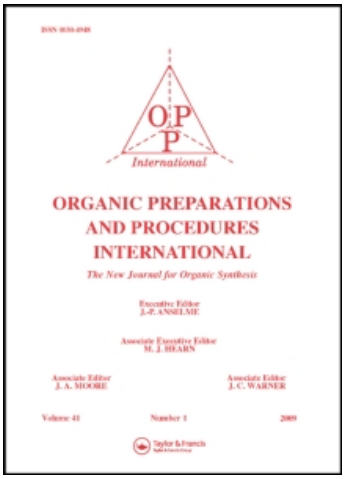

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PREPARATION OF 1-ARYL-3-(TETRA-0-ACETYL-2-DEOXY-D-GLUCOS-2-YL)UREAS

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PREPARATION OF 1-ARYL-3-(TETRA-O-ACETYL-2-DEOXY-D-GLUCOS-2-YL)UREAS

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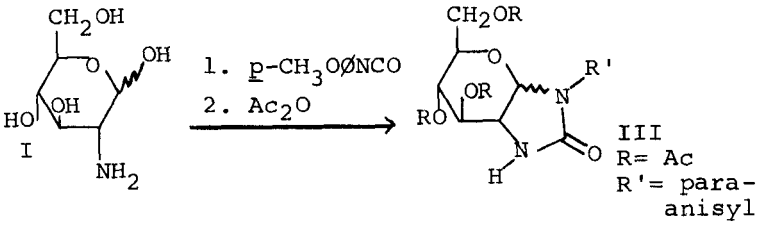
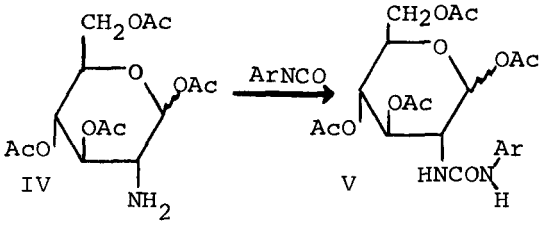
Streptozotocin, a glucosourea antibiotic, and its synthetic derivatives are of considerable considerable contemporary interest for their anti-tumor activity.[2-4] This interest, however, is tempered by the inherent toxicity to pancreatic beta cells by which streptozotocin can induce permanent frank diabetes.[3] A tetra-O-acetylated analog known as GCNU has recently been reported to display the anti-tumor behavior without the side effect of diabetogenicity.[5] Furthermore, we have discovered that several other O-acetylated N-aryl non-nitrosated streptozotocin derivatives retain the hyperglycemic behavior without the tumor cytotoxic effect.[6] Our interest in candidate agents which can be radiolabeled for pancreatic imaging or function measurement[7,8] and the potential interest by other researchers in pancreatic physiology in having compounds capable of effecting non-permanent hyperglycemia, prompts us to report our syntheses of these analogs.

An attempted direct synthesis of (Vb) by condensation of 2-amino-2-deoxy-D-glucose (I) with the aryl isocyanate (II) followed by in situ acetylation with acetic anhydride gave the imidazolidone (III, R= Ac, R'= p-anisyl). A similar imidazolidone (III, R=H, R'=CH_3), was obtained in the denitrosation of streptozotocin with sulfamic acid and on the attempted deacetylation of 1-methyl-3-(tetra-O-acetyl-2-deoxy-D-glucos-2-yl) urea with methanolic ammonia. Thus ring closures between urea

moieties at C-2 of a sugar and the anomeric carbon appear to have literature precedent and to preclude direct formation of (V) from (I) via the route indicated.



However, the desired N-aryl urea sugars (V) were obtained through the intermediacy of 1,3,4,6-tetra-0-acetyl-2-amino-2-deoxy-D-glucopyranose (IV) and the aryl isocyanates. (See Table 1) The requisite (IV) was

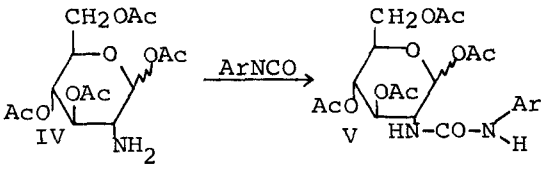


obtained by the method of Bergmann and Zervas[10]. Two aminophenyl urea sugars (Vg and Vh) were prepared by reduction of the corresponding nitro compounds (Ve,Vf). Nitrosation, at least in the case of the p-methoxy analog (Vb), does not occur on a urea nitrogen but upon the number 3 ring carbon to yield (Vi). Compounds (Va-c) were evaluated in a rat glucose tolerance assay and were found to display transient hyperglycemia.[6]

EXPERIMENTAL

3,4,6-(Tri-0-acetyl-2-deoxy-D-glucopyrano)[1,2-d] - [3-(4-methoxyphenyl)] imidazolidine-2-one (III). A solution of 2-amino-2-deoxy-D-glucose (1.0g, 5.58 mmol) in 10 ml pyridine was treated with 4-methoxyphenyl isocyanate (0.83 g, 5.58 mmol), stirred for 30 min at 25°C and then heated to 40°C for 1 hr. The yellow colored medium was cooled to 0°C and acetic anhydride (5.42 g, 53.09 mmol) was added dropwise over a period of 30 min.

TABLE 1
1-Aryl-3-(Tetra-O-acetyl-2-deoxy-D-glucos-2-yl) Ureas



Compd	Aryl[a]	Yield	mp. °C
Va	o-OCH_2CH_3	87	202-203
Vb	p-OCH_3	91	192-194
Vc	o-OCH_3	83	201-202
Vd	m-OCH_3	87	202-203
Ve	m-NO_2	88	198
Vf	p-NO_2	94	222 (decomp)
Vg	m-NH_2	87	200-201
Vh	p-NH_2	95	208-209
Vi	p-OCH_3-m-NO	63	160-162

	Analysis					
	Calcd			Found		
Compd	C	H	N	C	H	N
Va	54.11	5.92	5.49	54.07	5.90	5.34
Vb	53.22	5.68	5.64	53.19	5.72	5.56
Vc	53.22	5.68	5.64	53.15	5.70	5.46
Vd	53.22	5.68	5.64	53.48	5.70	5.60
Ve	49.32	4.93	8.22	49.28	5.00	8.03
Vf	49.32	4.93	8.22	49.19	4.97	7.96
Vg	52.39	5.65	8.73	52.21	5.75	8.45
Vh	52.39	5.65	8.73	52.26	5.83	8.54
Vi	(see text)					

The solution was stirred at 0°C for 1 hr then warmed slowly to 25°C with stirring continuing for 16 hr. After cooling to 0°, 100 ml of H_2O were

added. The white precipitate which resulted was collected and recrystallized from anhydrous ethanol yielding 0.77 g (31.5%) of III as white needles: mp 192-4°C; ir (nujol) 3380 (NH), 1750, 1725 (ester C=O), 1665 and 1640 cm^{-1} (imidazole C=O); nmr (acetone-d_6) δ 2.05 (m, 9H, CH_3-C=O), 3.80 (s, 3H, O-CH_3), 4.20 (m, 4H, O-CH_2, O-CH, N-CH), 5.25 (m, 2H, O-CH), 6.95 (d, 2H, Ar-H) and 7.4 (d, 2H, Ar-H).

Anal. Calcd for $C_{22}H_{24}N_2O_9$: C, 55.04; H, 5.54; N, 6.42

Found: C, 54.89; H, 5.79; N, 6.18.

1-Aryl-3-(tetra-O-Acetyl-2-deoxy-D-glucos-2-yl) Ureas (Va-f)(General Procedure) A solution of 2.0 g (5.2 mmol) of 1,3,4,6-tetra-O-acetyl-2-amino-2-deoxy-D-glucopyranose hydrochloride (IV) and 1.47 g (11.99 mmol) of sodium acetate in 65 ml of water was extracted with 3 x 30 ml portions of $CHCl_3$, dried with $MgSO_4$ and filtered. The clear filtrate was treated with 5.4 mmol of the corresponding aryl isocyanate and the resulting solution was refluxed for 15 min. Removal of the $CHCl_3$ in vacuo left white solids which were recrystallized from 1:1 EtOH:H_2O to analytical purity. Yields and physical properties are reported on Table I.

1-(3-Aminophenyl) or 1-(4-aminophenyl)-3-(tetra-O-acetyl-2-deoxy-D-glucos-2-yl) Urea (Vg-Vh) A solution of 1.0 g of the corresponding nitro compound (Ve & Vf) in 150 ml of methanol containing 0.2 g of 10% Pd on carbon was shaken in a Parr apparatus at 50 psi for 20 hrs. Removal of the catalyst and evaporation of the residue gave the anilino sugars (Vg and Vh) in 87% and 94% yield respectively. These were recrystallized from 1:1 petroleum ether (20°-40°) and ethyl ether to give the analytical samples (see Table).

1-(4-Methoxy-3-nitrosophenyl)-3-(tetra-O-acetyl-2-deoxy-D-glucos-2-yl) Urea (Vi) A solution of 1-(4-methoxyphenyl) -3-(tetra-O-acetyl-2-deoxy-D-glucos-2-yl)urea (Vb) (0.5 g, 1.0 mmol) in 10 ml HOAc at 15°C was

treated with $NaNO_2$ (0.10 g, 1.5 mmol, in 1.0 ml H_2O). One ml of conc HCl was added to the yellow colored medium, causing a bright yellow color to form. Stirring was continued for 90 min at 25°C then 100 ml of cold H_2O was added. After cooling to 0°, the yellow precipitate was collected and recrystallized from EtOH/H_2O yielding 0.33 g (62.9%)of (Vi) as small yellow needles: mp 160-162°C; ir (nujol) 3320, 3280 (NH), 1750 (sh), 1740 (ester C=O) and 1640 cm^{-1} (urea C=O), nmr (acetone-d_6) δ 2.00 (m, 12H, CH_3-C=O), 3.88 (s, 3H, O-CH_3) 4.12 (m, 4H, O-CH_2 N-CH, O-CH), 5.20 (m, 2H, 2 O-CH), 5.90 (d, 1H, anomeric H), 6.90 (s [broad], 1H, NH), 7.40 (m, 2H, Ar-H), 8.32 (d, 1H, Ar-H) and 9.18 ppm (s[broad], 1H, NH).

Anal. Calcd for $C_{22}H_{27}N_3O_{12}\cdot H_2O$: C, 48.62; N, 5.37; N, 7.73.

Found: C, 48.35; H, 5.02; N, 7.73.

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