affected. Because the progressive growth of cancers may require an ineffective immune response, altered transport, poorly regulated cell division, invasiveness and metastases, atypical recognition of hormone or other control signals, and/or failure to differentiate, drug-induced alteration of membrane structure may provide a useful approach to the therapeutic control of some types of cancers.

Surface-mediated properties might be affected by direct alteration of cell-surface carbohydrate structures or by indirect effects on carbohydrate biosynthetic processes. The role of 2-deoxy-2-acetamido-β-D-hexoses in membrane oligosaccharides and as precursors of sialic acids, as well as the observation of enhanced transport of *N*-acetylmannosamine in a hepatoma,[3] suggests that analogues of 2-deoxy-2-acetamido-β-D-hexoses might produce indirect metabolic or direct chemical alteration of membrane carbohydrate structures. Moreover, alteration of surface biochemistry by introduction of carbohydrate analogues makes possible the subsequent separation of derivatized cells by use of carbohydrate-specific lectins, permitting the study of more nearly homogeneous altered cell preparations as immunoprophylactic and immunotherapeutic vaccines.

In this paper we detail the syntheses of fluoro, chloro, and bromo analogues of 2-deoxy-2-(haloacetamido)-D-glucose and 2-deoxy-2-(haloacetamido)-D-galactose as the water-soluble free sugars and as the lipophilic tetra-*O*-acetates. The in vivo toxicity of the various analogues was determined in BDF_1 mice for use in in vivo test systems for chemotherapeutic effects. Friend erythroleukemia cells of DBA/2J origin in long-passage suspension culture were employed to establish cytostatic effects in culture and to monitor for the potential of the analogues to induce cellular differentiation. The toxicities of the chloroacetamido and bromoacetamido analogues in vivo and their cytostatic effects in culture were much greater for the lipophilic tetra-*O*-acetates than for the corresponding free sugars; however, no distinction was observed between the respective glucose and galactose analogues. Significant differences were seen in vivo between 2-deoxy-2-(fluoroacetamido)-D-glucose and 2-deoxy-2-(fluoroacetamido)-D-galactose both as the free sugars and as the peracetates.

Scheme I



Chemistry. The 2-halo analogues (fluoro, chloro, and bromo) of 2-deoxy-2-acetamido-D-glucose (GlcNFAc, **4**; GlcNClAc, **5**; and GlcNBrAc, **6**) and 2-deoxy-2-(acetamido)-D-galactose (GalNFAc, **10**; GalNClAc, **11**; and GalNBrAc, **12**) were prepared (Schemes I and II) by de-O-acetylation of the corresponding 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-(haloacetamido)-β-D-hexoses in aqueous methanol-triethylamine under conditions described by Lemieux and Driguez.[4] The absence of a protonated base prevented loss of halide. The method of Wolfram and

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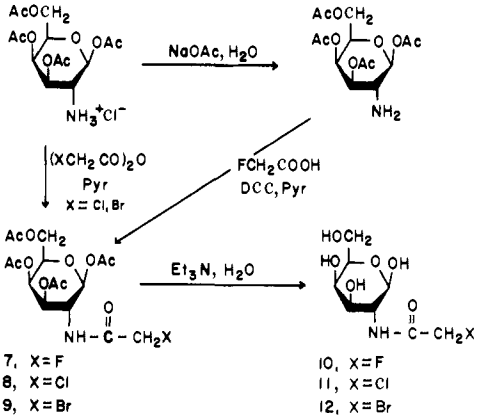
Table I. Chemical Properties of 2-Deoxy-2-(haloacetamido)-D-hexoses

compd	mp, °C found	mp, °C lit.	$[\alpha]^{25}_D$, deg found	$[\alpha]^{25}_D$, deg lit.	yield, %[a]	formula	analyses
1	186-187	185,[b] 176-179[c]	-6.5 (cl)	-1.2,[b] -5.4[c] (cl)	66	$C_{16}H_{22}NO_{10}F$	
2	169-169.5	165-166[d]	+3.9 (cl)		85	$C_{16}H_{22}NO_{10}Cl$	Cl
3	158.5-159	158[e]	+12.5 (cl)		65	$C_{16}H_{22}NO_{10}Br$	Br
4	172-173	161-163,[b] 189-192[f]		+23,[b] +31[f] (H_2O)	32	$C_8H_{14}NO_6F$	C, H, N, F
5	165-166.5	165-177[f]	+21 (H_2O)	+25[f] (H_2O)	43	$C_8H_{14}NO_6Cl$	C, H, N, Cl
6	138.5-141	147-150,[g] 153-154[h]	+22.5 (H_2O)	+27[h] (H_2O)	39	$C_8H_{14}NO_6Br$	Br
7	200-201		-9.4 (cl)		81	$C_{16}H_{22}NO_{10}F$	C, H, N, F
8	168-169		+1.2 (cl)		82	$C_{16}H_{22}NO_{10}Cl$	C, H, N, Cl
9	145-146		+36.3 (cl)		45	$C_{16}H_{22}NO_{10}Br$	C, H, N, Br
10	153-155		+55.5 (H_2O)		48	$C_8H_{14}NO_6F$	C, H, N, F
11	161.5-163		+44.6 (H_2O)		49	$C_8H_{14}NO_6Cl$	Cl
12	145-147	104-110[g]	+33.2 (H_2O)		25	$C_8H_{14}NO_6Br$	Br

[a] Yields reported refer to the highest purity recrystallized material obtained and are based on 1,3,4,6-tetra-*O*-acetyl-2-amino-2-deoxy-β-D-hexose as starting material. [b] See ref 6. [c] See ref 16. [d] See ref 20. [e] See ref 15. [f] See ref 17. [g] See ref 18. [h] See ref 19.

Scheme II



Bhat[5] was adapted to produce 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-(chloroacetamido)- and 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-(bromoacetamido)-β-D-hexoses [GlcNCl(Ac)$_5$, **2**; GalNCl(Ac)$_5$, **8**; GlcNBr(Ac)$_5$, **3**; and GalNBr(Ac)$_5$, **9**] by reaction of the appropriate haloacetylanhydride with 1,3,4,6-tetra-*O*-acetyl-2-amino-2-deoxy-β-D-hexose hydrochloride (Schemes I and II). The method of Dwek et al.[6] was used to prepare 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-(fluoroacetamido)-β-D-glucose [GlcNF(Ac)$_5$, **1**] and adapted to prepare the galactose analogue GalNF(Ac)$_5$ (**7**). The reaction utilized the dicyclohexylcarbodiimide-activated condensation of fluoroacetic acid with 1,3,4,6-tetra-*O*-acetyl-2-amino-2-deoxy-β-D-hexose. Table I summarizes the synthesized compounds and their characterization.

NMR spectral characterization of the tetra-O-acetylated halo analogues in both the gluco and galacto series indicated that in all cases the acetylated analogues were in the β configuration. This assignment is based on the absorption peaks for the anomeric proton which appear as a doublet between δ 5.83 and 5.95 with a coupling constant ($J_{1,2}$ = 8-9 Hz) characteristic of axial orientation as established by Horton[7] for acetylated derivatives of 2-deoxy-2-amino-D-glucopyranoses.

Results and Discussion

Patterns of in Vivo Toxicity. Comparison of in vivo effects of the 2-deoxy-2-(haloacetamido)-D-hexoses in BDF$_1$ mice (Table II) shows two important features. (a) Tetra-O-acetylated derivatives of both the glucose and galactose series were markedly more toxic than the free sugars in the case of the chloroacetamido and bromoacetamido analogues, with the increased toxicity being two- to threefold for the chloroacetamido compounds [GlcNCl(Ac)$_5$ vs. GlcNClAc and GalNCl(Ac)$_5$ vs. GalNClAc] and eight- to tenfold for the bromoacetamido compounds [GlcNBr(Ac)$_5$ vs. GlcNBrAc and GalNBr(Ac)$_5$ vs. GalNBrAc]. Toxicity in the case of the fluoroacetamido analogues was not affected in either series by the presence or absence of *O*-acetyl groups [GlcNF(Ac)$_5$ vs. GlcNFAc and GalNF(Ac)$_5$ vs. GalNFAc]. This pattern suggests that the chloroacetamido and bromoacetamido analogues exert their toxic effects as lipophilic alkylating agents, whereas the fluoroacetamido analogues do not depend on enhanced lipophilicity to express their biological actions. A similar pattern was also noted in our studies of fluoro, chloro, and bromo derivatives of esters of hydropropan-2-one.[8] (b) Toxicity of the chloroacetamido and bromoacetamido derivatives was independent of the nature of the parent sugar, since both the glucose and galactose analogues exhibited similar behavior [GlcNCl(Ac)$_5$ vs. GalNCl(Ac)$_5$; GlcNClAc vs. GalNClAc; GlcNBr(Ac)$_5$ vs. GalNBr(Ac)$_5$; and GlcNBrAc vs. GalNBrAc]. This finding is consistent with the hypothesis that these analogues exert their effects in vivo as nonspecific alkylating agents. In contrast, the fluoroacetamidoglucose derivative either as the free sugar (GlcNFAc vs. GalNFAc) or as the peracetate [GlcNF(Ac)$_5$ vs. GalNF(Ac)$_5$] was four- to fivefold more toxic than the corresponding galactose analogue. The specificity of the in vivo response to the toxicity of the fluoroacetamido

Table II. Effects of 2-Deoxy-2-(haloacetamido)-D-hexoses on BDF$_1$ Mice and on Cultured Friend Virus Induced Erythroleukemia Cells

compd	LD_{50},[a] mmol/kg	IC_{50},[b] μM
GlcNF(Ac)$_5$ (1)	0.17	60
GlcNFAc (4)	0.18	1000
GlcNCl(Ac)$_5$ (2)	0.94	8
GlcNClAc (5)	2.0	400
GlcNBr(Ac)$_5$ (3)	0.21	3
GlcNBrAc (6)	>2.4	ND[d]
GalNF(Ac)$_5$ (7)	0.98	60
GalNFAc (10)	0.74	ND
GalNCl(Ac)$_5$ (8)	0.67	15
GalNClAc (11)	1.5	ND
GalNBr(Ac)$_5$ (9)	0.22	4
GalNBrAc (12)	1.7	ND
GlcN(Ac)$_5$[c]	ND	400
chloroacetamide	ND	200
fluoroacetic acid[e]	0.1	ND

[a] Single dosage (ip) that killed 50% of the animals. [b] Concentration that inhibited cell multiplication of log-phase erythroleukemia cells by 50% after 3 days of continuous exposure, as compared to vehicle-treated control cells. [c] GlcN(Ac)$_5$ = 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-acetamido-β-D-glucose. [d] ND = not determined. [e] See ref 21.

analogues indicates that specific transport and/or specific metabolic events are required to convert the fluoroacetamido derivatives into toxic metabolites. GlcNFAc is presumably metabolized as an analogue of 2-deoxy-2-acetamido-β-D-glucose (GlcNAc) to generate fluoroacetate as a toxic metabolite. A hypothermic response in treated animals and the millimolar levels of GlcNFAc and its tetra-*O*-acetate for toxicity, as well as the absence of these effects at comparable doses of the galactose analogues, are consistent with this hypothesis, since 2-deoxy-2-acetamido-β-D-galactose (GalNAc) does not serve as a readily metabolizable exogenous carbohydrate source.

Cytotoxicity in Cell Culture. The proliferative capacity of Friend murine erythroleukemia cells in log-phase suspension culture was inhibited by relatively low concentrations of the tetra-*O*-acetates of the chloroacetamido and bromoacetamido analogues of the hexosamines without distinction between the glucose and galactose series [Table II, $GlcNCl(Ac)_5$, $GlcNBr(Ac)_5$, $GalNCl(Ac)_5$, and $GalNBr(Ac)_5$]. The bromoacetamido derivatives were slightly more cytotoxic than the chloroacetamido analogues. Again, as with in vivo toxicity, the analogue with free hydroxyl groups was much less cytotoxic in culture than was the corresponding tetra-*O*-acetate [$GlcNCl(Ac)_5$ vs. GlcNClAc and $GlcNF(Ac)_5$ vs. GlcNFAc]. In addition, the chloroacetamido analogue of GlcNAc (**5**) was no more cytotoxic than 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-acetamido-β-D-glucose or chloroacetamide. Thus, the marked cytotoxic effect of $GlcNCl(Ac)_5$ (**2**) appears to depend upon both the alkylating ability of the α-chloroacetamide and the enhanced lipophilicity conferred by the tetra-O-acetylated sugar moiety.

Effects of Analogues on Induction of Hemoglobin Synthesis. None of the carbohydrate analogues examined (**1–5** and **7–9**) when tested at their respective IC_{50} values (Table II) were able to promote erythroid differentiation of Friend leukemia cells as measured by induction of hemoglobin synthesis. GlcNFAc (**4**), under conditions that were totally noncytostatic, decreased the degree of differentiation induced by 4.5 mM bis(acetyl)diaminopentane (82.2 ± 2.4% benzidine-positive cells in the absence of GlcNFAc; 69.5 ± 1.7% in the presence of 1 mM GlcNFAc). A similar level of inhibition of induction by bis(acetyl)-diaminopentane was produced by 4 μM $GalNBr(Ac)_5$ (**9**), and a very strong inhibition (to 24.0 ± 0.6% benzidine-positive cells) was obtained with 0.4 mM GlcNClAc (**5**); in both of these cases the combined effects of carbohydrate analogue and inducing agent produced from 83 to 90% cytostasis.

Cytotoxicity in Vivo. In spite of the marked cytotoxic effects of several of the hexosacetamido derivatives in culture (Table II), none of the analogues produced a significant increase in the survival time of DBA/2 mice implanted intraperitoneally with 10^6 cultured Friend erythroleukemia cells, when drug treatments were administered intraperitoneally to the limit of toxicity of each agent on days 1, 2, and 3 after tumor transplantation. This neoplasm is relatively resistant to chemotherapeutic treatment, however, as demonstrated by our finding that very highly cytotoxic drugs, including methotrexate, daunorubicin, arabinosylcytosine, 5-fluorouracil, and 6-mercaptopurine, which have IC_{50} values with Friend cells in culture ranging from 0.02 to 0.2 μM, had no significant effect against the Friend erythroleukemia in vivo under the conditions employed above.

Experimental Section

General. Melting points were determined with a Büchi Model M-50 melting point apparatus and are uncorrected. IR spectra were recorded on a Beckman IR-33 spectrophotometer and NMR data on a Varian Associates A-60 spectrometer. Spectral data on all compounds were consistent with the proposed structures. Microanalyses were obtained from Galbraith Analytical Laboratories of Knoxville, Tenn. Halogen analyses (Cl and Br) were determined in this laboratory with an Amico-Cotlove chloride (bromide) titrator. For some previously reported compounds and for some free sugars derived directly from tetra-O-acetylated sugars, only halogen analyses were obtained. Melting points, optical rotations, percentage yields, and analytical results are given in Table I. TLC was carried out on cellulose sheets using BuOH–EtOH–saturating H_2O (4:1:5 v/v) as the developing solvent; compounds were visualized by spraying with a fresh solution of silver nitrate in methanolic sodium hydroxide–ammonium hydroxide. All of the haloacetamido derivatives of the free sugars gave R_f values of 0.45 in this system.

Biological. Toxicities (LD_{50} values) were determined by the intraperitoneal administration of single doses of each agent to 18–23-g BDF_1 mice (DBA/2J males × C57Bl/6 females), according to the method of Weil.[9] Emulsions of water-insoluble compounds were prepared with a glass homogenizer in sterile 0.85% NaCl after addition of Triton X-100 detergent to a final concentration of approximately 5%. Cells employed in this work were Friend murine virus induced leukemia cells of DBA/2J origin.[10] These cells were maintained and grown in suspension culture at 37 °C in a 10% CO_2 humidified atmosphere by once weekly passage of 10^5 cells/mL in Dulbecco's modified Eagle's medium supplemented with 10% fetal calf serum, 100 units/mL of penicillin, and 100 μg/mL of streptomycin. Drug cytotoxicity and induction of erythroid differentiation in culture were determined with exponentially growing cells inoculated in culture at a level of 10^5 cells/mL. Each compound was tested at various concentrations in order to determine IC_{50} levels. Control cultures were incubated with either no drug, a known antiproliferative agent, or a potent inducer of differentiation, bis(acetyl)diaminopentane.[11] Water-insoluble agents were dissolved in ethanol. The final ethanol concentration in the cultures did not exceed 0.125% and had no detectable effect on either cell proliferation or differentiation. After 3 days of incubation, cell numbers were determined using a Coulter counter. Determination of induction of erythroid cell differentiation was carried out by measuring the proportion of hemoglobin-containing cells using a benzidine peroxide stain as described by Orkin et al.[12]

Materials. D(+)-Glucosamine hydrochloride and D(+)-galactosamine hydrochloride were purchased from Sigma Chemical Co.; chloroaceticanhydride from Eastman Chemical Company; bromoaceticanhydride from Sapon Laboratories; and fluoroacetic acid from ICN. 1,3,4,6-Tetra-*O*-acetyl-2-amino-2-deoxy-β-D-glucose hydrochloride was prepared by the method of Bergman and Zervas,[13] and 1,3,4,6-tetra-*O*-acetyl-2-amino-2-deoxy-β-D-galactose hydrochloride was prepared according to Kim and Davidson.[14]

Syntheses. **1,3,4,6-Tetra-*O*-acetyl-2-deoxy-2-(fluoroacetamido)-β-D-glucose [$GlcNF(Ac)_5$]** (**1**) was prepared by the method of Dwek et al.[6] and recrystallized from ethanol: NMR ($CDCl_3$) δ 5.95 (d, 1 H-1, J_{HH} = 9 Hz), 4.8 (d, 2 H, FCH_2, J_{HF} = 48 Hz), 2.18–2.05 (overlapping q, 12 H, $4CH_3CO$).

1,3,4,6-Tetra-*O*-acetyl-2-deoxy-2-(fluoroacetamido)-β-D-galactose [$GalNF(Ac)_5$] (**7**) was prepared by an adaptation of the method of Dwek et al.[6] Tetra-*O*-acetyl-2-amino-2-deoxy-β-D-galactose (1.5 g, 4.3 mmol) was dissolved in a solution of $CHCl_3$ (20 mL) and dry pyridine (3.2 mL) at 2 °C. DCC (0.8 g, 4.3 mmol) and FCH_2COOH (0.8 mL) were added sequentially, and the mixture was stirred in the cold for 18 h. The mixture was filtered, and the filtrate was extracted with H_2O (2 × 40 mL), 1 N HCl (2 × 40 mL), and H_2O (2 × 40 mL) and dried (Na_2SO_4). The $CHCl_3$ was reduced to a few milliliters, and crystallization was induced by adding cold Et_2O. The product (**7**) was recrystallized from EtOH: NMR ($CDCl_3$) δ 5.9 (d, 1 H-1, J_{HH} = 8.5 Hz), 4.75 (d, 2 H, FCH_2, J_{HF} = 48 Hz), 2.2–2.0 (d of d, 12 H, $4CH_3CO$).

1,3,4,6-Tetra-*O*-acetyl-2-deoxy-2-(chloroacetamido)-β-D-glucose [$GlcNCl(Ac)_5$] (2). Tetra-*O*-acetyl-2-amino-2-deoxy-β-D-glucose (6.0 g, 15.6 mmol) was suspended in a cold solution of CH_2Cl_2 (66 mL) and pyridine (6.6 mL). Chloroaceticanhydride (5.4 g, 31.3 mmol) was added with vigorous stirring. The mixture was stirred in an ice bath for 15 min and then at room temperature

for 15 min. The solution was extracted with ice–water (2 × 66 mL) and dried (Na_2SO_4). The CH_2Cl_2 was flash-evaporated and the residue was triturated in cold Et_2O. The white solid (**2**) was recrystallized from EtOH: NMR ($CDCl_3$) δ 5.83 (d, H-1, J_{HH} = 9 Hz), 4.0 (s, $ClCH_2$), 2.1–2.03 (overlapping q, $4CH_3CO$).

1,3,4,6-Tetra-*O*-acetyl-2-deoxy-2-(chloroacetamido)-β-D-galactose [GalNCl(Ac)$_5$] (8) was prepared from tetra-*O*-acetyl-2-amino-2-deoxy-β-D-galactose as described for **2**: NMR ($CDCl_3$) δ 5.95 (d, H-1, J_{HH} = 9 Hz), 4.05 (s, $ClCH_2$), 2.2–2.05 (d of d, $4CH_3CO$).

1,3,4,6-Tetra-*O*-acetyl-2-deoxy-2-(bromoacetamido)-β-D-glucose [GlcNBr(Ac)$_5$] (3) and 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-(bromoacetamido)-β-D-galactose [GalNBr(Ac)$_5$] (9) were prepared as detailed for the chloroacetamido derivatives from the appropriate tetra-*O*-acetyl-2-amino-2-deoxy-β-D-hexose and bromoaceticanhydride: NMR ($CDCl_3$) for GlcNBr(Ac)$_5$ δ 5.85 (d, 1 H-1, J_{HH} = 8.5 Hz), 3.8 (s, 2 H, $BrCH_2$), 2.18–2.10 (br d, 12 H, $4CH_3CO$), and for GalNBr(Ac)$_5$ δ 5.95 (d, 1 H-1, J_{HF} = 8.5 Hz), 3.8 (s, 2 H, $BrCH_2$), 2.18–2.05 (d of d, 12 H, $4CH_3CO$).

2-Deoxy-2-(fluoroacetamido)-D-glucose (GlcNFAc) (4). Compound 1 (1.9 g, 4.7 mmol) was added to a solution of 80 mL of MeOH–Et_3N–H_2O (2:1:1 v/v) at 4 °C. After 40 h, the cold solution was flash evaporated to one-half of its original volume. Water (40 mL) was added to the residue and the solution was brought to pH 6 with Amberlite IR-120 (H^+). The resin was removed by filtration and the aqueous solution was flash-evaporated. The viscous residue was dissolved in chromatography solvent (BuOH–EtOH–saturating H_2O, 4:1:5 v/v) and fractionated on a microcrystalline cellulose column (2.5 × 64 cm). Fractions of approximately 15 mL were collected and those fractions containing the product were located by the R_f value (0.45) on cellulose sheets and flash-evaporated to dryness. The residue was crystallized from ethanol.

2-Deoxy-2-(fluoroacetamido)-D-galactose (GalNFAc) (10) was prepared by de-O-acetylation of **7**, as described for compound 4 above.

2-Deoxy-2-(chloroacetamido)-D-glucose (GlcNClAc) (5) was prepared by de-O-acetylation of **2**.

2-Deoxy-2-(chloroacetamido)-D-galactose (GalNClAc) (11) was prepared by de-O-acetylation of compound **8**.

2-Deoxy-2-(bromoacetamido)-D-glucose (GlcNBrAc) (6). Compound **3** (3.0 g, 6.4 mmol) was added to a solution of 80 mL of MeOH–Et_3N–H_2O (2:1:1 v/v) at −6 °C. The reaction mixture was stirred vigorously for 5 h. The resulting material was processed and crystallized as described for compound 4.

2-Deoxy-2-(bromoacetamido)-D-galactose (GalNBrAc) (12) was prepared by de-O-acetylation of **9**, as described for compound **6**.

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References and Notes

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Neuroleptics Related to Butaclamol. An Investigation of the Effects of Chlorine Substituents on the Aromatic Rings

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The synthesis of analogues of the antipsychotic drug butaclamol bearing chloro substituents on the benzene rings is described. On the basis of a perceived topographical similarity of a putative chlorophenylethylamine pharmacophore present in these analogues and in VUFB-10032 and doclothepin, agents related to octoclothepin which do not induce catalepsy, they have been tested for "noncataleptic" neuroleptic activity. None of the butaclamol analogues exhibit this type of activity. Depending on the position of the chlorine, the analogues either retained butaclamol-like activity or were inactive.

The demonstration that clozapine (I) is a clinically effective antipsychotic agent which does not cause extrapyramidal side effects[1] has stimulated a search for similar types of drugs. The observation that clozapine causes agranulocytosis[2] has intensified the search for "clozapine-like" agents which would be devoid of this toxic manifestation.

Clozapine differs strikingly in its biochemical and psychopharmacological profile[3] from the classical neuroleptics such as fluphenazine and haloperidol. Clozapine's

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