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THERMAL DEGRADATION OF 1-DEOXY-1-PIPERIDINO-D-FRUCTOSE

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ABSTRACT

Crystalline 1-deoxy-1-piperidino-D-fructose (**1**) was pyrolyzed in a sublimation apparatus at 106° and 0.1 torr. The sublimate-distillate collected consisted of piperidine acetate (43%); two piperidino derivatives of *C*-methyl reductone (28%); 4-hydroxy-2-piperidino-butanolactone (1.4%); and the piperidine amides of carbonic (6.5%), formic (1.6%), and acetic (5.1%) acids. Trace proportions of other volatile compounds were identified as 4-hydroxy-2,5-dimethyl-3(2*H*)-furanone; 2,5-dimethyl-3-piperidinofuran; 2-acetyl-3-piperidinofuran; 2-acetyl-3-piperidino-4,5-dihydrofuran; and the piperidides of glycolic, lactic, and butyric acids. Under the same pyrolysis conditions the piperidino *C*-methyl reductones isolated were degraded to carbonic, formic, and acetic piperidides. After separation of these compounds by preparative g.l.c., the products were identified by mass, i.r., and p.m.r. spectra; almost all were positively identified with compounds separately synthesized. The results indicate that piperidine is eliminated from C-1 and recombines at C-3 of the hexose carbon-skeleton before the primary C_4, C_2 fission occurs.

INTRODUCTION

The chemistry of the degradation of carbohydrates has practical significance in the food-processing industries. Besides the colors formed in sugar–amine browning reactions, the volatile compounds produced largely determine the acceptability of many heated foods through their flavor contributions[1–4]. Definition of the enolization, dehydration, and fission of sugar radicals, particularly as they react in combination with amines and amino acids, has contributed most to our knowledge of nonenzymic browning reactions[1,3–5]. The isolation of Amadori compounds (*N*-substituted 1-amino-1-deoxyglyculoses) from biological systems and from dehydrated foods have indicated these compounds as key intermediates in decompositions that lead to brown polymers and browned flavor-compounds[6].

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To clarify further the nonenzymic, browning reactions, the thermal degradation of pure Amadori compounds, having amino acid or alkylamino substituents, are being investigated in this laboratory. Because proline, hydroxyproline, and pyrrolidine participate in sugar degradations that produce breadlike aromas and flavors[7–9], we selected these amines for reaction with D-glucose to produce the intermediate Amadori compounds. Our inability to isolate high yields of crystalline 1-deoxy-1-pyrrolidino-D-fructose prompted substitution of 1-deoxy-1-piperidino-D-fructose (**1**) in the first study. The food-flavor aspects of this investigation have been discussed in a symposium and have been published[6], but without the experimental and mechanistic details given here. A similar study of the thermal degradation of 1-deoxy-1-prolino-D-fructose is nearly complete and will be reported later.

RESULTS AND DISCUSSION

The data summarized in Tables I–IV delineate the techniques and results used for structural identification of the pyrolysis products from **1**. Table I lists the relative retention times (g.l.c.) of the products isolated. In each comparative analysis, the synthetic compound had the same retention time as its corresponding pyrolysis product. The i.r. and p.m.r. data for the pyrolysis products were in agreement with those of the corresponding synthetic materials (Tables II and III). The comparative

TABLE I

G.L.C. ANALYSIS OF VOLATILE PYROLYSIS PRODUCTS FROM 1-DEOXY1-1-PIPERIDINO-D-FRUCTOSE (1)

Compound	*Relative retention time*[a]		*No. of sugar C atoms*	*% of distillate*
	15% Carbowax 20M[b]	*15% SE-30*[c]		
2	0.42[d]	0.14	2	43
	0.62[d]	0.28	1	1.6
3	1.0[d]	1.0	2	5.1
4	1.03[d]	1.22	4	Trace
5	1.15[e]	—	2	Trace
6	2.10[e]	2.07	3	Trace
7	1.84[e]	2.07	4	1.4
8	1.49[d]	2.66	1	6.5
9	1.40[d]	3.51	4	25.0
10	1.57[d]	3.06	4	3.0
11	2.02[d]	3.00	6	Trace
12	1.43[e]	0.74	6	10 (overall)
14	1.43[e]	3.51	6	Trace
15	1.27[e]	—	6	Trace
16	1.84[e]	—	6	Trace

[a] *N*-Formylpiperidine (**3**) was used as an internal standard. [b] Similar retention data were obtained from a 4 ft × 0.25-in 15% Carbowax 20M stainless-steel column. [c] Temperature programmed as follows: 100° and temperature program [d] Temperature programmed as follows: 50° (10 min), 100° (14 min), 150° (10 min), and 190°. [e] Temperature programmed as follows: 50° for 10 min, 100° for 14 min, and 150°.

TABLE II

I.R. ABSORPTION OF PYROLYSIS PRODUCTS FROM 1

Compound	*cm*$^{-1}$	*Compound*	*cm*$^{-1}$
3	1660, 1442, 1395, 1250	8	1720, 1449, 1362, 1150
4	1620, 1470, 1442, 1265	9	1610, 1420, 1362, 1245
5	1615, 1465, 1440, 1248	10	1665, 1555, 1450, 1360
6	3200(br)[a], 1640, 1442, 1390, 1268	11	3380, 1710(w)[a], 1660, 1615, 1555, 1450
7	3410, 1630, 1479, 1442, 1390	12	1700, 1630, 1435, 1365

[a]br, broad; w, weak.

TABLE III

P.M.R. DATA ON PYROLYSIS PRODUCTS FROM 1

Compound	τ (*H*)[a]
4	8.12 (3H), 8.45 (6H), 6.66 (4H)
9	8.38 (6H), 6.76 (4H)
10	8.40 (6H), 7.89 (3H), 6.48 (4H), 3.71 (1H)
11	8.40 (6H), 7.97 (3H), 6.77 (4H), 4.88 (1H), 2.56 (1H)

[a]Relative to tetramethylsilane.

TABLE IV

MASS SPECTRA OF PYROLYSIS PRODUCTS (P) FROM 1 *vs.* SYNTHETIC REFERENCE COMPOUNDS (S)

Compound		m/e (*relative* %)					
3	P	113 (96)	112 (31)	98 (40)	84 (57)	56 (100)	
	S	113 (98)	112 (35)	98 (35)	84 (61)	56 (100)	
4	P	127 (32)	112 (11)	85 (20)	84 (69)	73 (36)	
	S	127 (35)	112 (15)	85 (19)	84 (72)	73 (38)	
5	P	155 (40)	140 (40)	127 (52)	112 (40)	84 (100)	
	S	155 (47)	140 (52)	127 (66)	112 (31)	84 (100)	
6	P	143 (23)	112 (66)	97 (7)	84 (17)	69 (81)	
	S	143 (20)	112 (65)	97 (6)	84 (16)	69 (82)	
7	P	157 (14)	142 (6)	114 (7)	113 (53)	112 (72)	
	S	157 (14)	142 (5)	114 (11)	113 (64)	112 (100)	
8	P	169 (17)	125 (25)	111 (47)	110 (100)	96 (37)	
	S	169 (18)	125 (21)	111 (57)	110 (100)	96 (27)	
9	P	196 (11)	112 (17)	84 (100)			
	S	196 (9)	112 (15)	84 (100)			
10	P	169 (100)	152 (59)	126 (90)	98 (69)		
	S	169 (72)	152 (41)	126 (72)	98 (94)		
11	P	169 (100)	152 (59)	140 (11)	126 (94)	113 (39)	98 (95)
	S	169 (29)	152 (21)	140 (17)	126 (33)	113 (20)	98 (57)
12	P	128 (31)	85 (17)	57 (66)	45 (12)	43 (100)	
	S	128 (33)	85 (17)	57 (59)	45 (11)	43 (100)	
14	P	179 (27)	178 (12)	164 (17)	150 (13)	136 (18)	
15	P	193 (25)	178 (16)	164 (26)	150 (23)	109 (10)	
16	P	195 (25)	180 (11)	152 (4)	138 (10)	98 (9)	

mass spectra (Table IV) were identical except for the relative intensities of several peaks in compounds **5**, **10**, and **11**. These discrepancies undoubtedly arise from inherent differences between the two mass spectrometers employed in this study.

Fig. 1 shows structures of the products that were isolated and identified. Compounds **2–11** represent fragmentation products having one to four carbon atoms,

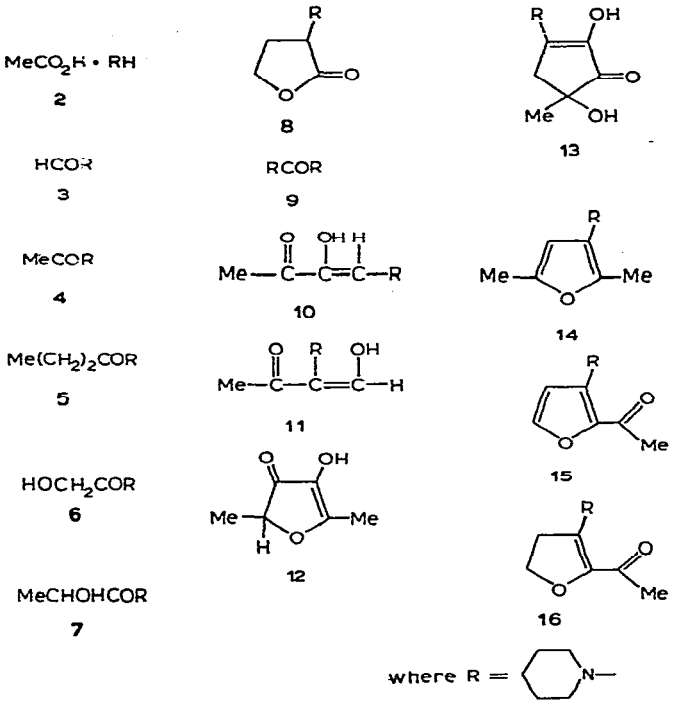


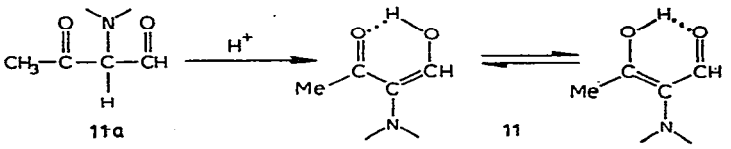
Fig. 1. Pyrolysis products from 1-deoxy-1-piperidino-D-fructose.

whereas compounds **12–16** are derived presumably from the dehydrated hexose. The chain lengths and yields of these products are given in Table I. Measurable yields are based on analyses of the synthetic reference compounds by g.l.c. The yield of compound **13** was determined by direct isolation of this product from the pyrolysis residue. The chain lengths and yields of these products indicate that a C_4, C_2 scission of the carbohydrate moiety occurs much more readily than C_3, C_3 splitting. The trace of lactic acid, the only 3-carbon compound found, could have arisen from the 4-carbon reductones.

The isolated, aminated 4- and 2-carbon compounds could have arisen from amination after dealdolization of the enolized and dehydrated hexose. Attempted amination of the most likely α-dicarbonyl intermediates however, under conditions similar to those used in the pyrolysis, did not produce the same aminated products; for example piperidinolysis of pyruvaldehyde did not produce compound **4**; diacetyl, **4**; diacetylformoin, **3** or **4**; and *C*-methyl reductone, **10**. Pyrolysis of **10** produced **2** (14.3%), **3** (36%), **4** (3.3%), and **9** (9.7%). Furthermore, compound **11**, on standing,

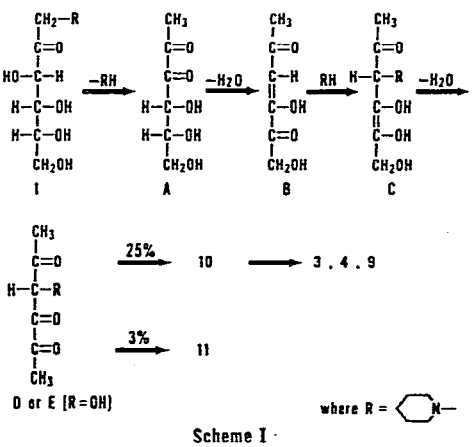
produces **2** and **3**. Hence, a portion of the 1- and 2-carbon fragments originate via the 4-carbon reductones, and the remainder of the 2-carbon fragments arise more directly by fission of unsaturated, 6-carbon intermediates.

The new amino reductone (**11**) was synthesized from 3-bromo-4,4-dimethoxy-2-butanone and piperidine. Substitution of piperidine for bromine, with no transamination during hydrolysis of the acetal group, should yield the keto-amino-aldehyde **11a**. The p.m.r. spectrum of the freshly prepared, synthetic compound



showed no resonance for a hydroxylic proton; moreover, a clear AX type of splitting pattern (J_{AX} = 12 Hz) was assigned to the adjacent methine protons in **11a**. Although the 3-ketoaldehyde form (**11a**) was clearly indicated from the p.m.r. spectrum in chloroform-*d*, the enolic amino reductone forms (**11**) preponderated in ordinary chloroform that contained a little alcohol. The i.r. spectra of solutions of both pyrolytic and synthetic products in chloroform showed stretching vibrations for enolic hydroxyl groups as a weak, irregular, broad band centered at 3380 cm^{-1}. Only weak carbonyl-stretching bands could be detected near 1700 cm^{-1}, whereas strong, broad, composite bands characteristic of enolized β-dicarbonyl compounds[10] and enaminoketones[11] were present at 1660 and 1555 cm^{-1}, with a weaker band visible[12] between them at 1615 cm^{-1}.

We now suggest an extended path (Scheme I) for the decomposition of the strongly basic Amadori compound. The main difference from the decomposition



Scheme I

path suggested by Hodge[13], Hodge *et al.*[14], Simon[15], and Simon and Heubach[16] lies in the formation of the C-3-aminated, 6-carbon intermediate D. A 1,4-addition to the dehydrated α,β-unsaturated hexose intermediate B, followed by loss of water, would account for D. Production of the isomeric 4-carbon reductones (**10** and **11**) and lack of their formation directly from diacetylformoin (E) or *C*-methyl reductone, implicate this intermediate. No significance is attached to the unequal yields of **10** and **11**, since **11** is quite unstable and difficult to quantitate. The suggested amination at C-3 is also supported by the later work of Peer *et al.*[17], who proposed a C-3 amino-substituted intermediate to account for the aminated products obtained in the reaction of amine salts with L-lyxose and L-rhamnose. Two separate routes from the same intermediate would account for two of the important, isolated products: **13** is important because it is the most abundant, and **12** because it has an extremely powerful caramel-like odor. Amination-cyclization and reduction, with cyclization of diacetylformoin (4-hydroxy-2,3,5-hexanetrione), would explain the presence of these two compounds. Compound **13** has been derived in 10% yield from the reaction of diacetylformoin (E) with piperidine[16]. 4-Hydroxy-2,5-dimethyl-3(2*H*)-furanone (**12**) was isolated in 10% yield from the reduction of E by using palladium on carbon as a catalyst[18]. Therefore, diacetylformoin (E, Scheme I) is indicated as an intermediate in the formation of the six-membered products that were isolated in our study.

Compound **14**, **15**, and **16** are tentatively identified (not confirmed by synthesis); components **14** and **16** are present in the fraction containing **12**. The combination g.l.c.-mass spectra of these components (Table IV) are consistent with their proposed structures.

The decomposition of the basic Amadori compound (**1**), proceeds by several routes; each yields compounds of organoleptic import. This report documents the complexity of thermal decomposition of a basic Amadori compound.

EXPERIMENTAL

Chromatographic methods. — A model 810 F & M gas chromatograph equipped with dual flame and dual thermal-conductivity detectors was used. Samples were injected onto a 4 ft × 0.25-in. copper column containing 15% of Carbowax 20M coated on 80–100 mesh Gas Chrom Q or onto a 6 ft × 0.25-in., 15% SE-30 copper column coated on 80-100 mesh Chromosorb W. Effluent fractions were collected in glass capillary-tubing, which was cooled by Dry Ice; quantitative analyses were made with the dual flame-detectors. Repeated collections were made with the Carbowax 20M column until sufficient quantities were obtained. This column was heated for 10 min at 50°, for 14 min at 100°, for 10 min at 150°, and at 190° for the rest of the program. The temperature was increased by 60° per min, and retention times were based on the moment of injection. The helium flow-rate was between 56 and 60 ml per min.

Spectrometric methods. — The i.r. spectra were obtained with a Perkin–Elmer

Model 612 spectrophotometer and from solutions in chloroform or carbon tetrachloride, except for **13**, which was determined in a KBr disc. The mass spectra were determined with either a Nuclide 90G or Bendix 12-100 Time-of-Flight spectrometer. The p.m.r. spectra were obtained with a Varian HA-100 instrument from solutions in chloroform-*d*, with Me_4Si as an internal standard.

Pyrolysis. — 1-Deoxy-1-piperidino-D-fructose[19] (**1**) (20 g) was heated for 5 h in a sublimator at 106° and 0.1 torr. The sublimate-distillate, trapped on the cold finger at 5–10°, was removed with chloroform. The average yield, after removal of solvent, was 2 g.

Syntheses. — *A. Amides.* *N*-Formylpiperidine (**3**) was prepared from ethyl orthoformate and piperidine[20]. *N*-Acetylpiperidine (**4**) was prepared from acetic anhydride and piperidine, and *N*-butyrylpiperidine (**5**), from butyroyl chloride and piperidine[21]. *N*-Lactyl and *N*-glycolyl piperidines (**7** and **6**) were made according to the procedure of Shapiro *et al.*[22].

B. 4-Hydroxy-2-piperidino-butanolactone[23] (**8**). To 50 ml of anhydrous benzene, 8.2 g of 2-bromo-4-hydroxy-butanolactone (Aldrich Chemical Co.) was added. Piperidine (b.p. 106°) (4.3 g) was added dropwise to this mixture. Anhydrous potassium carbonate (10 g) was then added, and the stoppered flask was shaken for 8 h and the mixture refluxed for an additional 2 h. The mixture was filtered and the filtrate evaporated *in vacuo*. The residue was distilled at 1.0 torr and the fraction boiling at 108–110° was collected (3 g). This fraction was shown by g.l.c to contain a single component: (*m/e*, relative %) 169 (18), 125 (21), 111 (57), 110 (100), 96 (37); i.r. (cm^{-1}) 1720, 1450, 1362, 1150.

C. Carbonylbis(piperidin-1-yl) (**9**). A solution of phosgene (2.9 g) in 50 ml of anhydrous benzene was added dropwise to a mechanically stirred solution piperidine (8.7 g) in anhydrous benzene (reaction slightly exothermic). The solution was stirred for an additional 2 h at room temperature. Water (75 ml) was added; the organic phase was removed and washed one time with a 5% solution of sodium carbonate and twice with water. After the organic phase had been dried (sodium sulfate) the solvent was removed *in vacuo*. The residue was distilled at 0.3 torr and the fraction boiling at 132–135° was collected (4.2 g, 84%). The compound solidified upon standing (m.p. 42–43°): (*m/e*, relative %) 196 (9), 112 (15), 84 (100); i.r. (cm^{-1}), 2980, 2935, 2850, 1612, 1478–1420 (6 bands), 1365, 1270, 1260, 1248; p.m.r. τ 8.38, 6.76 (H ratio 3/2).

Anal. Calc. for $C_{11}H_{20}N_2O$: C, 67.36; H, 10.20; N, 14.28. Found: C, 67.36; H, 10.25; N, 13.95.

D. 3-Hydroxy-4-piperidino-3-buten-2-one (*piperidino C-methyl reductone*) (**10**). This compound was prepared from bromodiacetyl and piperidine according to the procedure of Simon *et al*[24].

E. 4-Methoxy-3-buten-2-one[25]. A mixture of 50 g of 4,4-dimethoxy-2-butanone and 1.7 g of anhydrous sodium acetate was heated at 190° and the methanol formed was distilled off. The solution was cooled and the residue distilled at 12 torr. The fraction boiling at 64–73° (22.8 g) was collected. This material was shown to be pure

by g.l.c.; p.m.r.: τ 7.91 (3H, C-CH_3) 6.32 (3H, OCH_3) olefinic protons at τ 4.49 and 2.44 (2H), J_{AB} 13 Hz.

F. 3-Bromo-4,4-dimethoxy-2-butanone[26]. 4-Methoxy-3-buten-2-one (22.8 g) in 30 ml of carbon tetrachloride was treated dropwise with bromine (8.8 ml) in 10 ml of carbon tetrachloride. The stirred solution was kept below 10°. The total mixture was stirred for an additional 30 min and was added to 60 ml of methanol. This mixture was kept for 48 h at room temperature. Water (200 ml) was added and the organic phase was separated and washed 10 times (1 liter, total volume) with a 5% sodium carbonate solution. The organic phase was dried (sodium sulfate) and distilled under diminished pressure. The fraction boiling at 82–92° and 12 torr was collected (18.2 g). This material was stored in a dark bottle over anhydrous sodium carbonate. P.m.r. data: τ 7.70 (3H, C-CH_3), 6.64, 6.63 (3H each, OCH_3), 5.38, 5.9, AB pattern, J_{AB} 8 Hz; (*m/e*, relative %); no parent ion, M-31 at 179 (5); 181 (5) and is 97.5% of peak 179, 135 (8), 85 (10), 75 (100), 43 (45).

G. 4,4-Dimethoxy-3-piperidino-2-butanone. The preceding 3-bromo derivative (1 g) was dissolved in 50 ml of anhydrous benzene, and 2 g of anhydrous sodium carbonate, and an equimolar amount of piperidine were added. The mixture was covered with nitrogen and the stoppered flask was shaken for 4 h at room temperature and then the contents were refluxed for an additional 3 h.

After the solution had been filtered and concentrated, the residue was distilled. The fraction boiling at 110–115° and 0.3 torr was collected (1.05 g) and was shown to be pure by g.l.c.; p.m.r.: τ 8.55 (6H, piperidine), 7.84 (3H, CH_3-C), 7.32 (4H, piperidine); τ_A 5.46 (1H) and τ_B 6.78 (1H), J_{AB} 3.7 Hz, 6.65 (3H, OMe); 6.63 (3H, OMe); (*m/e*, relative %); 215 (2), 184 (18), 183 (8), 172 (31), 168 (32), 155 (8), 140 (43), 128 (8), 97 (100), 84 (8), 75 (78), 43 (43).

H. 4-Hydroxy-3-piperidino-3-buten-2-one (isopiperidino C-methyl reductone) (**13**). 4,4-Dimethoxy-3-piperidino-2-butanone (300 mg) was heated for 30 min with 6 ml of 50% acetic acid at 65–70° in a water bath. The hydrolyzate was concentrated *in vacuo* and dried by azeotropic distillation with ethanol. The residue was subjected to g.l.c. on a column of Carbowax 20M and the effluent was trapped at the retention time of the originally isolated isopiperidino *C*-methyl reductone. I.r. spectrum: 3380 (broad and weak), 1710 (weak), 1660, 1615, 1555 (strongest), and 1450 (multiple) cm^{-1}; p.m.r. (τ, H): 8.40 (6), C-CH_3 7.94 (3), 6.77 (4), 4.88 (H_X), 2.56 (H_A), J_{AX} ~12 Hz; see Table IV for mass spectral data.

I. Diacetylformoin was synthesized by the method of Steinbauer and Waldman[27].

Aminolyses of 2-dicarbonyl compounds. — Two sets of methanolic solutions were prepared containing 1 millimole of butanedione, pyruvaldehyde, and diacetylformoin. Equimolar amounts of piperidine in 0.5 ml of methanol were added to the first set and an equivalent amount of piperidine acetate and 1 ml of methanol were added to the second. All tubes were sealed, and in separate experiments, reactions were conducted at 0, 25, 50, and 100°; the reaction mixtures were examined by g.l.c. after 2, 4, and 5 h.

At the temperatures and times described, no products were formed, as shown by g.l.c., that had been previously isolated during pyrolysis of **1**.

Pyrolysis of piperidino C-methyl reductone (**10**). — Piperidino *C*-methyl reductone **10** (100 mg) was heated for 5 h at 110° in an evacuated, sealed tube. The resulting viscous product was dissolved in MeOH (total volume 2 ml) and was analyzed by g.l.c. The solution contained **3** (36%), **4** (3.3%), **2** (14.3%), and **9** (9.7%).

N-[*1-Methyl-1,2,3-trihydroxy-2-cyclopenten-4-ylidene*]-*piperidinium betaine* (*N→2 or 3*) (**13**) (*piperidino-hexose-reductone*). The pyrolysis residue was extracted into 1:1 methanol-acetone and the solution was then filtered, and cooled. The resulting precipitate had m.p. 227–230°; mixed m.p. with authentic piperidino-hexose-reductone gave no depression; a comparative i.r. analysis (KBr disc) gave identical spectra.

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