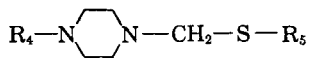
TABLE II

ARYLTHIOMETHYLPIPERAZINES



R_4	R_5	B.P. or M.P.[a]	Yield, %	n_D^{25}	Analyses[b] Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
C_6H_5—	C_2H_5—	79.8–81.9	64		66.06	65.95	8.53	8.42
o-CH_3—C_6H_4—	C_2H_5—	158–158.5(0.40)	52	1.5617	67.16	67.40	8.86	9.29
m-CH_3—C_6H_4—	C_2H_5—	172–174(0.30)	41	1.5723	67.16	67.50	8.86	8.85
p-CH_3—C_6H_4—	C_2H_5—	29.0–30.5	52		67.16	67.39	8.86	8.74
o-Cl—C_6H_4—	C_2H_5—	158–158.5(0.30)	57		57.65	57.70	7.07	6.65
m-Cl—C_6H_4—	C_2H_5—	185.5–186(0.50)	45	1.5879	57.65	57.80	7.04	6.65
p-Cl—C_6H_4—	C_2H_5—	68.7–71.8	42		57.65	57.65	7.04	7.14
o-CH_3O—C_6H_4—	C_2H_5—	180–180.5(1.30)	62	1.5704	63.12	63.30	8.32	8.17
CH_3—	C_2H_5—	76.0–78(0.70)	64	1.5008	55.12	55.01	10.41	10.39
C_6H_5—	n-C_4H_9—	179–180(0.70)	58	1.5637	68.13	68.19	9.15	9.11
o-CH_3—C_6H_4—	n-C_4H_9—	160–160.5(0.17)	64	1.5501	69.53	69.31	8.75	9.18
m-CH_3—C_6H_4—	n-C_4H_9—	167.5–168(0.20)	46	1.5590	69.53	69.21	8.75	9.01
p-CH_3—C_6H_4—	n-C_4H_9—	28.3–30.6	54		69.53	69.31	8.75	9.04
o-Cl—C_6H_4—	n-C_4H_9—	178–178.5(0.15)	48	1.5634	60.27	60.44	7.75	7.68
m-Cl—C_6H_4—	n-C_4H_9—	179.5–180(0.15)	72	1.5721	60.27	60.11	7.75	7.79
p-Cl-C_6H_4—	n-C_4H_9—	47.2–51.1	47		60.27	60.09	7.75	7.76
o-CH_3O—C_6H_4—	n-C_4H_9—	180–180.5(0.20)	57	1.5583	65.28	65.21	8.90	8.65
CH_3—	n-C_4H_9—	89–90(0.18)	62	1.4933	59.34	59.30	10.96	10.79
C_6H_5—	C_6H_5—	75.8–78.3	76		71.80	71.51	7.09	6.94
o-CH_3—C_6H_4—	C_6H_5—	55.6–57.7	49		72.45	72.40	7.43	7.14
m-CH_3—C_6H_4—	C_6H_5—	84.9–87.1	82		72.45	72.20	7.43	7.17
p-CH_3—C_6H_4—	C_6H_5—	138.9–141.4	81		72.45	72.25	7.43	7.49
o-Cl-C_6H_4—	C_6H_5—	52.6–56.5	63		64.03	64.21	6.01	6.06
m-Cl-C_6H_4—	C_6H_5—	101–103.1	79		64.03	64.10	6.01	5.65
p-Cl-C_6H_4—	C_6H_5—	83.9–85.0	75		64.03	64.00	6.01	6.26
o-CH_3O—C_6H_4—	C_6H_5—	67.2–71.1	50		68.75	68.70	7.06	7.13
CH_3—	C_6H_5—	112–113(0.15)	48	1.5734	64.80	64.91	8.16	8.02
C_6H_5—	p-CH_3—C_6H_4—	100–101.1	85		72.45	72.45	7.43	7.46
o-CH_3—C_6H_4—	p-CH_3—C_6H_4—	56.6–58.7	73		73.02	73.00	7.74	7.54
m-CH_3—C_6H_4—	p-CH_3—C_6H_4—	63–64.5	72		73.02	73.11	7.74	7.89
p-CH_3—C_6H_4—	p-CH_3—C_6H_4—	138.4–139.9	68		73.02	72.65	7.74	7.54
o-Cl—C_6H_4—	p-CH_3—C_6H_4—	66.0–68.0	78		64.95	64.96	6.36	6.36
m-Cl—C_6H_4—	p-CH_3—C_6H_4—	67.7–69.8	81		64.95	64.98	6.36	6.53
p-Cl—C_6H_4—	p-CH_3—C_6H_4—	103.1–105.2	81		64.95	65.39	6.36	6.25
o-CH_3O—C_6H_4—	p-CH_3—C_6H_4—	48.5–51.6	69		69.45	69.30	7.36	7.42
CH_3—	p-CH_3—C_6H_4—	33.4–36.5	36		66.06	66.15	8.53	8.52

[a, b] The same as in Table I.

amount of the piperazine (previously melted if necessary), causing in some cases a precipitation of an addition product. To this mixture was added an equivalent amount of 37% formaldehyde, and the mixture was refluxed with stirring for 3 hr. After cooling to room temperature, the product was extracted with ether. The ether extracts were combined and dried over anhydrous potassium carbonate. The ethereal solution was filtered and then passed over a column of aluminum oxide (Woelm, neutral, activity grade 1 for chromatography). The ether was removed at reduced pressure. If the residue crystallized, it was further purified by recrystallization from anhydrous ether, methanol, or ethanol. The oils were distilled at reduced pressures.

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Some Glycosyl Derivatives of Piperazine

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Piperazine derivatives are of current interest because they display a diversity of pharmacological properties,[3] and the biological importance of such glycosylamines as the nucleosides has long been

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(3) *The Dispensatory of the United States of America*, A. Osol and G. E. Farrar, Jr., ed., Lippincott Co., Philadelphia, 1955, p. 1807; M. Harfenist and E. Magnien, *J. Am. Chem. Soc.*, 80, 6257 (1958) and earlier papers.

known.[4,5] This work was undertaken to ascertain the nature of the products formed when aldoses react with piperazine.

Glycosylamines have been prepared by numerous methods, direct condensation of the sugar and base (such as primary aromatic amines or piperidine) alcoholic solution being the most convenient.[5] Reaction of the base with an acetylated glycosyl halide[6,7] followed by de-acetylation[8] has the advantage of producing glycosylamines in which the ring size and anomeric configuration of the sugar are known,[9] but this method has limitations where secondary amines are employed since glycoseens may be formed.[10]

Both of these methods have been applied to the reaction of piperazine with various aldoses. Amorphous products were obtained from D-galactose, D-mannose, L-arabinose, and L-rhamnose whereas crystalline products were formed from D-glucose and D-xylose. Analytical data showed that di-β-glycosylpiperazines were formed from D-glucose, D-galactose, and D-xylose, each of which gave a crystalline derivative upon acetylation.

From paper chromatographic studies no evidence could be found for the formation of monosubstituted glycosyl derivatives of piperazine when the above *N,N'*-diglycosylpiperazines were hydrolyzed with dilute acid. When *N*-acetylpiperazine was used in place of piperazine and treated with one mole each of D-glucose, D-xylose, 2,3,4,6-tetra-*O*-acetyl-α-D-galactosyl bromide, a crystalline derivative was obtained only in the case of D-glucose. This compound, *N*-acetyl-*N'*-glucosylpiperazine, was hydrolyzed rapidly in aqueous solution, liberating glucose, despite the accompanying rise in *p*H.

The stability of the diglucosyl and dixylosyl derivatives of piperazine may be related to the symmetry and conformational character of these molecules in the β,β'-configuration. The greater ease of hydrolysis of the monoglucosyl monoacetyl compound may be due in part to loss of this symmetry, although the lower basicity may also be a contributing factor.

EXPERIMENTAL

Solvent systems used in paper (Whatman No. 1) chromatography were: (A) the upper phase of 1-butanol (40): ethanol (10):water (49):concentrated ammonia (1),[11] and (B) ethyl acetate (5):1-butanol (5):pyridine (10):water (6) Ninhydrin in acetone and *p*-anisidine hydrochloride in aqueous 1-butanol were used as spray reagents to reveal glycosylamines.

I. (a) *N,N'-Di-*D*-glucopyranosylpiperazine.* Anhydrous D-glucose (1 g.) was heated under reflux with piperazine (0.25 g., distilled from a mixture of the commercial hexahydrate and excess of solid potassium hydroxide) in absolute methanol (10 ml.) for 1 hr.[12] On cooling, a crystalline product separated. This was collected by filtration, washed with ethanol and with ether, and dried over calcium chloride, yielding *N,N'*-di-D-glucopyranosylpiperazine (1.2 g.) as colorless prisms, m.p. 180–181°, $R_{glucose}$ 0.6 in solvent (A).

Anal. Calcd. for $C_{16}H_{30}O_{10}N_2$: C, 46.82; H, 7.37; N, 6.83. Found: C, 46.70; H, 7.32; N, 6.87.

The product was not hygroscopic, gave a slightly alkaline reaction in water, and was insoluble in a wide range of organic solvents. In the presence of 2 equiv. of hydrochloric acid, $[\alpha]_D^{16}$ of an aqueous solution of the glycosylamine rose from +23° (5 min.) to +45° (equil., 35 min.). Extrapolation indicated a low negative value for the initial rotation.

(b) *Octa-O-acetyl-N,N'-di-*D*-glucopyranosylpiperazine. Method (i).* *N,N'*-Di-D-glucopyranosylpiperazine (0.3 g.) was shaken continuously with dry pyridine (50 ml.) and acetic anhydride (6 ml.) in a stoppered flask for 12 hr., at the end of which time practically all of the solid had dissolved. The solution was filtered and concentrated *in vacuo* at 40°. The residual solid was recovered by filtration, washed with water, drained (yield 90%), and recrystallized from a 1:1 mixture of ethanol and methanol to give the octaacetate as clusters of fine needles, m.p. 227°, $[\alpha]_D^{16}$ approx. 0° (pyridine, c = 0.3).

Anal. Calcd. for $C_{32}H_{46}O_{18}N_2$: C, 51.46; H, 6.21; N, 3.75. Found: C, 51.80; H, 5.94; N, 3.84.

Method (ii). Anhydrous piperazine (0.5 g.) was warmed with 2,3,4,6-tetra-*O*-acetyl-D-glucosyl bromide (4.72 g.) in sodium-dried benzene (30 ml.) containing silver oxide (or silver carbonate) (5 g.) and anhydrous calcium sulfate (1 g.) for 5 hr. The reaction mixture was cooled and filtered through a bed of cellulose powder, and the filtrate was evaporated to a small bulk and chromatographed on alumina (column dimensions 20 × 2.5 cm.) using benzene enriched with increasing amounts of ethyl acetate. After removal of the low-melting material that was eluted first the above octaacetate (0.24 g.) was recovered, m.p. and mixed m.p. [with the compound prepared by method (i)] 226°.

(c) *De-acetylation of octa-O-acetyl-N,N'-di-*D*-glucopyranosylpiperazine.* The octaacetate (0.10 g.) was dissolved in hot absolute methanol (100 ml.) and sodium (0.03 g.) was added to the cooled solution. After keeping for 3 hr., more sodium (0.03 g.) was added and the reaction was allowed to proceed for a further 16 hr. at room temperature. Upon nucleation of the solution with *N,N'*-di-D-glucopyranosylpiperazine and keeping for 2 days at room temperature the solution deposited the glycosylamine, m.p. and mixed m.p. 183–184°, in 80% yield.

(d) *N-Acetyl-N'-*D*-glucosylpiperazine.* Silver carbonate (0.5 g.) was added to a solution of mono-*N*-acetylpiperazine hydrochloride[13] (0.5 g.) in methanol. The mixture was stirred and warmed for 0.5 hr. and then filtered. Sufficient methanolic hydrogen chloride was added to remove any residual silver carbonate from solution and to render the solution slightly acid, after which the mixture was filtered. To the filtrate were added D-glucose (0.5 g.) and anhydrous calcium sulfate (2.0 g.) and the mixture was heated under reflux, samples being removed periodically and examined on

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paper chromatograms using solvent A. After 25 hr. about 10% of free glucose remained in solution, so a further quantity (0.75 g.) of the free base in methanol solution was added and heating was continued for 48 hr. A chromatogram then showed the presence of free base and the new product ($R_{glucose}$ 1.6) only. After filtering the mixture methanol was removed from the filtrate by distillation *in vacuo* and the residue was extracted with dry ether to remove excess of *N*-acetylpiperazine. The remaining glycoside was recrystallized from ethanol giving *N*-acetyl-*N'*-D-glucosylpiperazine (0.4 g.) as colorless prisms, m.p. 136–138°, raised to 146–147° by further recrystallization. The compound was not deacetylated on treatment with sodium dissolved in methanol.

Anal. Calcd. for $C_{12}H_{22}O_6N_2$: C, 49.65; H, 7.64; N, 9.65. Found: C, 48.6; H, 7.50; N, 9.20.

Measurement of $[\alpha]_D^{22}$ of this compound in water (c = 1.01) showed values of −4° (6 min.) rising to 0° (3 days), during which time the *p*H rose from 7.5 to 8.1. Free glucose was detected chromatographically 6 min. after preparation of the solution. On boiling an aqueous solution of the glycosylamine $[\alpha]_D^{22}$ rose to +25° (16 min.) at which time the *p*H was 9.3 and much free glucose (approx. 60%) was present.

Acetic anhydride (0.4 ml.) was added to a solution of *N*-acetyl-*N'*-D-glucosylpiperazine (0.022 g.) in pyridine (5 ml.) and the mixture was kept for 16 hr. at room temperature. Solvents were removed by distillation *in vacuo*, and the residual oil was triturated with cold ether; colorless prisms identical (m.p. and mixed m.p.) with the starting material were recovered. The experiment was repeated using the same quantities of material, which were heated under reflux for 0.5 hr. Recrystallization from ether of the product, isolated as before, gave *N*-acetyl-*N'*-D-glucosylpiperazine tetraacetate, m.p. 138–139°, depressed to 130° on admixture with the starting material.

II. (a) *N,N'-Di-D-galactosylpiperazine.* D-Galactose (1 g.) and anhydrous piperazine (0.5 g.) were heated under reflux in methanol (10 ml.) for 3 hr. The resulting clear solution was allowed to cool, and excess of ether was added. A yellowish amorphous precipitate, which proved to be extremely hygroscopic, was formed; fractional precipitation from a concentrated solution in methanol by the addition of ether gave a solid amorphous product ($R_{glucose}$ 0.9, streaking, in solvent A) which was chromatographically free from galactose.

Anal. Calcd. for $C_{16}H_{30}O_{10}N_2$: N, 6.83. Found: N, 6.66.

(b) *Octa-O-acetyl-N,N'-di-D-galactopyranosylpiperazine.* A mixture of anhydrous piperazine (0.5 g.), 2,3,4,6-tetra-*O*-acetyl-α-D-galactosyl bromide (4.7 g.), silver carbonate (3.0 g.), and anhydrous calcium sulfate (2.0 g.) was warmed in benzene (40 ml.) for 5 hr. The mixture was then cooled and filtered and the filtrate was evaporated to a dark sirup. Chromatography on alumina using benzene as eluting solvent gave the above octaacetate in 13% yield, m.p. 230°, $[\alpha]_D^{23}$ −10° (benzene, c = 1.09) after recrystallization from ethanol–petroleum ether (b.p. 40–60°).

Anal. Calcd. for $C_{32}H_{46}O_{18}N_2$: C, 51.46; H, 6.21; N, 3.75. Found: C, 51.6; H, 6.18; H, 3.82.

De-acetylation of a portion of the octaacetate with sodium in methanol gave the amorphous glycosylamine, chromatographically similar to the substance prepared by direct condensation of galactose with piperazine.

III. (a) *N,N'-Di-D-xylosylpiperazine.* D-Xylose (1 g.) was heated under reflux with anhydrous piperazine (0.5 g.) in anhydrous methanol (10 ml.) for 0.75 hr. Colorless crystals of *N,N'*-di-D-xylosylpiperazine separated on cooling. These were collected by filtration, washed with ethanol and ether, and recrystallized from ethanol; m.p. 145–146°, $[\alpha]_D^{24}$ −37° (pyridine, c = 0.48).

Anal. Calcd. for $C_{14}H_{26}O_8N_2$: C, 47.97; H, 7.48; N, 8.00. Found: C, 47.6; H, 7.26; N, 7.96.

Like the diglucosyl derivative, this compound was not hygroscopic and was sparingly soluble in ethanol. Paper chromatography of the compound could best be accomplished using solvent B, but even in this mixture there was a tendency to streak.

(b) *Hexa-O-acetyl-N,N'-di-D-xylosylpiperazine.* Acetic anhydride (5 ml.) was added to a solution of *N,N'*-di-D-xylosylpiperazine (0.1 g.) in pyridine (30 ml.) and the mixture was kept at room temperature for 12 hr. On evaporation of solvent *in vacuo* a crystalline mass (0.15 g.) was obtained which on recrystallization from ethanol gave the hexaacetate, m.p. 220–221°.

Anal. Calcd. for $C_{26}H_{38}O_{14}N_2$: C, 51.83; H, 6.36; N, 4.65. Found: C, 52.6; H, 6.75; N, 4.36.

IV. *Reaction of piperazine with other sugars.* Piperazine was heated for varying times with L-arabinose, D-mannose, and L-rhamnose in ethanol solution. In each instance evidence was obtained by paper chromatography (using solvent B) that condensation had occurred but crystalline products could not be isolated.

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N-(D-Glucosyl) and Related Derivatives of Some Arylethylamines, Including Histamine

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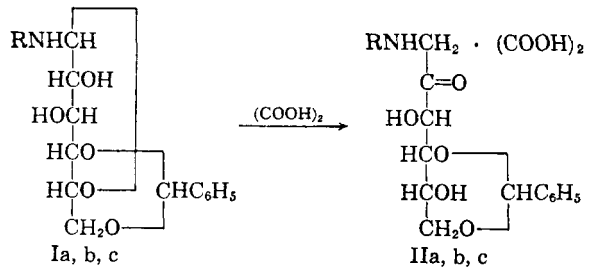
The discovery[1] that *N*-(4,6-*O*-benzylidene-D-glucosyl) derivatives of aliphatic amines undergo the Amadori rearrangement with uncommon ease suggested the extension of this reaction to the physiologically active arylethylamines.

This note reports the successful application of this sequence to the primary amines, histamine, phenethylamine, and *d*-α-methylphenethylamine (*d*-amphetamine). Reaction of these bases with 4,6-*O*-benzylidene-D-glucose[2] in methanol gave the *N*-(D-glucosyl) derivatives Ia,b,c in good yields



Ia, b, c IIa, b, c

a. R = 4-Imidazolylethyl
b. R = $C_6H_5CH_2CH_2$
c. R = *d*-$C_6H_5CH_2CH(CH_3)$

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