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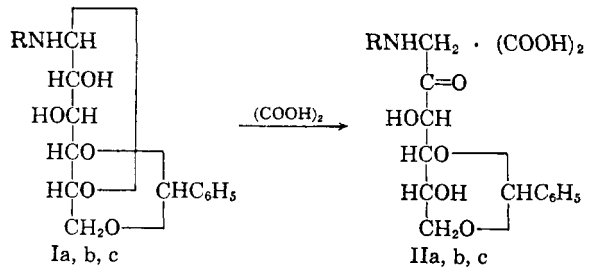
The discovery[1] that *N*-(4,6-*O*-benzylidene-D-glucosyl) derivatives of aliphatic amines undergo the Amadori rearrangement with uncommon ease suggested the extension of this reaction to the physiologically active arylethylamines.

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*-$C_6H_5CH_2CH(CH_3)$

(1) F. Micheel and A. Frowein, *Chem. Ber.*, 90, 1599 (1957).

(2) L. Zervas, *Ber.*, 64, 2289 (1931).

(80–90%). Further treatment with oxalic acid in methanol induced rapid rearrangement of Ia,b,c to the derivatives IIa,b,c, isolated as the oxalic acid salts. All three of these Amadori products II possessed characteristic reducing properties and showed ketonic carbonyl absorption in the infrared.

All attempts to achieve these reactions with the secondary amine *dl-N,α*-dimethylphenethylamine (deoxyephedrine) failed. Neither the stepwise nor the one-step approach to the D-fructose derivative II led to anything but recovery of starting materials.

Two reasons necessitate the assignment of structures Ia and IIa to the histamine derivatives. First, the markedly greater nucleophilic character of the side-chain nitrogen atom *vs.* the ring nitrogen atom is well known,[3] and second, both Ia and IIa, like histamine itself, give a positive Pauly diazo reaction[4] with diazotized sulfanilic acid. A free imino group in the imidazole ring is said to be one prerequisite for the occurrence of this reaction.[5]

Although the benzylidene groups of IIa and IIc were readily removable by mild acid hydrolysis,[1] the resulting D-fructose derivatives were not isolable in crystalline form, either as bases or as salts with a number of acids. Only amorphous hygroscopic products were obtained. However, their retention of characteristic reducing properties indicates that the essential structure survived.

Preliminary tests suggest that the characteristic physiological activities of these amines are severely attenuated by conversion to their *N*-(D-glycosyl) derivatives.

EXPERIMENTAL[6]

Histamine. A solution of 50.98 g. (0.166 mole) of histamine phosphate in 200 ml. of water was treated with a solution of 157.0 g. (0.498 mole) of barium hydroxide octahydrate in 700 ml. of water. The precipitated barium phosphate was filtered by suction and washed well with hot water. The combined filtrate and washings were concentrated under diminished pressure in a rotating evaporator. The residual mixture of solid and oil was extracted with ten 200-ml. portions of boiling chloroform. The combined extracts were filtered and concentrated on the steam bath; the last traces of solvent were removed under diminished pressure. The residual pale-yellow oil (15.4 g.; 84%) solidified slowly on cooling. It was suitable for use without further purification.

N-(4,5-O-Benzylidene-D-glucosyl)histamine (Ia). A solution of 15.4 g. of histamine in 20 ml. of warm (40–50°) methanol was added in one portion to a warm solution of 35 g. of 4,6-*O*-benzylidene-D-glucose[2] (m.p. 178–180°) in 100 ml. of dry methanol. After standing at room temperature for 3 hr., the crystallized product was collected at the suction filter and dried in a vacuum oven at 60°. The product Ia (45.6 g.; 89%), m.p. 109.5–111°, contained one molecule of methanol of crystallization and was analytically pure.

Anal. Calcd. for $C_{18}H_{23}N_3O_5 \cdot CH_3OH$: C, 58.00; H, 6.92; N, 10.68. Found: C, 57.73; H, 6.98; N, 10.61. $[\alpha]_D^{26}$ −63.2° (*c* 1.045 in pyridine). In alkaline solution, it reduced neither methylene blue nor 2,6-dichloroindophenol. With diazotized sulfanilic acid in the presence of excess sodium carbonate, it gave a deep-red color.

N-(4,6-O-Benzylidene-D-glucosyl)phenethylamine (Ib). When 9.68 g. (0.08 mole) of phenethylamine and 21.6 g. of 4,6-*O*-benzylidene-D-glucose were used in the above procedure, 26.3 g. (88%) of Ib was obtained, m.p. 100–103°.

Anal. Calcd. for $C_{21}H_{25}NO_5$: C, 67.91; H, 6.79. Found: C, 67.60; H, 7.08.

Instability of the product was indicated by a progressive decrease of melting point with time (m.p. 95–100° after several days).

N-(4,6-O-Benzylidene-D-glucosyl)d-α-methylphenethylamine (Ic). The reaction of 2.70 g. (0.0243 mole) of *d*-α-methylphenethylamine [b.p. 82° (14 mm.); n_D^{25} 1.5161] with 5.4 g. of 4,6-*O*-benzylidene-D-glucose in the usual manner did not immediately lead to a crystalline product from the reaction. However, removal of the methanol by concentration under diminished pressure in a rotating evaporator gave 7.2 g. of crude Ic, m.p. 53–58°. Two recrystallizations from benzene raised the m.p. to 59–61°, but the product was still not analytically pure.

Anal. Calcd. for $C_{22}H_{27}NO_5$: C, 68.55; H, 7.05. Found: C, 66.34; H, 7.31.

During 2 weeks at room temperature, this compound decomposed to a red oil.

4,6-O-Benzylidene-1-deoxy-1-histamino-D-fructose oxalate (IIa). To a solution of 31.4 g. (0.08 mole) of Ia in 360 ml. of methanol was added, at room temperature, a solution of 10.2 g. of oxalic acid dihydrate in 40 ml. of methanol. The solution soon became turbid and deposited a light-brown oil which finally set to a tan solid. Collection at the filter, followed by drying, gave 26.9 g. of crude product, m.p. 130–138°. This was recrystallized by dissolving it in 40 ml. of hot water, treating with charcoal, filtering through a heated funnel, washing the filter with 20 ml. of hot water, and adding 120 ml. of methanol to the combined filtrate and washings. Cooling and filtering gave 11.0 g. of nearly colorless IIa, m.p. 143–146° dec. Two more recrystallizations from water alone gave a white crystalline powder, m.p. 152–154°, dec., after turning brown, at 147°.

Anal. Calcd. for $C_{18}H_{23}N_3O_5 \cdot (COOH)_2$: C, 53.21; H, 5.58. Found: C, 53.15; H, 5.88. $[\alpha]_D^{26}$ −58.8° (*c*, 1.122 in water).

The infrared absorption spectrum (potassium bromide) exhibited a carbonyl band at 1724 cm.$^{-1}$ (5.80 μ). In alkaline solution, this product rapidly reduced both methylene blue and 2,6-dichloroindophenol. With diazotized sulfanilic acid in the presence of excess sodium carbonate, it gave a deep-red color.

4,6-O-Benzylidene-1-deoxy-1-(phenethylamino)-D-fructose oxalate (IIb). Treatment of 14.84 g. (0.04 mole) of Ib with 4.88 g. of oxalic acid dihydrate according to the preceding method gave 12.6 g. of crude IIb, m.p. 141–151°. Several recrystallizations of a sample from water gave colorless filaments, m.p. 150–153° dec., after darkening at 141°.

Anal. Calcd. for $C_{21}H_{25}NO_5 \cdot 1/2(COOH)_2$: C, 63.45; H, 6.29; N, 3.36; O, 26.90. Found: C, 63.47; H, 6.60; N, 3.39; O, 26.94. $[\alpha]_D^{28}$ −72.6° (*c*, 1.211 in 50% pyridine-water). This compound likewise reduces methylene blue rapidly in alkaline solution.

(3) For example, O. Gerngross, *Z. physiol. Chem.*, **108**, 50 (1919) showed that histamine can be monobenzoylated on the amino nitrogen atom only; and M. Rocha E. Silva, *J. Pharmacol. Exptl. Therap.*, **77**, 198 (1943) prepared α-aminoacylhistamines involving only the amino group. Furthermore, if Ia possesses the ring nitrogen "glycoside" structure, it should show marked solvolytic instability relative to that of Ib and Ic. This is not the case. [Compare T. Wieland and G. Schneider, *Ann.*, **580**, 159 (1953), who showed that *N*-acylimidazoles are extremely sensitive to solvolysis and aminolysis.]

(4) H. Pauly, *Z. physiol. Chem.*, **42**, 508 (1904).

(5) R. Fargher and F. Pyman, *J. Chem. Soc.*, **115**, 217 (1919); R. Burian, *Ber.*, **37**, 696 (1904); and O. Gerngross, *loc. cit.*[3]

(6) Melting points are corrected and were determined using a Fisher-Johns melting-point block.

4,6-O-Benzylidene-1-deoxy-1-(d-α-methylphenethylamino)-D-fructose oxalate (IIc). A solution of compound Ic in 150 ml. of methanol was prepared, as described above, from 20.7 g. of *d*-α-methylphenethylamine and 41.4 g. of 4,6-*O*-benzylidene-D-glucose. To this filtered solution was added, in one portion at room temperature, a filtered solution of 18.7 g. of oxalic acid dihydrate in 100 ml. of methanol. After standing overnight at room temperature, the reaction mixture was concentrated almost to dryness, and the crystalline product (68 g., m.p. 123–129° with decomposition) was collected at the filter. Recrystallization from 170 ml. of 95% ethanol gave 26 g., m.p. 126–130°. Two more recrystallizations of a sample gave pure IIc, m.p. 130–131°.

Anal. Calcd. for $C_{22}H_{27}NO_5.(COOH)_2$: C, 60.62; H, 6.15. Found: C, 60.47; H, 6.35. $[\alpha]_D^{26}$ −26.4° (*c* 1.110 in H_2O).

This product rapidly reduces methylene blue in alkaline solution.

Acknowledgment. The author is indebted to Mr. E. F. Shelberg and Mr. William Washburn and their associates for the microanalyses and infrared spectra, respectively, and to Mr. Nick Ryan for technical assistance.

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5-Amino-3-chloropyridazine. A Clarification

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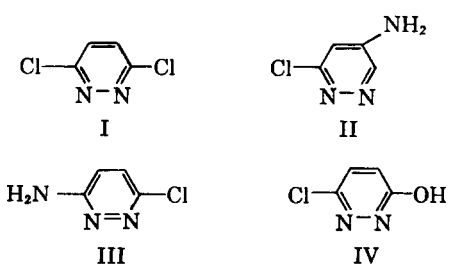
Recently Steck[1] reported that the treatment of 3,6-dichloropyridazine (I) with sodium amide yielded a product whose structure was suggested to be 5-amino-3-chloropyridazine (II). This structure was based on a melting point depression on admixture with authentic 3-amino-6-chloropyridazine (III).



Such a rearrangement appeared somewhat surprising in view of the high reactivity of a chlorine atom of 3,6-dichloropyridazine to direct displacement.[2] A similar rearrangement, involving 3-bromopyridine, has been reported by Levine and Leake[3]; however, this involved a relatively inert halogen atom.

Our attempts to repeat Steck's experiment resulted in the isolation of 3-chloro-6-hydroxypyridazine (IV) in low yield, together with a 50% recovery of the starting material, 3,6-dichloropyridazine. A direct comparison of the presumed 5-amino-3-chloropyridazine[4] with authentic 3-chloro-6-hydroxypyridazine established that they were indeed the same. The latter was prepared by a modification of Steck's method[5] of acid hydrolysis of 3,6-dichloropyridazine. The identity was based on elemental analysis, mixed melting point, and infrared comparisons of the two products.

Evidently in the original experiment the 3,6-dichloropyridazine largely survived the sodium amide treatment. It was then extracted by the hydrochloric acid, and underwent hydrolysis during the process of concentration in the acid medium. The possibility that 3-amino-6-chloropyridazine was formed in more than a minor amount in the attempted amination of 3,6-dichloropyridazine was eliminated, since this amine was shown to be inert to refluxing 6*N* hydrochloric acid.

EXPERIMENTAL[6]

3-Chloro-6-hydroxypyridazine.[5] Five grams (0.034 mole) of 3,6-dichloropyridazine in 300 ml. of 0.6*N* hydrochloric acid was refluxed for 3 hr. After removal of the unchanged 3,6-dichloropyridazine by steam distillation, the reaction mixture was concentrated at reduced pressure and was then chilled. A white, crystalline solid (2.3 g., 53%) was obtained, melting at 141.5–142.0°. Recrystallization from ethyl acetate raised the melting point to 142.0–142.5°.

Anal. Calcd. for $C_4H_3ClN_2O$: C, 36.80; H, 2.32; Cl, 27.17; N, 21.45. Found: C, 36.90; H, 2.54; Cl, 27.82; 27.02, 27.24; N, 21.67, 21.22.

Anal.[7] of the supposed 5-amino-3-chloropyridazine. Found: C, 36.87; H, 2.53; Cl, 27.24; N, 20.98, 21.44, 21.80.

The melting point of this sample was 141.5–142.0° and this was not depressed on admixture with our sample of 3-chloro-6-hydroxypyridazine. Infrared spectra of the two samples were identical; they were obtained in potassium bromide disks on a Perkin-Elmer Infracord Spectrophotometer Model 137.

Attempted hydrolysis of 3-amino-6-chloropyridazine. One gram of 3-amino-6-chloropyridazine in 60 ml. of 6*N* hydrochloric acid was refluxed for 1.5 hr. The cooled solution was adjusted to *p*H 8 and chilled to yield a white precipitate. The dried product (912 mg., 91.2%) melted at 221.5–222.5°; m.p. of starting material, 213.0–214.0°; mixed m.p. 215.0–216.0°. Infrared spectra of the two samples were identical.

Acknowledgments. We wish to thank Mr. L. Brancone and staff for the analyses reported herein.

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(1) E. A. Steck, *J. Org. Chem.*, **24**, 1597 (1959).

(2) See, among others, J. Druey, K. Meier, and K. Eichenberger, *Helv. Chim. Acta*, **37**, 121 (1954).

(3) R. Levine and W. W. Leake, *Science*, **121**, 780 (1955).

(4) We wish to thank Dr. E. A. Steck of Wilson Laboratories, Chicago 9, Ill., and Dr. G. D. Wessinger of the Sterling-Winthrop Research Institute, Rensselaer, N. Y., for furnishing us with a sample of the compound in question.

(5) E. A. Steck and R. P. Brundage, *J. Am. Chem. Soc.*, **81**, 6511 (1959).

(6) All melting points are corrected.

(7) Performed in our laboratories.