STRUCTURE OF PIPERIDINO-HEXOSE-REDUCTONE

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Abstract—The structure of piperidino-hexose-reductone, first described by Hodge and co-workers, was clarified by degradation reactions. Dihydro-anhydro-piperidino-hexose-reductone, obtained from piperidino-hexose-reductone in a clear way, was synthesized by reacting 1-methyl-4-chloro-*cyclo*penten(1)-ol(2)-one(3) with piperidine.

Over the past 5 years Hodge *et al.*[1,2] have described new types of reductones. Crystalline amino reductones, $R_2N \cdot C_6H_7O_3$, and their anhydro derivatives, $R_2N \cdot C_6H_5O_2$, were prepared quite generally from both aldo- and keto-hexoses in reaction with various neutral or basic secondary amine salts; a nitrogen-free crystalline reductone was obtained by the same reaction applied to L-rhamnose.[2,3] Investigations of the scope of the reaction, preparative conditions, and antioxidant properties of the reductones are reported elsewhere.[3,4,5] Clarification of structure has been confined to piperidino-hexose-reductone because experiments have shown that the other amino-hexose-reductones in all probability have analogous structures.

Piperidino-hexose-reductone (I) with the summation formula $C_{11}H_{17}NO_3$ reduces exactly two equivalents of iodine in acetic acid solution. The test of Weygand and Csendes[6] with titanium (IV) salt and pyridine is positive. Moreover, the following customary reagents for reductones are reduced in the cold: Tillmans reagent (2:6-dichlorophenolindophenol) in acid solution, methylene blue in alkaline solution, and silver nitrate in acid or ammoniacal solution. An aqueous solution of I gives no perceptible color with ferric chloride in acid solution. However, if the aqueous solution is buffered with sodium acetate, either before or after adding ferric chloride—or, if the test is conducted with alcoholic solutions—an intense Prussian blue color is formed. This color gradually disappears on standing.

PIPERIDINO-HEXOSE-REDUCTONE AND ITS DERIVATIVES

I   Piperidino-hexose-reductone = N-[1-methyl-1,2,3-trihydroxy-*cyclo*penten(2)-ylidene(4)]-piperidinium betaine (N → 2 or 3)

[1] J. E. Hodge and C. E. Rist, *J. Amer. Chem. Soc.* **75**, 316 (1953).
[2] J. E. Hodge and B. E. Fisher, *Chem. Engng. News* **32**, 1436 (1954); *Abstracts of Papers presented at the 125th Meeting of the Amer. Chem. Soc., Kansas City*, 1954, p. 4D. American Chemical Society; *Ibid.* 130*th Meeting of the Amer. Chem. Soc., Atlantic City*, 1956, p. 23D. American Chemical Society (1956).
[3] J. E. Hodge, E. C. Nelson and B. E. Fisher, *J. Amer. Chem. Soc.* In preparation.
[4] J. E. Hodge and C. D. Evans, *U.S.Pat.* 2806794. (September 17, 1957).
[5] C. D. Evans, H. A. Moser, P. M. Cooney and J. E. Hodge, *J. Amer. Oil Chem. Soc.* **35**, 84 (1958).
[6] F. Weygand and E. Csendes, *Ber. Dtsch. Chem. Ges.* **85**, 45 (1952).

II Piperidino-hexose-reductone mono-O-methyl ether (nonreducing) = N-[1-methyl-1:2-dihydroxy-3-methoxy-*cyclo*penten(2)-ylidene(4)]-piperidinium betaine (N → 2)

IIa Piperidino-hexose-reductone mono-O-methyl ether (reducing) = N-[1-methyl-1-methoxy-2:3-dihydroxy-*cyclo*penten(2)-ylidene(4)]-piperidinium betaine (N → 2 or 3)

III Piperidino-hexose-reductone di-O-methyl ether = N-[1-methyl-1:3-dimethoxy-2-hydroxy-*cyclo*penten(2)-ylidene(4)]-piperidinium betaine (N → 2)

IV Piperidino-hexose-reductone monoacetate = N-[1-methyl-1:2-dihydroxy-3-acetoxy-*cyclo*penten(2)-ylidene(4)]-piperidinium betaine (N → 2)

V 1-Methyl-4-piperidino-*cyclo*pentanol-(2 or 3)

VI Anhydro-piperidino-hexose-reductone = N-[1-methylene-2:3-dihydroxy-*cyclo*penten(2)-ylidene(4)]-piperidinium betaine (N → 2 or 3)

VIa Anhydro-piperidino-hexose-reductone monoacetate = N-[1-methylene-2-hydroxy-3-acetoxy-*cyclo*penten(2)-ylidene(4)]-piperidinium betaine (N → 2)

VIb Anhydro-piperidino-hexose-reductone mono-O-methyl ether = N-[1-methylene-2-hydroxy-3-methoxy-*cyclo*penten(2)-ylidene(4)]-piperidinium betaine (N → 2)

VII Dihydro-anhydro-piperidino-hexose-reductone = N-[1-methyl-2:3-dihydroxy-*cyclo*penten(2)-ylidene(4)]-piperidinium betaine (N → 2)

VIIa Dihydro-anhydro-piperidino-hexose-reductone monoacetate = N-[1-methyl-2-hydroxy-3-acetoxy-*cyclo*penten(2)-ylidene(4)]-piperidinium betaine (N → 2)

VIII Phenylhydrazine derivative of I, identical with the phenylhydrazine derivative of VI

VIIIa Mono-O-acetyl derivative of VIII

VIIIb Dihydro derivative of VIII

IX Hydrogenation product of VIII, $C_6H_9NO_2$

X Methylsuccinic acid

XI Citramalic acid

XII Methiodide of V

XIII Methylreductic acid

XIV 1-Methyl-4-chloro*cyclo*penten(1)-ol(2)-one(3)

XV *Iso*methylreductic acid = 1-methyl-*cyclo*penten(1)-diol(2,4)-one(3)

XVI 1-Methyl-4-piperidino-*cyclo*penten(3)-ol(3)-one(2)

XVII Piperidino-hexose-reductone chloride hydrochloride = 1-methyl-1-chloro-2:3-dihydroxy-4-piperidino-*cyclo*pentadiene(2,4) hydrochloride

XVIII Anhydro-piperidino-hexose-reductone hydrochloride
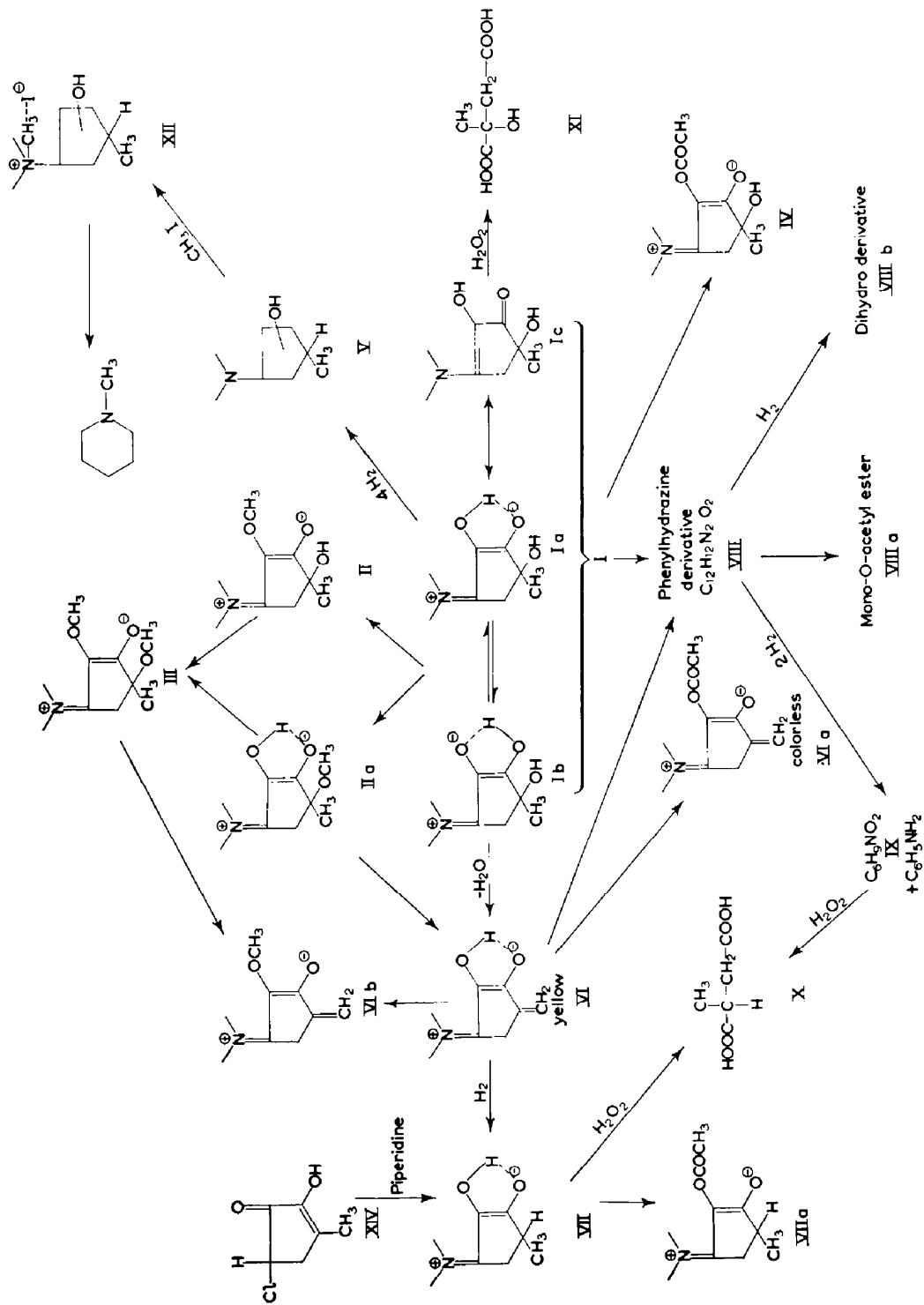
Piperidino-hexose-reductone contains one C-methyl group according to Kuhn–Roth oxidation results and the iodoform reaction.[2,3] The positive iodoform reaction also shows that the carbon atom adjacent to the methyl group bears oxygen.

Two hydroxyl groups are indicated by the preparation of two different mono-O-methyl ethers (II) and (IIa). The di-O-methyl ether (III) that is obtained directly from I or from either II or IIa by remethylation, is a neutral compound that cannot be further methylated. Because III also cannot be acetylated and shows no reaction with carbonyl reagents, it must be assumed that I possesses only two real hydroxyl functions. Because III is neutral, the third nonsubstitutable oxygen atom in III may be considered as an enolate anion that is neutralized within the molecule by the cationic nitrogen of the piperidino group. Therefore, an inner salt or betaine–like structure is indicated. Furthermore, because one of the two mono-O-methyl ethers (IIa) shows reductone reducing power, the third, nonsubstitutable oxygen and the amino or imino function must be capable of participation in the tripartite mesomeric reducing group.

Only one of the two hydroxyl groups of I that can be methylated is acetylated with acetic anhydride. The nonreducing mono-O-acetyl derivative (IV) is readily hydrolyzed in dilute acetic acid yielding I and indicating that IV is an enolic ester.

Piperidine is easily split from I by mineral acids and hot, strong alkali; therefore, the piperidino radical is in a labile configuration. During acid hydrolysis the N-free radical undergoes a yet unexplained transformation.

Piperidino-hexose-reductone is not hydrogenated at room temperature in alcohol or glacial acetic acid with reduced platinum dioxide catalyst. However, in mineral acid solution four moles of hydrogen are consumed, and a substance with the summation formula $C_{11}H_{21}NO$ (V) is formed; i.e. two hydroxyl groups are hydrogenolytically removed. One mole of methyl iodide is accepted by V to form the quaternary salt (XII), and N-methylpiperdine is obtained from XII by the Hofmann degradation. This result indicates that heterocyclic quaternary nitrogen is not present in the structure, as was previously suspected.

Upon heating in n-butanol that contains 10 to 15 per cent hydrogen chloride by weight, I is dehydrated. The acidic hydrochloride that crystallizes from the hot reaction mixture is converted by sodium acetate solution to the yellow, neutral compound (VI) with the summation formula $C_{11}H_{15}NO_2$. In contrast to I, VI takes up one mole of hydrogen very quickly at room temperature in glacial acetic acid with platinum or Raney nickel catalyst. If the hydrogenation is stopped here, an amino reductone with summation formula $C_{11}H_{17}NO_2$ (VII) is isolated. Both VI and VII show reductone–reducing power and give a deep-blue color with ferric chloride in alcoholic solution. C-methyl determinations according to Kuhn–Roth showed no methyl group in VI and one methyl group in VII.

Piperidino-hexose-reductone reacts with phenylhydrazine very slowly in acetic acid, but rapidly in hot mineral acid solution. Piperidine and water are split out, and a phenylhydrazone or phenylazo derivative (VIII), $C_{12}H_{12}N_2O_2$, is formed in 97 per cent of the theoretical yield. Two isomers can be separated by paper chromatography. These two interconvertible forms were isolated. The anhydro product (VI) reacts readily with phenylhydrazine in hot acetic acid solution to yield the same composite product (VIII) that is obtained from I.

By catalytic hydrogenation of VIII, aniline and a crystalline reductone with the summation formula $C_6H_9NO_2$ (IX) are formed. Aniline is split out also by the action

of sodium hydrosulphite on VIII. If the catalytic hydrogenation is stopped after one mole of hydrogen is taken up, a dihydro compound (VIIIb) $C_{12}H_{14}N_2O_2$ can be isolated. Oxidation of IX with hydrogen peroxide splits out carbon dioxide and yields methylsuccinic acid (X) which is obtained also from VII by oxidation with hydrogen peroxide. Oxidation of I with hydrogen peroxide yielded the highly significant degradation product $C_5H_8O_5$ which was isolated and identified as citramalic acid (XI); i.e. α-methyl-α-hydroxysuccinic acid. Oxidation of I with potassium permanganate or sodium hypobromite gave oxalic acid.

The finding of citramalic acid among the degradation products of piperidino-hexose-reductone and the isolation of methylsuccinic acid from the dihydro-anhydro derivative (VII) allows the supposition that piperidino-hexose-reductone contains the carbon skeleton of the cyclic "diketone" that Meyerfeld[7] discovered in beech tar oil. Rojahn and Rühl[8] showed that this compound is enolic and gave it the structure of 1-methyl-cyclopenten(1)-ol(2)-one(3). Hesse and Böckmann[9] synthesized the methyl-cyclopentenolone and converted it by chlorination and hydrolysis to methylreductic acid (XIII). Then they oxidized methylreductic acid with silver oxide

XIII   XIV
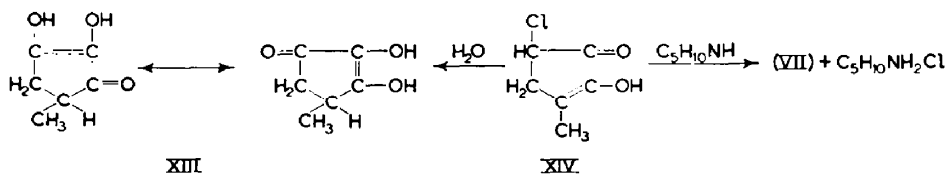
and obtained methylsuccinic acid (X). More recently Hesse and Brieg[10] have demonstrated a simple synthesis of methylreductic acid by halogenation of the methylcyclopentenolone from wood tar. They showed Meyerfeld and Ohlgart's compound to be 1-methylcyclopenten(3)-ol(3)-one(2) in aqueous solution, and the chloro compound obtained from it proved to be 1-methyl-4-chlorocyclopenten(1)-ol(2)-one(3) (XIV). Hydrolysis of XIV gave methylreductic acid in good yield. The structure of XIV was proved by synthesis and oxidative degradation.

A product identical with VII is obtained by the reaction of XIV with piperidine with the splitting out of hydrogen chloride. The identity of VII with the reaction product of XIV with piperidine was proved by analysis, melting point, mixed melting point, U.V. and I.R. spectrum, and by a Debye–Scherrer photograph of the crystalline powder. Particularly, the complete agreement of the two I.R. spectra in the so-called "fingerprint" region showed that the two products represent the same compound.

The position of the double bond in the dihydro-anhydro compound (VII) is not established by the synthesis. Since VII is a reductone like I, it must be assumed that the reaction between 1-methyl-4-chlorocyclopenten(1)-ol(2)-one(3) and piperidine occurs with a tautomeric rearrangement. Such a rearrangement occurs also during the preparation of methylreductic acid by saponification of XIV, according to Hesse, et al.[11] These authors isolated a nonreductone intermediate product that is isomeric

[7] J. Meyerfeld, Chemikerztg. 36, 549 (1912).
[8] C. A. Rojahn and F. Rühl, Ber. Dtsch. Pharm. Ges. 264, 211 (1926).
[9] G. Hesse and K. Böckmann, Liebigs Ann. 563, 37 (1949).
[10] G. Hesse and K. Breig, Liebigs Ann. 592, 120 (1955).
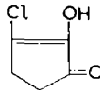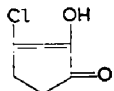[11] G. Hesse, F. Exner and H. Hertel, Liebigs Ann. 609, 57 (1957).

with methylreductic acid. For this isomer the structure of a 1-methyl*cyclo*penten(1)-diol(2,4)-one(3) (XV) was demonstrated. In view of the tautomeric shifts required by

XV   XVI
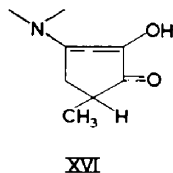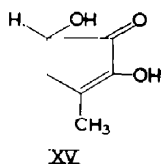
the conversion of XV to XIII, formulation of the dihydro-anhydro compound as VII, derived from XVI, is justified.

Betaine-like structures are proposed for I and VII on the basis of their high melting points and low solubilities in nonpolar solvents. Measurements of the dipole moments of VII in dioxane gave 5·0 D (Table 1).

TABLE 1. DIPOLE MOMENTS OF THE AMINO REDUCTONES AND RELATED
SUBSTANCES IN DIOXANE

Experimentally determined moments		Estimated moments	
I	4·55 D	Ia	13–15 D
II	8·1 D	Ib	10 D
III	6·2 D	Ic	2·2 D
VI	5·9 D		
VII	5·0 D		2·4 D
	1·65 D		

Furthermore VII, VI, and I showed no true carbonyl band in the I.R. spectra. The sharp band at 1667 cm⁻¹ for VII, at 1660 cm⁻¹ for VI, and at 1680 cm⁻¹ for I, is attributed to an enolized carbonyl group in a conjugated system.[12] A very broad band in the range 1520–1570 cm⁻¹ for each of the three reductones probably arises from both C=C and C=N double bonds in the resonating system. Vinylogs of amides characteristically absorb at 1540 cm⁻¹.[12] Such a broad band is possible for a betaine-like structure. This interpretation is plausible also because, from the experimental findings, one oxygen function in I is neither hydroxyl nor carbonyl nor ether grouping, III is a neutral compound, and only one hydroxyl group in VI and VII can be acetylated or methylated. The results of further dipole measurements are tabulated in Table 1.

The value found for chloro*cyclo*pentenolone is smaller than the estimated value. That may have its basis in the fact that a planar five-membered ring was assumed in the estimation, and the moments of the polar group were projected in this plane. Therefore maximum values are obtained by calculation. The values found for I and

[11] N. H. Cromwell, F. A. Miller, A. R. Johnson, R. L. Frank and D. J. Wallace, *J. Amer. Chem. Soc.* 71, 3337 (1949).

VII lie far above those which were calculated from the formulations Ic and XVI. The O-methyl ethers II and III show dipolarity to even higher degree than I and VII. The methyl ethers would be expected to give moments of only 2 to 3 D, if they were derived from the structure Ic.

In addition to the keto structures Ic and XVI, a betaine-like formulation must be assumed as a further limiting form. However, the dipole moment found is significantly smaller than that calculated for a pure betaine form. More characteristic for this determination is the dielectric increment that was measured for I, II, and III (Table 2). The values found lie between 6 and 9 and therefore are much too small for a pure betaine structure. For example, Greenstein and Wyman[13] found a dielectric increment of 24·4 for o-aminocyclohexane carboxylic acid, and 60 for the corresponding meta compound. Hence I and VII and their derivatives could not be correctly represented by a single formula. For example, it was obligatory to draw upon the three formulas Ia, Ib, and Ic to represent I.

TABLE 2. DIELECTRIC INCREMENTS OF
I, II AND III IN 70 PER CENT ETHANOL

|	$\delta\varepsilon/\delta c$
I	7·5 $\pm$ 1
II	6·1 $\pm$ 1
III	9·3 $\pm$ 1

Whereas the position of the enolic hydrogen in the formulas for piperidino-hexose-reductone (Ia, Ib) is, of necessity, not fixed, one is obliged to determine the position of the enolic hydroxyl (enolate anion) in the enediol–inactive mono-O-methyl ether. The following arguments are given to substantiate formula II: (1) Periodate is rapidly consumed by II in aqueous solution at 0°, pH 4. A hydrolysis before the periodate oxidation is therefore improbable; and also because II, in contrast to I, does not form a phenylhydrazone even after long heating in mineral acid solution. (2) In agreement with the I.R. spectra of α:β-unsaturated β-tertiary aminoketones (Cromwell et al.[12]), II as well as I and VII shows a sharp band (keto) at about 1665 cm^{-1} and a broad band at 1515–1575 cm^{-1}. Cromwell found no such displacement of the carbonyl frequency for α-aminoketones. Therefore it is assumed that the potential carbonyl group stands in the β-position to the piperidino radical. (3) It is to be considered that a mesomerism in the sense of Ia $\leftrightarrow$ Ic is possible only when the methoxyl group is at C^3.

The same arguments hold for formulations of the mono-O-acetyl compounds, VIa and VIIa.

The relationship between VII and I is believed to be fixed by the several cycles of interconversions of I to VI (e.g. I $\rightarrow$ XVII $\rightarrow$ XVIII $\rightarrow$ VI; I $\rightarrow$ XVII $\rightarrow$ IIa $\rightarrow$ VI; I $\rightarrow$ II $\rightarrow$ VIb = I $\rightarrow$ III $\rightarrow$ VIb = I $\rightarrow$ IIa $\rightarrow$ III $\rightarrow$ VIb = I $\rightarrow$ VI $\rightarrow$ VIb) which were demonstrated step by step with isolation and analysis of each intermediate. For the demonstration of the relationship between I and VII, it is most important that the intermediate VI possesses a terminal methylene group as a consequence of splitting out the tertiary hydroxyl group with one hydrogen of the methyl group. No C-methyl

[13] J. P. Greenstein and J. Wyman, J. Amer. Chem. Soc. 60, 2341 (1938).

group is present in VI according to the Kuhn–Roth determination, but it is present again after hydrogenation of VI to VII.
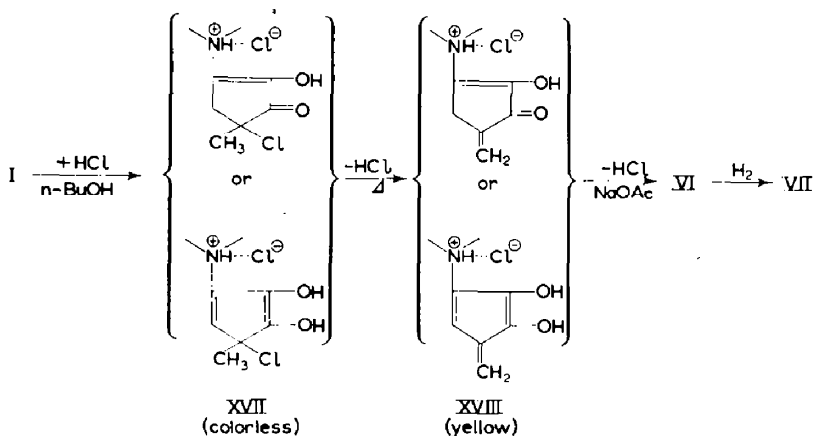
The colorless (XVII) and yellow (XVIII) hydrochlorides which were isolated are both strongly acidic and yield ionic chlorine in aqueous solution. The colorless chloride–hydrochloride (XVII) yields acetic acid by Kuhn–Roth oxidation (after precipitation of the chlorine with silver sulfate); therefore it retains the C-methyl group. When XVII is allowed to stand in methanol at 25°, the tertiary O-methyl ether (IIa) with reductone properties is obtained through its hydrochloride. A tertiary hydroxyl or chloride would be expected to methylate under these conditions. Methanol is eliminated from IIa by heating it in n-butanol-hydrogen chloride, thereby producing XVIII and VI. Likewise, methanol is eliminated from the di-O-methyl ether (III) to yield the same mono-O-methyl ether (VIb) that is obtained by direct methylation of VI, or by dehydration of II.

The formulated relationship of I, VI, and VII is supported also by their U.V. spectra. The principal maxima and extinction coeffcents of the three substances in methanol are presented in Table 3.

TABLE 3. PRINCIPAL MAXIMA AND EXTINCTION COEFFICIENTS OF AMINO REDUCTONES IN METHANOL

Compound	λ_{max}	$E_{1\,cm}^{1\%}$
(I) piperidino-hexose-reductone	315	1510
(VI) anhydro derivative of I	360	1250
(VII) dihydro derivative of VI	315	1516

For a complete description of VI and XVIII, fulvene–betaine structures probably should be considered on the following grounds: Aside from the phenylhydrazine derivatives, only VI and XVIII of all the derivatives made are inherently colored. They show strong yellow color as do fulvenes. The test of Rosen[14] for nucleophilic aromatic

[14] M. J. Rosen, *Analyt. Chem.* **27**, 111 (1955).

nucleus is positive for VI. Different structure in I and VI is shown by titrations with Tillmans reagent. Although I reduces this reagent instantly in acid solution below pH 4, and also in alkaline solution, it reduces very slowly at pH 6 to pH 7 at 25°. Donation of a proton to either the nitrogen atom in Ic or to the oxygen atom in the betaine–like structures is doubtless a prerequisite for reductone formation from I. In contrast, VI reduces Tillmans reagent instantly in neutral aqueous solution, which indicates that the nitrogen or oxygen is more readily if not already protonated. After a few milliliters of Tillmans reagent (or iodine) is consumed, VI. yields dark purplish-brown substance(s) in a manner resembling the behavior of pyrogallol under these conditions, and quantitative titration is thereby precluded. Finally, the empirical rule of Saytzeff dictates that the dehydration of I should involve one of the methylene, not methyl, hydrogens. Because methyl hydrogen definitely is involved, a tautomeric shift of one of the methylene hydrogens to the imino nitrogen (as in the lower formula of XVII) is postulated to precede the dehydrochlorination.

Nevertheless, these facts stand against the pure fulvene structure (XIX): (1) The mono-O-acetyl compound (VIa), isolated in 58 per cent yield, is colorless. (2) Only one active hydrogen was found by the method of Zerewitinoff. Also, by isotopic exchange experiments on VI in water that contained tritium, smaller tritium values than that calculated for one exchangeable hydrogen were always found. (3) In the region 900–1600 cm^{-1}, VI shows so many absorption bands that do not correspond with typical fulvene bands. The characteristic fulvene band at 900 cm^{-1} is observed, but against it the γ(CH) *cis* band of conjugated double bonds is not observed.

XIX
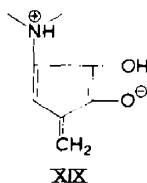
Investigation toward clarification of the mode of formation of I from C^{14}-labelled glucose are in progress at the Technische Universität of Berlin-Charlottenburg.

EXPERIMENTAL

Part I: By J. E. HODGE and B. E. FISHER

Piperidino-hexose-reductone mono-O-methyl ether (II). Piperidino-hexose-reductone, 4·23 g (20 mmoles), was slurried in dimethylsulphate, 4·1 g (30 mmoles), and 5 N sodium hydroxide, 6 ml (30 mmoles), was added dropwise with continual swirling of the mixture. The flask was cooled to keep the temp below 20°. After standing at 25° for 15 min, the clear, yellow solution was neutralized with a few drops of dilute sulphuric acid, then it was extracted with chloroform. Evaporation of the dried extracts gave a syrup which crystallized completely. Colorless prisms were obtained by re-crystallization from 45 ml benzene, 3·5 g (77 per cent of theory), m.p. 140–142°. A second re-crystallization from acetone gave the pure compound, m.p. 144°. (Found: C, 63·6; H, 8·50; N, 6·13; OCH$_3$, 14·9; C$_{12}$H$_{19}$NO$_3$ (225·28) requires: C, 63·97; H, 8·50; N, 6·22; OCH$_3$, 13·78%).

When 1 mole of II was treated with 4·6 moles sodium metaperiodate, it consumed 2·5 moles in 1 hr, 2·8 moles in 24 hr, 3·0 moles in 48 hr, and 3·1 moles in 72 hr. Formaldehyde could not be detected.

Kuhn–Roth analysis for C-methyl gave 1·0 mole of acetic acid per mole of compound. The iodoform test was positive, but the yield was low. Tillmans reagent was not reduced in dilute acetic acid. After hydrolysis in hot 2 N hydrochloric acid, Tillmans reagent was reduced. No hydrogen was

taken up in neutral aqueous solution with Adams platinum dioxide catalyst; however, when the solution was made 0·1 N with hydrochloric acid, 3·4 moles of hydrogen per mole of II was absorbed at 25°. The hydrogenated solution consumed periodate at 5° (3·3 moles in 6 hr) and yielded no formaldehyde. Ferric chloride gave a red-purple color.

Ultra-violet absorption measurements gave λ_{max} 299 mμ; $E_{1cm}^{1\%}$ 1530 in water and dilute alkali. In 0·1 N hydrochloric acid: λ_{max} 298 mμ; $E_{1cm}^{1\%}$ 1435.

A yellow *picrate* of II melted at 147°. (Found: N, 12·3 (Dumas) $C_{18}H_{22}N_4O_{10}$ requires: N, 12·32%).

Remethylation of II in dimethyl sulphate–sodium hydroxide gave the *di-O-methyl ether* (III), m.p. 58–59·5°, described below.

Piperidino-hexose-reductone di-O-methyl ether (III). Piperidino-hexose-reductone, 21·1 g (0·100 mole), was stirred in water under nitrogen at 5° while dimethyl sulphate, 50 g (0·39 mole), and 52 g of 50 per cent (wt/wt) sodium hydroxide (0·65 mole) were dropped simultaneously into the reaction mixture for 30 min. The clear solution was allowed to stand and warm to 18° for 2 hr. Methylation was then repeated by dropping 13 g of dimethyl sulphate (total, 0·50 mole) into the strongly alkaline solution while stirring it. After the solution had stood 16 hr at 25°, a syrupy product was isolated by chloroform extraction. It was dissolved in 200 ml of *n*-heptane at 85°. Filtration and cooling gave 22·2 g (two crops), 93 per cent of theory, m.p. 56°. One gram of the mono-O-ether (II) was removed from the crude product by fractional recrystallization from *n*-heptane. The pure *di-O-methyl ether* melted at 58–59·5°. (Found: C, 65·4; H, 8·86; N, 5·84; OCH$_3$, 26·1; $C_{13}H_{21}NO_3$ (239·31) requires: C, 65·24; H, 8·84; N, 5·85; OCH$_3$, 25·92%).

The compound was soluble in water and in organic solvents. The aqueous solution was neutral and did not reduce Tillmans reagent or hot Fehling solution. Addition of ferric chloride gave only a faint brownish-purple color. The iodoform test was negative. Hydrolysis in 2 N sulphuric acid at 100° produced a solution that reduced Tillmans reagent strongly at 25°.

The *di-O-methyl ether*, m.p. 58–59°, was formed also by methylation of IIa with dimethyl sulphate and sodium hydroxide. The mixed melting point with the product described above was not lowered.

Piperidino-hexose-reductone monoacetate (IV). Piperidino-hexose-reductone, 2·11 g, was suspended in 40 ml acetic anhydride and the mixture was heated at 65° for 15 min until a clear, nearly colorless solution was obtained. Storage of the solution at 0° for 2 days produced white crystals which were filtered off, washed with ether, and dried *in vacuo* at 56°; yield, 0·88 g, m.p. 170°. The filtrate was distilled under vacuum at 50° leaving a dry crystalline residue. Suspension of the residue in ether, storage at 0°, with isolation as before gave 1·62 g, m.p. 168–169°; total yield 2·50 g, 98 per cent of theory. Recrystallization from anhydrous ethyl acetate did not raise the melting point. Acetylation of I in pyridine at 25° with excess acetic anhydride gave the same compound in 92 per cent yield. (Found: N, 5·54; CH$_3$CO, 16·7; $C_{13}H_{19}NO_4$ (253·29) requires: N, 5·53; CH$_3$CO, 16·99%).

The *mono-O-acetyl* derivative did not reduce Tillmans reagent in 3 N acetic acid at 25°. However, after heating the acetic acid solution to 100° and cooling to 25°, it reduced Tillmans reagent instantly. When the heated acetic acid solution was neutralized with sodium hydroxide, I crystallized (56 per cent of theory); m.p. 230° (decomp), mixed m.p. with I not lowered.

The *acetyl* derivative in absolute ethanol gave a stable blue color with one drop of alcoholic ferric chloride solution. Tillmans reagent was not reduced. In absolute methanol and in acetate-buffered acetic acid solution (pH 4·6) the *mono-O-acetyl* derivative gave no deep color with ferric chloride solution; whereas I gave a deep blue color in parallel experiments under both conditions. In methanol Tillmans reagent was reduced and, also, the yellow color of added ferric chloride soon disappeared, indicating a reduction of ferric to ferrous ion.

Piperidino-hexose-reductone-hydrochloride. Piperidino-hexose-reductone, 8·5 g, was suspended in 25 ml absolute methanol under nitrogen, and 20 ml of a solution of hydrogen chloride (19 per cent wt/vol) in methanol was added. The clear yellow solution which formed was stored at 0°. Dilution with ether gave a colorless crystalline precipitate, 7·4 g, m.p. 120–121° (decomp with gas evolution). (Found: C, 53·38; H, 7·30; N, 5·69; $C_{11}H_{18}ClNO_3$ (247·72) requires: C, 53·33; H, 7·32; N, 5·65%).

Five grams of the hydrochloride was intimately mixed with 5 g of sodium acetate trihydrate, then 25 ml water was added under a nitrogen atmosphere. The crystalline form changed and, after standing at 25°, the precipitate was filtered off, washed with water and acetone, and dried. Yield 4·2 g, 98 per cent of theory, m.p. 229–231° (decomp); the mixed melting point of this compound with I was unchanged.

Piperidino-hexose-reductone chloride hydrochloride (XVII). Piperidino-hexose-reductone, 5·30 g, was suspended in 25 ml *n*-butanol and 50 ml of a cold solution of hydrogen chloride (21 per cent wt/wt) in *n*-butanol was added under nitrogen. After the clear yellow solution had warmed to 20° over 15 min, it was filtered, whereupon crystallization began in the filtrate. Dilution with ether, storage at 0°, filtration, followed by ether washing and drying, produced 5·65 g of white crystals, 85 per cent of theory, m.p. 167° (decomp). The product was purified by stirring it in 40 ml butanol–hydrogen chloride at 35° for 10 min, adding ether, cooling, and filtering as before. Yield 4·6 g, m.p. 168° (decomp). (Found: C, 50·4; H, 6·54; N, 5·29; Cl, 23·7; $C_{11}H_{17}Cl_2NO_2$ (266·17) requires: C, 49·63; H, 6·44; N, 5·26; Cl, 26·64%).

After precipitation of the chlorine with silver sulphate, Kuhn–Roth oxidation gave 0·5 mole of acetic acid per mole of compound. The compound (XVII) was not stable; it turned bright yellow in moist air and lost hydrogen chloride and turned brown on long storage in a desiccator over calcium chloride. Piperidino-hexose-reductone could not be recovered from the purified compound after neutralization with sodium acetate. The strongly acidic aqueous solution of XVII reduced Tillmans reagent instantly; and, when buffered with sodium acetate, it gave a deep blue-green color with ferric chloride solution.

Piperidino-hexose-reductone mono-O-methyl (and mono-O-ethyl) ether hydrochloride. Piperidino-hexose-reductone chloride hydrochloride (XVII), 10·0 g, was allowed to stand in 50 ml absolute methanol at 25° for several hr. The orange-colored solution was filtered then concentrated under vacuum to a crystalline residue which was rinsed onto a suction filter with ether. Dried *in vacuo* over calcium chloride for 48 hr, the product weighed 9·0 g, 93 per cent of theory, m.p. 138° (decomp). A sample that was recrystallized from methanol–hydrogen chloride–ether melted with decomposition at 144°. (Found: C, 55·08; H, 7·76; N, 5·35; $C_{12}H_{20}ClNO_3$ (261·75) requires: C, 55·06; H, 7·70; N, 5·35%).

A corresponding *mono-O-ethyl ether hydrochloride* was formed similarly by allowing XVII to stand in absolute ethanol for 1 hr at 25°; m.p. 142–143° (decomp). Yield, 60 per cent of theory. (Found: C, 56·65; H, 7·95; OC_2H_5, 15·6; $C_{13}H_{22}ClNO_3$ (275·77) requires: C, 56·62; H, 8·04; OC_2H_5, 16·33%).

Piperidino-hexose-reductone mono-O-methyl ether with reductone properties (IIa). The mono-O-methyl ether hydrochloride described in the preceding paragraph, 6·0 g, was partially dissolved in 15 ml cold water under nitrogen. Immediately thereafter 4·5 ml of 5 N sodium hydroxide was added to reduce the pH to 4. Stirring the clear, orange-red solution caused crystallization to occur, and 3·7 g of crude tan product was isolated. Two recrystallizations from benzene–light petroleum ether gave dense, colorless crystals, m.p. 153–154·5°. (Found: C, 64·17; H, 8·33; N, 6·12; OCH_3, 14·0; $C_{12}H_{19}NO_3$ (225·28) requires: C, 63·97; H, 8·50; N, 6·22; OCH_3, 13·78%).

This *mono-O-methyl ether* was more soluble in organic solvents and less soluble in water than II. Like I, it gave a neutral aqueous solution that reduced Tillmans reagent very slowly; however, when a drop of acetic acid was added to the blue solution, it turned red then decolorized immediately. The compound consumed exactly two equivalents of iodine in dilute acetic acid solution. Ferric chloride gave a Prussian blue color in ethanol, like I, but unlike II.

Conversion of mono-O-methyl ether (IIa) *to VI with loss of methanol.* The mono-O-methyl ether with reductone properties (IIa), 0·5 g, was dispersed in 3 ml *n*-butanol and 3 ml of a solution of hydrogen chloride (21 per cent wt/wt) in *n*-butanol was added. Heating until solution occurred followed by cooling gave a yellow *hydrochloride*, 0·35 g, m.p. 173–175° (decomp). Stirring the *hydrochloride* in 3 M sodium acetate solution, followed by recrystallization from acetone, gave bright yellow crystals, m.p. 196–197° (decomp), identical in all properties with VI. C-methyl determination by the method of Kuhn–Roth gave only a trace of acetic acid.

Anhydro-piperidino-hexose-reductone hydrochloride (XVIII). Piperidino-hexose-reductone, 320 g (1·51 moles), was suspended in 250 ml *n*-butanol and 1490 g of a cold solution of 10 per cent (wt/wt) hydrogen chloride in *n*-butanol was added while stirring under nitrogen atmosphere. The reductone partially dissolved in the cold then crystallized as the colorless chloride–hydrochloride (XVII) m.p. 168° (decomp). Upon heating the mixture with steam to 55° in 8 min, XVII dissolved; then, at 60–65° (10–12 min) a second *hydrochloride*, yellow in color, began to crystallize from solution. The reaction mixture was held at 66–70° for 15 min, then it was cooled rapidly to 22° and filtered. The filter-cake was washed with butanol, then with ether, and dried in a vacuum desiccator over calcium chloride to constant weight; yield 285 g, 82 per cent of theory. A sample of the product, recrystallized from

methanol–hydrogen chloride–ether, melted at 175–182° with decomposition. (Found: C, 58·0; H, 7·10; Cl, 15·3; $C_{11}H_{16}ClNO_2$ (229·70) requires: C, 57·51; H, 7·02; Cl, 15·44%).

This *hydrochloride,* in contrast to XVII, was quite stable (unchanged after standing 3 years in a screw-capped vial). The *picrate* salt of VI, m.p. 166°, also was stable.

Anhydro-piperidino-hexose-reductone (VI). The hydrochloride of anhydro-piperidino-hexose-reductone (XVIII), 275 g (1·20 moles) was stirred with 1 liter of water under nitrogen at 25° while a filtered solution of 204 g sodium acetate trihydrate (1·50 moles) in water was rapidly run in through a large-bore tube with outlet under the surface of the stirred mixture. Rapid and thorough stirring was continued for 30 min after neutralization (pH 4·5). The yellow crystalline precipitate was filtered off with suction, washed with five 200 ml portions of water, and dried over calcium chloride in vacuum desiccators to constant weight. Yield 226 g, 97·5 per cent of theory; m.p. 188–191° (decomp). This product was recrystallized from 1·75 liters of absolute ethanol; the solution was filtered through a steam-heated funnel before crystallization. A second recrystallization of 207 g from 2·25 liters of absolute ethanol gave glistening yellow flakes from which ethanol evaporated very slowly in air. Drying at 75° in a vacuum oven gave 172 g, opaque, straw-like crystals, m.p. 197–198° (decomp). A third recrystallization from acetone gave glistening yellow prismatic needles of the same melting point. (Found: C, 68·40; H, 7·82; N, 7·19; mol. wt. (Signer) 213; $C_{11}H_{15}NO_2$ (193·24) requires: C, 68·37; H, 7·82; N, 7.25%). One active hydrogen was shown at 23° and 95° by the method of Zerewitinoff.

Only 0·06 mole of acetic acid was produced per mole of VI by the Kuhn–Roth oxidation. Tillmans reagent and iodine were reduced instantly in neutral aqueous solution as well as in dilute acetic acid; however, dark oxidation products formed and prevented quantitative titration. The enediol reaction with titanium trichloride in methanol and in pyridine according to Weygand and Csendes[6] was positive. Ferric chloride gave a deep blue color which rapidly disappeared, leaving a dark red-brown solution.

Two absorption maxima were observed in the ultra-violet: In methanol: λ_{max} 360, 230; $E_{1cm}^{1\%}$ 1250, 684, respectively. In *iso*-octane: λ_{max} 358, 228. In water: λ_{max} 353, 228 (absorptions rapidly lost). In 0·1 N hydrochloric acid: λ_{max} 330; $E_{1cm}^{1\%}$ 1310. In 0·1 N sodium hydroxide λ_{max} 400; $E_{1cm}^{1\%}$ 342 (rapidly lost). Infra-red absorptions showed a sharp band at 1660 cm^{-1} and a broad band at 1525–1575 cm^{-1}. No band was evident in the true carbonyl range.

Anhydro-piperidino-hexose-reductone mono-O-methyl ether (VIb). Anhydro-piperidino-hexose-reductone, 4·83 g (25 mmoles), was suspended and stirred in freshly distilled dimethyl sulphate, 12·6 g (100 mmoles), at 5° under nitrogen. Sodium hydroxide, 16 ml of 6 N (96 mmoles), was dropped into mixture while keeping the reaction temp below 30°. After stirring for 1 hr at 25°, the amber-coloured solution was extracted repeatedly with chloroform. The combined extracts were back-extracted with water, then dried over sodium sulphate, and distilled. Water was added to the syrupy distillation residue to produce the hydrated crystals described below, 9·4 g, m.p. 66–68·5°. Drying over phosphorus pentoxide in a vacuum desiccator at 25° for several days gave anhydrous crystals, 4·4 g, 85 per cent of theory, m.p. 58–60°. Remethylation with methyl sulphate-sodium hydroxide, and also with methyl iodide–silver oxide, gave only *mono-O-methyl ether,* m.p. 58–60°. (Found: C, 69·65; H, 8·25; N, 6·76; OCH$_3$, 15·3; $C_{12}H_{17}NO_2$ (207·26) requires: C, 69·54; H, 8·25; N, 6·76; OCH$_3$, 14·97%).

Kuhn-Roth analysis for C-methyl gave only 0·13 mole of acetic acid per mole of compound. An aqueous solution of the ether was neutral, did not reduce Tillmans reagent, and gave no deep color with ferric chloride.

Piperidino-hexose-reductone mono-O-methyl ether (II) *hydrochloride.* Ten millimoles of II, 2·25 g, was dissolved in 15 ml of a *n*-butanol solution that contained 19 per cent hydrogen chloride (wt/vol). The mixture warmed spontaneously, and soon after solution white crystals separated. After standing overnight, the crystals were drawn off, washed with *n*-butanol, then with ether. Yield, 0·5 g, m.p. 148–149° (decomp, with reddening before melting). (Found: C, 54·8; H, 7·72; OCH$_3$, 12·18; $C_{12}H_{20}NO_3Cl$ (261·75) requires: C, 55·06; H, 7·70; OCH$_3$, 11·85%).

An aqueous solution of the compound was strongly acidic, gave a precipitate of silver chloride with silver nitrate solution, did not reduce Tillmans reagent, and gave a purple color with ferric chloride, the same as the color given by II. Treatment with sodium acetate solution gave II, m.p. 143–144°.

Anhydro-piperidino-hexose-reductone mono-O-methyl ether (VIb) *formed from* II *and from* III. Ten millimoles of II, 2·25 g, was suspended in 25 ml *n*-butanol and 25 ml of a *n*-butanol solution that contained 19 per cent hydrogen chloride (wt/vol) was added. The solution was heated on a steam bath under reflux for 1 hr; then the clear, orange solution was concentrated under vacuum. Crystallization occurred during concentration. Dilution with ether, filtration, and drying produced 2·05 g of crude hydrochloride which was recrystallized from ethanol–ether–hydrogen chloride; recovery 1·40 g, m.p. 140–142° (decomp). The hydrochloride was stirred in 10 ml 3 M sodium acetate solution, yielding 1·25 g of air-dried crystalline product. Recrystallization from water gave glistening flakes of a colorless, hydrated compound, m.p. 69·0–69·5°. (Found: C, 48·86; H, 9·13; N, 4·69; OCH_3, 10·77; H_2O (by drying under vacuum over P_2O_5 at 25°), 30·24; $C_{12}H_{17}NO_2 \cdot 5H_2O$ (297·34) requires: C, 48·47; H, 9·15; N, 4·71; OCH_3, 10·44; H_2O, 30·29%).

The hydrated crystals readily lost all water upon storage in a vacuum desiccator over a dehydrating agent. A clear liquid formed on applying vacuum. When dry, the liquid could be induced to crystallize completely by rubbing, m.p. 57–59·5°. When a few drops of water were added, the crystalline pentahydrate regenerated immediately. This cycle of drying and rehydration was repeated twice without significant loss.

In the same way this peculiar *pentahydrate* was formed starting with the di-O-methyl ether, III. Sixty mg of recrystallized *pentahydrate*, m.p. 68·5°, was produced from 0·33 g of III. (Found: C, 48·7; H, 9·24; N, 4·55; OCH_3, 9·44; H_2O, 30·97%).

The *pentahydrates* from II and from III were shown to be identical with that formed directly by methylation of VI by the method of mixed melting point. Also, a mixture of anhydrous crystals from II, III, and VI showed no lowering of the melting point.

Anhydro-piperidino-hexose-reductone monoacetate (VIa). Anhydro-piperidino-hexose-reductone, 1·93 g, was dissolved in 25 ml acetic anhydride at 25°. Two ml dry pyridine was added, and the solution was stored at 0° for 2 days. Distillation of the solvent under vacuum, with several additions of anhydrous ethyl acetate, gave a syrupy residue which, upon dilution with anhydrous ether, produced a crystalline product, 1·35 g, m.p. 81–83°, 58 per cent of theory. Two recrystallizations from petroleum ether gave the pure compound as dense, colorless prisms, m.p. 83°. (Found: C, 66·76; H, 7·22; CH_3CO, 17·8; $C_{13}H_{17}NO_3$ (235·27) requires: C, 66·36; H, 7·28; CH_3CO, 18·30%).

When acetylation was tried in the usual way, i.e. pouring the pyridine-acetic anhydride solution into ice water, VI was recovered in nearly quantitative yield. The acetyl derivative dissolved quickly in ether, benzene, and ethyl acetate. Tillmans reagent was reduced in both methanol and dilute acetic acid, leaving a brown-discolored solution. The blue color produced with ferric chloride rapidly turned to orange-brown in the manner noted for VI.

Kuhn–Roth oxidation gave 0·96 mole of acetic acid per mole of compound arising from the O-acetyl radical, indicating the absence of a C-methyl group on the 5-carbon ring.

Dihydro-anhydro-piperidino-hexose-reductone (VII). In a 300 ml stainless steel hydrogenation bomb, 19·3 g (0·10 mole) of VI, 135 ml of absolute ethanol, and 3 g of Raney nickel catalyst were shaken under 1,300 lb/in² hydrogen pressure for 1 hr at 25°. After filtration and concentration of the filtrate under vacuum (nitrogen atmosphere), a syrup was obtained which crystallized completely upon stirring vigorously with ether. The residue when filtered off, washed with ether, and dried, yielded 18·1 g, (93 per cent of theory) m.p. 151–153°. Two recrystallizations from absolute ethyl acetate (88 per cent recoveries) gave a pure, colorless compound, m.p. 154–155°.

The same compound was prepared by hydrogenation in glacial acetic acid (or absolute ethanol) at 25°, 45 lb/in² hydrogen pressure, Adams platinum dioxide catalyst. Yield, 75 per cent of theory. (Found: C, 68·0; H, 8·72; N, 7·17; mol. wt. 195 (by iodine titration); $C_{11}H_{17}NO_2$ (195·25) requires: C, 67·66; H, 8·78; N, 7·17%).

The dihydro compound reduced two equivalents of Tillmans reagent in acetic acid solution. Like I, it gave a blue color with ferric chloride in ethanol, or in acetate-buffered dilute acetic acid. The test of Weygand and Csendes[6] with titanium chloride in pyridine and in methanol was positive. Kuhn–Roth oxidation gave 0·5 mole of acetic acid per mole of compound.

The ultra-violet absorption curves for VII were virtually duplicates of the corresponding curves for I. In methanol: λ_{max} 315 mμ; $E_{1cm}^{1\%}$ 1516. In water: λ_{max} 305; $E_{1cm}^{1\%}$ 778. In 0·1 N hydrochloric acid: λ_{max} 298; $E_{1cm}^{1\%}$ 1277. In 0·1 N sodium hydroxide: λ_{max} 345; $E_{1cm}^{1\%}$ 335 (rapidly lost). The infra-red absorption curve showed a sharp band at 1667 cm^{-1} and a broad band at 1520–1580 cm^{-1} with no absorption in the true carbonyl range.

Dihydro-anhydro-piperidino-hexose-reductone monoacetate (VIIa). Following the acetylation procedure prescribed for VI, VII yielded colorless crystals after two recrystallizations from *n*-heptane, m.p. 92°, 47 per cent of theory. (Found: C, 66·2; H, 7·90; CH₃CO, 17·5; C₁₃H₁₉NO₃ (237·29) requires: C, 65·80; H, 8·07; CH₃CO, 18·14%).

Phenylhydrazine derivative of piperidino-hexose-reductone (VIII). Phenylhydrazine hydrochloride, 3·00 g (21 mmoles), was dissolved in 250 ml water at 80°. Under an atmosphere of nitrogen 4·23 g (20 mmoles) of I was added to the stirred aqueous solution, and the reaction mixture was held at 80–83° for 2 hr until the acidic solution had become nearly neutral and nonreducing toward Tillmans reagent. The deep red crystalline product was filtered off with suction and washed with hot water. The dried substance weighed 4·20 g, 97 per cent of theory, m.p. 202–204°. Two recrystallizations from 100 volumes of acetone gave straw-like, opaque, deep yellow needles, m.p. 205°. Brilliant deep red prisms, m.p. 204–205°, formed from alcohol. However, when these thick prisms were finely pulverized, the color was deep yellow. They gave no lowering of the melting point with the opaque crystals from acetone. Both recrystallized products gave a single, yellow-fluorescing spot under ultra-violet light (of the same R_f after paper chromatography in butanol–acetic acid–water; cf. VIII in Part II). Both products had the same analysis: (Found: C, 66·7; H, 5·58; N, 13·0 (Dumas); C₁₂H₁₂N₂O₂ (216·23) requires: C, 66·65; H, 5·59; N, 12·96%).

Kuhn–Roth oxidation gave 0·94 mole of acetic acid per mole of compound, indicating the presence of one C-methyl group. The iodoform test was negative. Reaction with sodium hydrosulphite in aqueous ethanol at 85° gave 80 per cent of the theoretical amount of aniline, isolated as benzanilide, m.p. 161°. The mixed melting point with an authentic sample was 161°.

Phenylhydrazine derivative of anhydro-piperidino-hexose-reductone (VIII). Anhydro-piperidino-hexose-reductone (VI) was reacted as described in the preceding paragraph with phenylhydrazine hydrochloride, producing 76 per cent of the theoretical amount of VIII, identical in all properties and in C, H, N, and C-methyl analyses with the C₁₂H₁₂N₂O₂ compound described above. The same compound was obtained in nearly quantitative yield from the reaction of VI with phenylhydrazine in 3 N acetic acid solution. In acetic acid under these conditions, I reacted very slowly and only a small amount of the red product was formed. The crude products showed both types of spots described for the paper chromatography of VIII in Part II. After recrystallization, only the slower moving, yellow-fluorescing spot was obtained.

Mono-O-*acetyl ester of* VIII (VIIIa)

Acetylation of VIII with a 4-molar excess of acetic anhydride in pyridine at 25° gave two *mono*-O-*acetyl* derivatives of different melting points. The lower melting ester crystallized from the reaction mixture within a few min. Upon recrystallization from ethanol it melted at 120–121°. The higher melting ester was more soluble in the reaction mixture but was less soluble in ethyl acetate. Repeated recrystallization from ethyl acetate gave brilliant yellow, felted needles, m.p. 177°. Both esters gave the same analyses within the experimental error: (Found: C, 65·02; H, 5·48; CH₃CO, 16·2; C₁₄H₁₄N₂O₃ (258·27) requires: C, 65·10; H, 5·46; CH₃CO, 16·67%).

Acetylation of the crude red product, that gave two spots by paper chromatography gave proportionately more of the lower melting acetate.

Part II: By F. Weygand, H. Simon and W. Bitterlich

Hydrogenation of piperidino-hexose-reductone to 1-*methyl-4-piperidino-cyclopentanol-*(2 *or* 3) (V). Platinum dioxide (200 mg) was prehydrogenated in a hydrogenation vessel. A solution of 4·22 g I (20 mmoles) in 100 ml 2 N sulphuric acid was run into the vessel along with a stream of hydrogen. After 20 hr at room temp 95 per cent of the calculated amount of hydrogen for 4 moles per mole of I was absorbed. The filtrate from the catalyst was stirred with barium carbonate until it became alkaline. After the addition of dilute sodium hydroxide, the solution was extracted with ether. Upon distillation of the ether the product partially volatilized and separated in the form of colorless crystals in the condenser. However, 1·2 g of the crystalline material remained in the distillation flask. After sublimation the purified product melted at 71°. (Found: C, 71·94; H, 11·36; N, 7·66; C₁₁H₂₁NO (183·29) requires: C, 72·06; H, 11·55; N, 7·64%).

One active hydrogen was shown by the method of Zerewitinoff. The substance is extremely volatile and, for example, cannot be dried at room temp *in vacuo* over phosphorus pentoxide.

Methiodide (XII) *and Hofmann degradation of* V. One g V was heated with a tenfold excess of

methyl iodide in 20 ml nitromethane under reflux. After distillation of the nitromethane and recrystallization of the product, the m.p. was 142°. (Found: N, 4·42. $C_{12}H_{24}INO$ (325·23) requires: N, 4·31 %).

For the Hofmann degradation, 1 g of the quaternary iodide (XII) was transformed to the free base with silver oxide. The solution was frozen and then dried. The residue was decomposed at 150° to yield N-*methyl-piperidine* by distillation. The base was isolated as the *picrate*, m.p. 148°. (Found: N, 16·76; $C_{12}H_{16}N_4O_7$ (328·28) requires: N, 17·05 %).

Phenylhydrazine derivative of piperidino-hexose-reductone (VIII). Piperidino-hexose-reductone (4·22 g, 20 mmoles) was dissolved in 110 ml 1 N hydrochloric acid and 4·30 g phenylhydrazine was added. Phenylhydrazine hydrochloride separated at first but later dissolved upon warming. At about 70° the phenylhydrazone separated in the form of glittering orange-colored leaflets. Upon further warming the crystals became darker in color and were transformed to needles. After 10 min standing in a boiling-water bath, the deep red crystalline mass was filtered off, washed with dilute hydrochloric acid, and then with water. Yield 4·23 g, 97 per cent of theory.

Chromatographic investigations on paper showed that the product obtained consisted of a mixture of two forms. One form showed an R_F value of 0·76 in butanol–acetic acid–water (4 : 1 : 1) and fluoresced in ultra-violet light. The orange-coloured product that was obtained by short heating of the reaction mixture at 70° consisted preponderantly of this form (R_F 0·76), m.p. 189°. The other form showed an R_F value of 0·83 and absorbed ultra-violet light. By recrystallization from nitrobenzene or acetoacetic ester, the form of R_F 0·83 was obtained as yellow- or orange-colored crystals, preponderantly. The melting point and mixed melting point of these differently recrystallized products were the same: 194°. (Found: C, 66·48; H, 5·68; N, 13·02; mol. wt., 230·7; Calc. for $C_{12}H_{12}N_2O_2$: C, 66·65; H, 5·59; N, 12·96 %, mol. wt., 216·23).

Hydrogenation of the phenylhydrazine derivative of piperidino-hexose-reductone (VIII → IX). A suspension of VIII, 8 g, in 150 ml of 80 per cent alcohol was hydrogenated with platinum (from 150 mg PtO_2) in a shaking vessel. After uptake of 800 to 900 ml of hydrogen within 2 to 3 hr, the rate of hydrogenation decreased. All substance had dissolved after 3 to 4 days. After an additional day hydrogenation was stopped. The solution was filtered from the catalyst and evaporated under nitrogen. Upon taking up the hydrogenated product in hot water, the incompletely hydrogenated substance remained undissolved. The filtrate was again concentrated *in vacuo* under nitrogen, and the residue was recrystallized from acetone, yielding 2 to 3 g of colorless to weak yellow leaflets, m.p. 200–202°.

Paper chromatography with *n*-butanol–acetic acid–water (4 : 1 : 1) showed the main product at R_F 0·67. A small amount of a second, enediol-active product was detected at R_F 0·81.

Only 3 hr were required when the hydrogenation was repeated at 60°.[15] The yield of crude, cream-colored product was 90 per cent of theory. Two recrystallizations from 125 volumes of acetone (75 per cent yields) gave the colorless product of m.p. 200–203°. (Found: C, 56·60; H, 7·04; N, 11·0; $C_6H_9NO_2$ (127·14) requires: C, 56·68; H, 7·13; N, 11·02 %).

The compound reduced two equivalents of iodine in dilute acetic acid solution and gave Prussian blue color with ferric chloride in ethanol.

Dihydro derivative of VIII (VIIIb). Four g VIII was heated in 150 ml 80 per cent ethanol until dissolved. After cooling, a part of the substance separated as dark red crystals. The mixture was hydrogenated at room temp with 100 mg platinum dioxide. Under these conditions the suspended material dissolved completely, and a yellow precipitate formed after the uptake of 1 mole of hydrogen. The hydrogenation vessel was evacuated and filled with nitrogen. By decanting under a bell jar of nitrogen, the catalyst was separated, and the product was filtered off and dried. (Found: C, 65·62; H, 6·73; N, 12·68; $C_{12}H_{14}N_2O_2$ (218·25) requires: C, 66·04; H, 6·44; N, 12·84 %).

Oxidation of IX *to methylsuccinic acid.* One millimole of IX (127 mg) was dissolved in 50 ml water by heating. While the solution was kept hot, 4 millimoles of hydrogen peroxide in the form of a 3 per cent solution was dropped in. After about 4 hr standing at 40–50°, the residue obtained by evaporation was extracted with acetone, and after repeated drying it was sublimed at 1 mm. The monoammonium salt of *methylsuccinic acid* so obtained ($C_5H_{11}NO_4$) was dissolved in dilute hydrochloric acid. After distilling off the acid, the dry residue was extracted with anhydrous acetone to yield the free *methylsuccinic acid*. Sublimation gave the pure acid, m.p. 112°. (Found: C, 45·37; H, 6·03; $C_5H_8O_4$ (132·11) requires: C, 45·46; H, 6·06 %).

[15] By E. C. Nelson of the American Group.

Identity with *methylsuccinic acid* was proved by melting point, mixed melting point with authentic material and also by preparation of an anil (m.p. 104–106°) and a β-napthylimide (m.p. 160–161°).

Oxidation of VII *to methylsuccinic acid.* After dissolving 1·3 millimoles of VII in hot water and treating with 0·6 ml 30 per cent hydrogen peroxide solution, the reaction mixture was held for 10 min in a boiling-water bath. Gas was eliminated and the solution turned yellow. Evaporation under vacuum, addition of dilute hydrochloric acid, and reconcentration under vacuum gave a residue which was taken up in acetone; the piperidine hydrochloride was removed by filtration, the acetone evaporated, and the residue sublimed to yield *methylsuccinic acid*, m.p. 112°, identical with the product described in the preceding section.

Oxidation of piperidino-hexose-reductone to citramalic acid. Ten g I was dissolved in 300 ml water by heating. The solution was treated at 90° with 23 ml of 30 per cent hydrogen peroxide solution and was kept hot on the water bath for 30 min. Carbon dioxide was eliminated. After cooling, 30 g lead acetate was added. The precipitate which formed over 24 hr was dried and finely pulverized in a mortar. A strong stream of hydrogen sulphide was led into an aqueous suspension of this material for 2 hr. After filtering from the lead sulphide and evaporating under vacuum, the syrupy residue was taken up in 50 ml water. Di*cyclo*hexylamine was added to a significant alkaline reaction, then the excess amine was removed by extraction with petroleum ether. The syrup obtained after evaporation of the aqueous solution under vacuum crystallized after 2 days (8·9 g). The dried material was extracted once at the boiling point with 20 ml benzene and then was further extracted five times with 50 ml portions of benzene. The crystalline precipitates that formed in the various fractions during storage in the ice chest were dried and their melting points determined. Crystals from the second and third fractions were recrystallized from benzene (m.p. of the di*cyclo*hexylamine salt 137–140°). The free acid was obtained as a syrup by dissolving the salt in water and shaking with the acid form of a cation–exchange resin. Crystallization occurred upon cooling in ether to −78° and rubbing. After two recrystallizations from a mixture of ethyl acetate–petroleum ether (2 : 1), pure *citramalic acid* was obtained, m.p. 117°.

The melting point of a mixture of the oxidation product with synthetic *citramalic acid* was not lowered. Also, the melting points and mixed melting points of the di*cyclo*hexylamine salts, obtained by degradation of I, and the synthetically produced reference compound were not lowered (137–140°). (Found: C, 40·76; H, 5·60; $C_5H_8O_5$ (148·11) requires: C, 40·54; H, 5·44%).

Reaction of 1-*methyl*-4-*chloro*cyclo*penten*(1)-*ol*(2)-*one*(3) *with piperidine.* The chloro derivative of methyl *cyclo*pentenolone (XIV), 4·47 g, was dissolved in 30 ml benzene and this solution was dropped slowly into 40 ml piperidine that was held in an ice-salt mixture. After standing for 2 hr at room temp, the crystalline mass was drawn off by suction, and the filtrate was evaporated *in vacuo* under nitrogen between 35 and 40°. The residue was stirred with water; then filtration and recrystallization from a mixture of benzene-ligroin (2 : 3) gave the desired product, m.p. 153·5°, in yield better than 75 per cent of theory.

To compare this synthetic material with the dihydro-anhydro-piperidino-hexose-reductone (VII), both preparations were sublimed at 1 mm. (Found: C, 67·95; H, 8·90; N, 7·49; $C_{11}H_{17}NO_2$ (195·25) requires: C, 67·66; H, 8·78; N, 7·17%).

The mixed melting point of a mixture of VII and the synthetic material showed no depression. Also, the Debye–Scherrer photograph and the I.R. spectrum are exactly identical with those of VII.

The same compound was obtained in an analogous way from 1-methyl-2:3-diketo-4-chloro-pentane[10] and piperidine.