in this case; the relative proportions of products of type VII and X, and of other by-products, depends very markedly upon the substitution pattern of the octalone studied: between 80% of indane in cases a and c, to 80% of tetralin in cases b and d.

The most remarkable features of this aromatization are its ease and cleanliness in the case where no angular methyl group hinders it, with HBr/AcOH, *p*-TsOH/AcOH, CF₃CO₂H or polyphosphoric acid (PPA). For example the trimethyloctalone (VIc) with PPA at 150° gives quantitatively the trimethyltetralin (VIIc) in two minutes.

*Institut de Chimie,
Université de Strasbourg,
Faculté des Sciences,
Esplanade,
Strasbourg,
France*

Philippe Bey
Florence Lederer
Guy Ourisson

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Synthesis of 8-Hydroxypurine Nucleosides

Recently, 8-hydroxynucleosides draw attention of many investigators, because of their biological interest.¹⁻³⁾ From the chemical point of view, they also are interest as the key intermediate of the synthesis of purine cyclonucleosides^{4,5)} having O-anhydro linkage.

In order to meet this requirement, many attempts were made in this laboratory to hydrolyze halogen atom substituted at 8-position. However, the acid lability of purine nucleoside and alkaline instability of 8-hydroxypurine nucleoside gave only unsatisfactory results.

We found that, when 8-bromo derivatives of adenosine and guanosine were heated in acetic acid with excess of sodium acetate, desired 8-hydroxy compounds were obtained in a good yield. 8-Bromoguanosine (I) was heated with ten fold excess of anhydrous sodium acetate (fused freshly) in glacial acetic acid at 118° for 3 hours. Resulting white solid has $\lambda_{\text{max}}^{\text{pH } 2} \text{ m}\mu$: 242, 292; $\lambda_{\text{max}}^{\text{pH } 7} \text{ m}\mu$: 242, 292; $\lambda_{\text{max}}^{\text{pH } 10} \text{ m}\mu$: 251, 279. The similar solubility of this compound with that of sodium acetate in many solvents made it difficult to purify this specimen. In order to circumvent this difficulty 2',3'-O-isopropylidene-8-bromoguanosine (II) was reacted in acetic acid with sodium acetate and 2',3'-O-isopropylidene-8-hydroxyguanosine*¹ (III) was obtained as a hard glass. Acidic removal of isopropylidene group gave 8-hydroxyguanosine (IV), m.p. >180°(decomp.), in 38% yield. *Anal.* Calcd. for C₁₀H₁₃O₆N₅·½H₂O: C, 38.96; H, 4.54; N, 22.72. Found: C, 38.80; H, 4.72; N, 22.21. Ultraviolet absorption properties: $\lambda_{\text{max}}^{\text{pH } 2} \text{ m}\mu$: 245.5, 292.5; $\lambda_{\text{max}}^{\text{pH } 7} \text{ m}\mu$: 245.5, 292.5; $\lambda_{\text{max}}^{\text{pH } 10} \text{ m}\mu$: 258, 280. Infrared absorption $\nu_{\text{max}}^{\text{Nujol}} \text{ cm}^{-1}$: 1720 (8-CO). Paper chromatography: R_f 0.10 (1-butanol-water, 86:14), R_f 0.69 (water, pH 10). This sample was identical in many respects with that obtained above. 8-Hydroxyguanosine

*¹ Although 8-hydroxypurine may be obtained *via* an 8-acetoxy compound, the latter compound could not be isolated.

1) H. S. Forrest, D. Hatfield and J. M. Lagowski: J. Chem. Soc., 1961, 963.

2) R. Lohrmann, J. M. Lagowski, H. S. Forrest: *Ibid.*, 1964, 452.

3) D. Hatfield, R. A. Greenland, H. L. Stewart, J. B. Wyngaarden: Biochim. Biophys. Acta, 91, 163 (1964).

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Chart 1.

was fairly stable to the acidic treatment (0.1N hydrochloric acid at 100° for 1 hour) and labile to the alkaline hydrolysis (0.1N sodium hydroxide even at room temperature) as reported in the case of uric acid riboside.¹⁾ When 8-hydroxyguanosine (IV) was reacted with nitrous acid in 20% sulfuric acid,*² a compound having ultraviolet absorption properties ($\lambda_{\text{max}}^{\text{pH } 1} \text{ m}\mu$: 232, 289; $\lambda_{\text{max}}^{\text{pH } 10} \text{ m}\mu$: 248, 303) was obtained. Paper chromatography (Rf 0.21 in 1-butanol-water, 86:14; Rf 0.64 in water, pH 10) also indicated the identical properties reported for uric acid 9-ribose.*^{3,3)}

This reaction was then applied to 8-bromo-5'-O-acetyl-2',3'-O-isopropylideneadenosine (VI) using 5 equivalents of sodium acetate. After the reflux of 2.5 hours 8-hydroxy derivative (VII) was obtained as a hard glass in the quantitative yield. Ultraviolet absorption properties: $\lambda_{\text{max}}^{0.1\text{N HCl}} \text{ m}\mu$: 262, 284; $\lambda_{\text{max}}^{0.1\text{N NaOH}} \text{ m}\mu$: 280. Infrared absorption: $\nu_{\text{max}}^{\text{Nujol}} \text{ cm}^{-1}$: 1740 (ester CO), 1715 (8-CO). Thin-layer chromatography: Rf 0.28 (silica gel, chloroform-ethanol, 35:5). Paper chromatography: Rf 0.70 (1-butanol-water-conc. ammonia, 7:1:2). Acidic hydrolysis of this compound gave 8-hydroxyadenine, $\lambda_{\text{max}}^{\text{pH } 9} \text{ m}\mu$:

*² When the deamination reaction was carried out in dilute acetic acid, ultraviolet absorption was diminished after 2 hr. at room temperature (unpublished experiments by K. Muneyama).

*³ After completion of this experiments, we were aware of the work of Holmes, *et al.*⁶⁾ of the synthesis of uric acid 9-ribose by another route.

6) R. E. Holmes, R. K. Robins: J. Am. Chem. Soc. 87, 1772 (1962).

277; $\lambda_{\text{max}}^{\text{PH}^4}$ m μ : 268; $\lambda_{\text{max}}^{\text{PH}^1}$ m μ : 263, 278 (identical with those reported by Cavalieri and Bendich⁷⁾). Paper chromatography: Rf 0.26 (1-butanol-water, 86:14).

Thus a versatile method of introduction of hydroxyl group to the 8-position of purine nucleosides was established. The application of this method to the various nucleosides is in progress in this laboratory.

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Faculty of Pharmaceutical Sciences,
Hokkaido University,
Kita-12-jo, Nishi-5-chome, Sapporo

Morio Ikehara (池原森男)
Hiroshi Tada (多田 宏)
Kei Muneyama (宗山 敬)

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A Total Synthesis of Coenzyme A via Thiazoline Intermediate^{*1}

In the previous paper,¹⁾ the authors described a novel synthesis of D-pantethine (IIIa), one of the biosynthetic intermediates of coenzyme A from D-pantothenic acid,²⁾ which comprises the interim formation of thiazoline derivative from D-pantothenonitrile (Ia) followed by acid hydrolysis thereof (hereafter referred to as the thiazoline method). This method seems to be applicable to the syntheses of other metabolites from D-pantothenic acid including coenzyme A itself. The present communication deals with the syntheses of coenzyme A and dephospho coenzyme A by the thiazoline method.

Three independent papers on the total synthesis of coenzyme A³⁻⁵⁾ have so far been published, each of which employed in principle the condensation of D-pantetheine derivatives with adenine nucleotides, differing in the procedure for pyrophosphate bond formation. The present method is characterized in building up aletheine moiety in coenzyme A structure in the last step of the synthetic route.

The key intermediates used in the present experiment are P¹-adenosine-3'-phosphate-5'P²-D-pantothenonitrile 4'-pyrophosphate (Ib) for coenzyme A, and P¹-adenosine-5'P²-D-pantothenonitrile 4'-pyrophosphate (Ic) for dephospho coenzyme A. For the preparation of Ib and Ic, it is essential at the outset to establish the synthesis of D-pantothenonitrile 4'-phosphate (V). D-Pantothenonitrile (Ia) was treated with dibenzyl phosphorochloridate in anhydrous pyridine to furnish a syrupy substance (IV), $[\alpha]_D^{25} +19.1^\circ$ (EtOH), in 73.2% yield. Catalytic hydrogenation of IV over palladium-charcoal afforded V, $[\alpha]_D^{25} +11.4^\circ$ (H₂O), IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 2250 (C $\equiv$ N), in 69% yield as its barium salt (C₉H₁₅O₆N₂PBa·2H₂O).

^{*1} A part of this communication was read at the Kanto Branch Meeting of the Pharmaceutical Society of Japan, May, 1965, Tokyo.

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