

The 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (V). **Method A. Hydrochloric Acid.**—To 73 g. (0.38 mole) of 3,6-dimethyl-6-phenyltetrahydro-1,3-oxazine (III) was slowly added with external cooling 100 g. (1.0 mole) of concentrated hydrochloric acid. The mixture was stirred on a steam-bath for 6 hr. After cooling it was poured into 300 ml. of water and made basic with excess 50% sodium hydroxide. The amine was taken up in benzene, dried and distilled to give 57 g. (86%) of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (V), b.p. 85–90° (0.8 mm.). This crystallized and melted at 40–42° after recrystallization from heptane.

Method B. Sulfuric Acid.—A similar experiment using 50 g. (0.26 mole) of 3,6-dimethyl-6-phenyltetrahydro-1,3-oxazine (III) and 150 g. (1.0 mole) of 66% sulfuric acid gave 36 g. (80%) of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (V).

Anal. Calcd. for $C_{12}H_{15}N$: N, 8.09. Found: N, 8.04.

The hydrochloride melted at 251–252° after recrystallization from acetone containing a small amount of isopropyl alcohol. A mixed m.p. with the hydrochloride from method A was 249–251°.

Anal. Calcd. for $C_{12}H_{15}NCl$: Cl, 16.9. Found: Cl, 16.9.

A 1.73-g. (0.01 mole) sample took up 0.01 mole of hydrogen over 5% palladium on alumina in 95% ethanol at room temperature and at atmospheric pressure. The picrate of the resulting 1-methyl-4-phenylpiperidine melted at 235–237°, lit.⁴ m.p. 236–237°, lit.⁵ m.p. 239–240°.

Method C. Direct Preparation from α -Methylstyrene, Formaldehyde and Methylamine Hydrochloride.—A mixture of 280 g. (4.15 moles) of methylamine hydrochloride and 680 g. (8.38 moles) of 37% aqueous formaldehyde was stirred and warmed until homogeneous. There was added 472 g. (4.00 moles) of α -methylstyrene and the mixture was stirred vigorously while the temperature was raised to 75°. Heating was discontinued and the ensuing exothermic reaction was controlled by external cooling so that the temperature remained at 90–100°. When the exotherm had subsided the mixture was stirred on a steam-bath for one hour and then cooled to 50°. There was added slowly 340 g. (3.40 moles) of concentrated sulfuric acid with external cooling so that the temperature did not rise above 70°. When the addition was complete the mixture was stirred for 3 hr. at 90–95°, cooled, poured into 2 l. of water and ex-

tracted with benzene. The aqueous portion was made basic with excess 50% sodium hydroxide and the amine was taken up in benzene, dried and distilled to give 361 g. (52%) of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (V), b.p. 80–100° (0.9 mm.).

Anal. Calcd. for $C_{12}H_{15}N$: N, 8.09. Found: N, 8.18.

The hydrochloride melted at 250–252° after recrystallization from a 20:1 acetone-isopropyl alcohol mixture. A mixed m.p. with the hydrochloride from method B was 250–252°.

Anal. Calcd. for $C_{12}H_{15}NCl$: C, 68.72; H, 7.69; N, 6.68; Cl, 16.9. Found: C, 68.64; H, 7.72; N, 6.77; Cl, 16.7.

1-Methyl-4-phenyl-4-piperidinol (IV). **A. By Rearrangement of 3,6-Dimethyl-6-phenyltetrahydro-1,3-oxazine (III).**—A mixture of 96 g. (0.50 mole) of redistilled 3,6-dimethyl-6-phenyltetrahydro-1,3-oxazine (III) and 50 g. (0.51 mole) of 37% hydrochloric acid was stirred on a steam-bath for 5 hours, cooled, poured into 300 ml. of water and made basic with excess 50% sodium hydroxide. The amine was taken up in toluene, dried and distilled to give 72 g. of material, b.p. 84–114° (1.2 mm.), and 14 g. (14.6%) of 1-methyl-4-phenyl-4-piperidinol (IV), b.p. 114–129° (1.2 mm.). This crystallized and after recrystallization from a toluene-heptane mixture melted at 115–116°.

Anal. Calcd. for $C_{12}H_{17}NO$: C, 75.35; H, 8.96; N, 7.33. Found: C, 75.52; H, 8.83; N, 7.31.

The lower boiling material contained 7.66% nitrogen.

B. By Hydration of 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (V).—Into a solution of 10 g. (0.058 mole) of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (V) in 200 ml. of glacial acetic acid was slowly bubbled anhydrous hydrogen bromide during 2 hours while the temperature was maintained at 10–20° by external cooling. The mixture was then allowed to warm to room temperature and stand overnight. The acetic acid was removed by distillation under reduced pressure below 45°. The residue was dissolved in 200 ml. of water at room temperature and then heated on a steam-bath for 2 hours, cooled and made basic with excess 50% sodium hydroxide. The solid amine was filtered off and recrystallized from heptane-toluene to give 8 g. (73%) of 1-methyl-4-phenyl-4-piperidinol (IV), m.p. 113–115°.

Anal. Calcd. for $C_{12}H_{17}NO$: C, 75.35; H, 8.96; N, 7.33. Found: C, 75.39; H, 8.90; N, 7.22.

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[CONTRIBUTION FROM THE RESEARCH AND DEVELOPMENT DEPARTMENT, U. S. NAVAL POWDER FACTORY]

Reaction of Silver Penta-*O*-acetyl-D-gluconate with Bromine¹

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When the silver salt of penta-*O*-acetyl-D-gluconic acid is treated with bromine, the carboxylic acid group is lost as carbon dioxide and *aldehyde*-1-bromopenta-*O*-acetyl-D-arabinose is formed. The structure of this compound was proved by converting the compound into known *aldehyde*-D-arabinose hexa-*O*-acetate by means of silver acetate and also by reducing the *aldehyde*-1-bromopenta-*O*-acetyl-D-arabinose to D-arabitol by means of lithium aluminum hydride. D-Arabitol was identified as the penta-*O*-acetate.

One of the authors has reported² that the thoroughly dry silver salt of alginic acid (a polymanuronic acid) is decarboxylated when a suspension of the salt in carbon tetrachloride is treated with bromine. The over-all reaction by which this decarboxylation occurs has been extensively investigated³ on a large number of aliphatic and aromatic acids, and it is known that the aldehyde

with one less carbon atom can be obtained from the α -hydroxy acids.^{4,5} So far as we are aware, however, the decarboxylation of the sugar acids by the treatment of their silver salts with halogen has not been investigated.

Although the sugar acids can be decarboxylated by treating the corresponding amide with hypochlorite⁶ or by treating the calcium salt of the acid with hydrogen peroxide in the presence of

(1) Published with permission of the Bureau of Ordnance, Navy Department. The opinions and conclusions are those of the authors.

(2) F. A. H. Rice, Abstracts 127th Meeting, Am. Chem. Soc., (Cincinnati, Ohio) **11E**, (1955).

(3) J. Kleinberg, *Chem. Revs.*, **40**, 381 (1947).

(4) R. O. Herzog and R. Leiser, *Monatsh.*, **22**, 357 (1901).

(5) A. Lüttringhaus and D. Schade, *Ber.*, **74B**, 1565 (1941).

(6) R. A. Weerman, *Rec. trav. chim.*, **37**, 16 (1917).

ferrous iron⁷ it was considered of interest to investigate a method of decarboxylation which necessitated a non-aqueous system and hence might be used with compounds sensitive to acid or alkaline conditions.

The reaction of the silver salt of a hexonic acid acetate such as penta-*O*-acetyl-D-gluconic acid with halogen should lead to the *aldehydo*-1-halo-pentose acetate. Such compounds have been prepared⁸ by treating the *aldehydo* sugar acetate with acetyl chloride.

The silver salt-bromine reaction is very sensitive to traces of moisture. Lüttringhaus and Schade⁵ state that even when moisture is excluded with great care the free acid corresponding to the silver salt is formed. In our experience small samples of the silver salt of penta-*O*-acetyl-D-gluconic acid which had been dried for several days at 100° gave essentially a quantitative yield of carbon dioxide on treatment with bromine and yielded a thick sirup which analyzed correctly for an *aldehydo*-monobromopentose penta-*O*-acetate. Samples of over a gram however gave low yields of carbon dioxide (50%) with, however, corresponding amounts of the *aldehydo*-monobromopentose penta-*O*-acetate. The silver salt decomposed readily on heating over 100° so it was impossible to use more rigorous conditions of drying. However, when samples of approximately 10 g. of silver salt were stirred for several hours with phosphorus pentoxide and excess silver oxide before the addition of bromine, almost quantitative yields of carbon dioxide and the bromopentose penta-*O*-acetate were obtained.

That the compound formed from D-gluconic acid penta-*O*-acetate was *aldehydo*-1-bromo-D-arabinose penta-*O*-acetate is shown by the fact that treatment with silver acetate gave *aldehydo*-D-arabinose hexa-*O*-acetate and reduction with lithium aluminum hydride followed by acetylation yielded arabitol penta-*O*-acetate.

If, as has been suggested,^{3,9} the silver salt-bromine reaction proceeds *via* a slow ionization of the carboxyl carbon followed by the formation of the C-Br bond we could expect to get both an α - and β -bromopentose penta-*O*-acetate. This might account for both the non-crystallinity of our bromopentose and the optical rotation which is low compared to the corresponding compound obtained from L-arabinose.¹⁰ The problem is under investigation.

Experimental

Preparation of Silver Penta-*O*-acetyl-D-gluconate.—Penta-*O*-acetyl-D-gluconamide (m.p. 183°, $[\alpha]^{22D} +23^\circ$) was prepared after the manner of Robbins and Upson.¹¹ The free acid was obtained by treating the amide with nitrosyl chloride¹² in alcohol-free chloroform. The penta-*O*-acetyl-D-gluconic acid was crystallized from toluene¹³ to yield the anhydrous acid which had m.p. 110° and $[\alpha]^{20D} +11^\circ$ (alcohol-free chloroform, *c* 2) in agreement with the values reported in the literature.

- (7) O. Ruff, *Ber.*, **31**, 1573 (1893); **32**, 553 (1899).
 (8) M. L. Wolfrom, *THIS JOURNAL*, **57**, 2498 (1935).
 (9) M. Rottenberg, *Experientia*, **7**, 432 (1951).
 (10) G. E. Felton and W. Freudenberg, *THIS JOURNAL*, **57**, 1637 (1935); M. L. Wolfrom and M. Konigsberg, *ibid.*, **60**, 288 (1938).
 (11) G. B. Robbins and F. W. Upson, *ibid.*, **60**, 1788 (1938).
 (12) M. L. Wolfrom, M. Konigsberg and D. I. Weisblat, *ibid.*, **61**, 574 (1939).
 (13) R. T. Major and E. W. Cook, *ibid.*, **58**, 2474 (1936).

Anal. Calcd. for C₁₅H₂₂O₁₂: C, 47.53; H, 5.46. Found: C, 47.45; H, 5.44.

The penta-*O*-acetyl-D-gluconic acid was converted into its silver salt by treatment with silver oxide in acetone. Ten grams of penta-*O*-acetyl-D-gluconic acid was dissolved in 50 ml. of acetone, 2.8 g. of silver oxide was added and the mixture was stirred for several hours at room temperature. The silver salt precipitated as a grayish crystalline magma and was filtered on a fritted glass funnel. The compound was recrystallized from hot water, and the salt analyzed for the monohydrate.

Anal. Calcd. for C₁₅H₂₁O₁₂·Ag·H₂O: C, 36.17; H, 4.36; ash, 21.8. Found: C, 36.08; H, 4.32; ash, 21.93.

The anhydrous form was obtained by drying the silver salt for several days in a high vacuum at 100°.

Anal. Calcd. for C₁₅H₂₁O₁₂·Ag: C, 36.45; H, 4.11; ash, 22.5. Found: C, 36.42; H, 4.08; ash, 22.4.

Decarboxylation of Silver Penta-*O*-acetyl-D-gluconate with Bromine in Carbon Tetrachloride.—The anhydrous silver salt of penta-*O*-acetyl-D-gluconic acid (0.511 g.) was dried for two days at 100° and then suspended in 20 ml. of redistilled carbon tetrachloride. One milliliter of a solution of bromine in carbon tetrachloride (1:10 by volume) was added and the mixture stirred for two hours at room temperature; it was then heated at 80° for 4 hours, until the evolution of carbon dioxide had ceased. Nitrogen gas which had been freed from carbon dioxide and dried by passing it first through soda-lime and then through concd. sulfuric acid was used to sweep out the carbon dioxide formed by the reaction. After passing through the water cooled condenser the gases were passed through two traps cooled in Dry Ice and acetone (to remove any bromine vapor) and finally into a 0.2 *M* barium hydroxide solution. The quantity of carbon dioxide evolved was determined by titrating the barium hydroxide solution with 0.1 *N* hydrochloric acid to *pH* 8 (Beckman *pH* meter), and subtracting the value so obtained from a blank.

Anal. Calcd. for 0.511 g. of silver penta-*O*-acetyl-D-gluconate (as ml. of 0.1 *N* HCl) 19.9. Found: 20.

The reaction mixture was filtered through a fritted glass funnel and the filtrate concentrated to yield a thick sirup.

Anal. Calcd. for C₁₅H₂₁O₁₀·Br: C, 40.83; H, 4.80; Br, 18.12. Found: C, 40.91; H, 4.38; Br, 18.47.

The optical rotation was $[\alpha]^{21D} +21^\circ$ (CHCl₃, *c* 5). Although samples of under a gram gave a quantitative yield of carbon dioxide when treated as above, samples of 2 to 10 g. gave yields of carbon dioxide between 50 and 80%.

For samples over a gram the following modified procedure was used: Silver penta-*O*-acetyl-D-gluconate (12.75 g.) was suspended in 50 ml. of carbon tetrachloride and 1 g. of phosphorus pentoxide together with 7 g. of silver oxide added. The mixture was chilled in Dry Ice and acetone until it formed a semisolid mass. At this point 20 ml. of a solution of bromine in carbon tetrachloride (1:10 by volume) was added and the mixture allowed to stand at room temperature for 2 hours. The mixture was then heated at 80° for 4 hours. Carbon dioxide was evolved equivalent to 390 ml. of 0.1 *N* hydrochloric acid (theoretical 493 ml. of 0.1 *N* hydrochloric acid). After filtration through a fritted glass filter the solution was concentrated at room temperature under reduced pressure to a thick sirup. After the sirup had been triturated with 50 ml. of petroleum ether (b.p. 35–55°), which was then removed by decantation, it was dried for several hours under high vacuum at room temperature. A halogen determination showed Br, 14.1 (calcd. 18.2); weight 10.6 g.

The sirup was dissolved in 100 ml. of alcohol-free chloroform and extracted with cold (ice-water) sodium bicarbonate solution (4 × 50 ml.) and then with 50 ml. of ice-water. The chloroform solution was then dried over anhydrous sodium sulfate, filtered and concentrated at room temperature under reduced pressure to yield a sirup, which was dried under high vacuum in a desiccator.

Anal. Calcd. for C₁₅H₂₁O₁₀Br: C, 40.83; H, 4.80; Br, 18.12. Found: C, 40.73; H, 4.39; Br, 18.82.

The aqueous sodium bicarbonate phase was acidified with hydrochloric acid (*pH* 3) and extracted with chloroform. The chloroform phase was dried over anhydrous sodium sul-

fate and concentrated at room temperature under reduced pressure to dryness. The sirup that resulted was crystallized from toluene and had m.p. 110° alone or when mixed with an authentic sample of penta-*O*-acetyl-D-gluconic acid.

Preparation of aldehydo-D-Arabinose Hexa-*O*-acetate.—The sirup obtained from the decarboxylated silver salt of penta-*O*-acetyl-D-gluconic acid (2.0 g.) was dissolved in 10 ml. of toluene, 2.0 g. of dry silver acetate¹⁴ was added and the mixture heated under reflux for five minutes. After standing overnight at room temperature the mixture was filtered and two volumes of petroleum ether (b.p. 35–55°) added to the filtrate. A gummy solid separated. This was separated by decantation and dissolved in chloroform (25 ml.). The chloroform solution was extracted with half-saturated sodium bicarbonate solution (two 10 ml. portions), ice-water (10 ml.) and then dried over anhydrous sodium sulfate, filtered and concentrated at room temperature under reduced pressure. Crystals were obtained from ethanol, m.p. 89–90°, $[\alpha]^{21}_D +29^\circ$ (CHCl₃, *c* 5) in accord with the values reported for aldehydo-D-arabinose hexa-*O*-acetate.¹⁵ The melting point showed no depression upon admixture with aldehydo-D-arabinose hexa-*O*-acetate prepared from D-arabinose.³

Reduction with Lithium Aluminum Hydride.—Two grams of the sirup obtained from the decarboxylation of silver penta-*O*-acetyl-D-gluconate was reduced in 50 ml. of anhy-

drous ether with excess lithium aluminum hydride¹⁶ (1 g.) at room temperature for 2 hours.

After treatment with 20 ml. of water and 50 ml. of acetic acid, the ether was removed and the aqueous solution concentrated to dryness under reduced pressure at 35–40°. The dry powder so obtained was acetylated by adding it to a chilled (0°) 50-ml. solution of acetic anhydride and 2 ml. of *concd.* sulfuric acid and then allowing the mixture to stand at room temperature overnight. The acetylation mixture was poured into 500 ml. of ice-water containing 4 g. of sodium acetate, which after several hours was extracted with chloroform (four 50 ml. portions). The chloroform solution was dried over anhydrous sodium sulfate and concentrated to dryness to yield a sirup which crystallized from ethanol; m.p. 75°, $[\alpha]^{22}_D +35^\circ$ (CHCl₃, *c* 5).

Anal. Calcd. for C₁₅H₂₂O₁₀: C, 49.96; H, 6.11. Found: C, 49.53; H, 6.08.

The compound showed no depression in melting point when mixed with arabitol penta-*O*-acetate prepared from D-arabinose by sodium borohydride¹⁷ reduction and acetylation.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES, THE UPJOHN CO.]

“Enamine” Derivatives of Steroidal Carbonyl Compounds. IV. Structural Considerations¹

BY JAMES L. JOHNSON, MILTON E. HERR, JOHN C. BABCOCK, ANNE E. FONKEN, JAMES E. STAFFORD AND FREDERICK W. HEYL

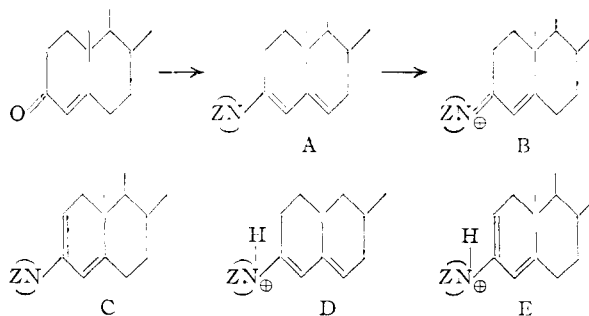
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The condensation products of secondary amines with Δ^4 -3-ketosteroids are shown to be 3-amino-3,5-dienes. In the presence of strong acids these “enamines” isomerize to ternary iminium salts: $>C=C-C=C-N< \rightarrow H-C=C-C=C-N^{\oplus}<$.

Reactions with alkyl halides in non-polar solvents yield the normal quaternary salts: $>C=C-C=C-N^{\oplus} \leftarrow R X^{\ominus}$. The ultraviolet, polarimetric, infrared and chemical data which support these conclusions are discussed. A simplified preparation of enamines is described.

Condensation of aldehydes and ketones with secondary amines was first described by Mannich and Davidsen.² The reaction was subsequently modified and applied to steroids by Heyl and Herr,³ who found that selectivity in the protection of aldehyde or ketone functions of polycarbonyl steroids could be achieved by a suitable choice of amine reagent. Primarily on the basis of their strong levorotation the enamines formed from Δ^4 -3-ketosteroids were inferred to be 3,5-dienes (A) rather than the alternative 2,4-dienes (C).⁴ Other evidence was reported, however, which appeared to favor the homoannular diene structure.⁴

Further study has shown these enamines of α,β -unsaturated ketosteroids to be highly reactive and labile compounds, the specific structures of which are determined by their solvent environment. The heteroannular system (A) has been established as the species existing in neutral solvent. In



strongly acid solutions these enamines rearrange rapidly to the stable ternary iminium salts (B). Upon reaction with alkyl halides in non-polar solvents, on the other hand, the enamines yielded the normal N-alkyl quaternary salts. These transformations were accompanied by diagnostic changes in rotation and in ultraviolet and infrared absorption.

Ultraviolet and Infrared Absorption Studies.—In ether solution the pyrrolidinyl enamines of Δ^4 -3-ketosteroids (Table I) exhibited ultraviolet absorp-

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(2) C. Mannich and H. Davidsen, *Ber.*, **69**, 2106 (1936).

(3) Reference 1 and preceding papers.

(4) Reference 1, footnote 6.