A typical simulated spectrum (in this case with g_x = 1.775, g_y = 1.690, g_z = 1.790, A_x = 425 G, A_y = 485 G, A_z = 865 G) is shown in Figure 2.

Of the handful of rhenium esr spectra that have been reported previously, two are of axial rhenium(VI) species. Garif'yanov[10] reported $g_\perp$ = 1.77, $g_\parallel$ = 1.90, $A_\perp$ = 400, and $A_\parallel$ = 480 G for $ReOCl_4$ (frozen solution) and Mertis, *et al.*,[11] give $g_\perp$ = 1.94 and $g_\parallel$ = 2.25 for $ReO(CH_3)_4$. The g values for the heteropoly anion are similar to those for $ReOCl_4$ and we have noted that g values for other d^1 species, V(IV),[8] Mo(V)[7], and W(V),[12] in Keggin anions are comparable with, but generally slightly smaller than, those for the corresponding oxopentachloro complexes.

The hyperfine parameters for the heteropoly anion are the largest that have been observed for any transition metal ion. The very large value for A_z in particular results in partial resolution, observable in the lowest field hyperfine line, of the two magnetic isotopes of rhenium, ^{185}Re (37.07%) and ^{187}Re (62.93%). This is the first esr resolution of isotopic nuclei whose magnetic moments differ by only 1%.

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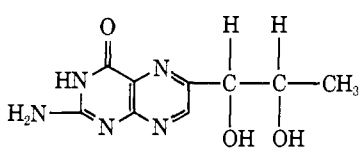
Paul T. Meiklejohn, Michael T. Pope,* Ronald A. Prados
Department of Chemistry, Georgetown University
Washington, D. C. 20057
Received June 22, 1974

An Unequivocal Total Synthesis of L-*erythro*-Biopterin[1]

Sir:

L-*erythro*-Biopterin (**1**), apparently in its 5,6,7,8-tetrahydro form, is a wide-spread naturally occurring



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enzyme cofactor identified in the phenylalanine-to-tyrosine[2] and tyrosine-to-dopa[3,4] conversions, in melanin synthesis,[5,6] and in tryptophan[7-10] and dihydroorotic acid[11] hydroxylation. It has furthermore been implicated in a broad spectrum of other biological oxidation reactions including the conversion of long chain alkyl ethers of glycerol to fatty acids and glycerol, the 17-α-hydroxylation of progesterone, and the biosynthesis of the prostaglandins.[2,12] In addition, indirect evidence supports the suggestion that tetrahydrobiopterin and/or closely related tetrahydropterins play a critical role in cellular electron transport, including photosynthesis.[2] Biopterin itself appears to be a ubiquitous natural product, found in microorganisms, insects, algae, amphibia, and mammals,[2,13] and is the most abundant of the naturally occurring pterins found in human urine.[14]

As a consequence of this apparent wide-spread utilization of biopterin (or reduced biopterin) in metabolic processes, there has been considerable contemporary interest in its synthesis. Most approaches involve the condensation of 2,4,5-triamino-6-hydroxypyrimidine with a suitable sugar intermediate,[15-18] and, as a consequence, give mixtures of 6- and 7-isomers which then must be separated by laborious, and often destructive, chromatographic techniques. The only unequivocal synthesis of biopterin appears to be that of Andrews, Barber, and Tong,[19] which involves the condensation of 2-amino-4-chloro-5-nitro-6-hydroxypyrimidine with the appropriate α-aminoketone prepared from 5-deoxy-L-arabinose, followed by reductive cyclization. A later synthesis developed by Viscontini appears to be much less satisfactory.[20]

We describe in this communication a new total synthesis of pure L-*erythro*-biopterin which, because of the complete absence of the 7-isomer, eliminates the extensive purification procedures which have plagued most previous attempts to prepare this enzyme cofactor. As with the Andrews, Barber, and Tong route,[19] our synthesis also commences with 5-deoxy-L-arabinose (**5**), for which we have developed a much improved synthesis. Thus, L-rhamnose (**2**) was converted to its dithioacetal (**3**) (85%) by acid-catalyzed reaction with ethyl mercaptan essentially according to the procedure of Zissis and Richtmyer.[21] Oxidation to L-rhamnose bissulfone (**4**) has previously been described[22] utilizing aqueous perpropionic acid, which gave a mixture of the desired bissulfone **4** and a vinyl sulfone. By contrast,

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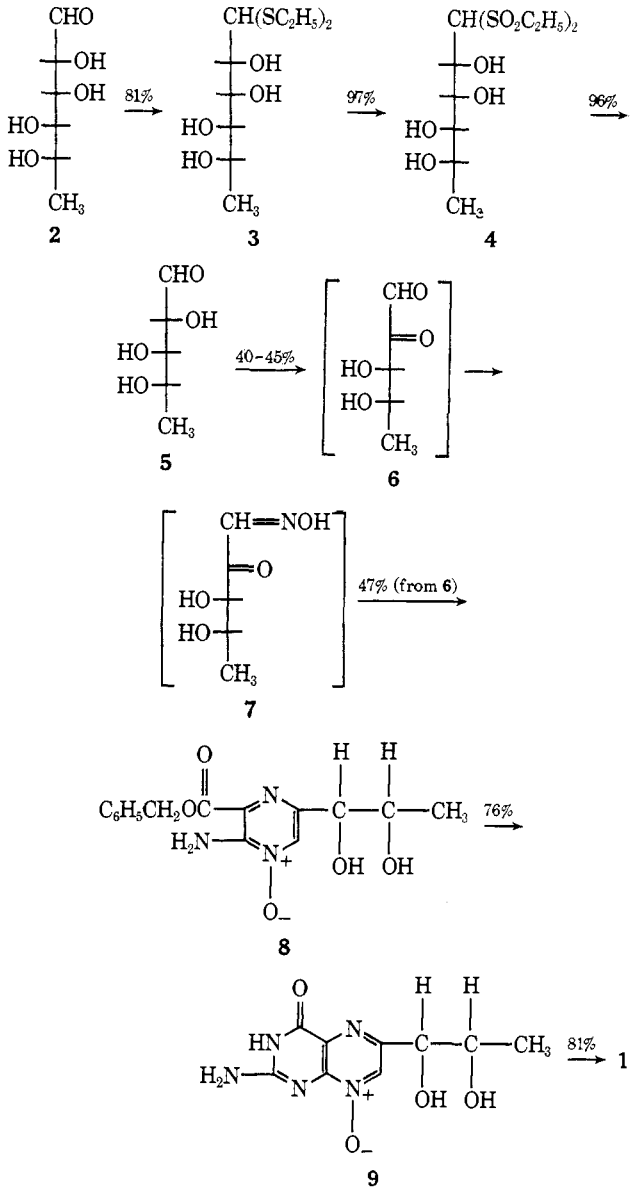
we have found that this oxidation to the bissulfone may be effected in 97% yield by *m*-chloroperbenzoic acid in anhydrous dioxane. Conversion of **4** to 5-deoxy-L-arabinose (**5**) can then be carried out in 96% yield with dilute aqueous ammonia at room temperature, followed by deionization with Amberlite-IR-120 and IR-4B resins (Scheme I).

Scheme I



The conversion of 5-deoxy-L-arabinose (**5**) to L-*erythro*-biopterin (**1**) was carried out as follows. Oxidation of 1.2 g of **5** in 6 ml of water and 75 ml of ethanol with 12.0 g of cupric acetate hydrate was carried out by boiling for 7 min, cooling immediately to 0°, filtering to remove excess reagent, and passing the filtrate through a 2.5 × 14 cm column of Dowex 50-WX4, using methanol as the eluting solvent. The crude osone, obtained by evaporation of the methanol,[23] was dissolved in 3 ml of water, the pH adjusted to 3.5, and 0.6 g of acetone oxime was added. After 6 hr at 50°, the reaction mixture was diluted with 15 ml of water, extracted with ether to remove excess acetone oxime, and evaporated. To the crude α-ketoaldoxime (**7**) was then added 1.1 g of benzyl α-aminocyanoacetate methanesulfonate,[25] and the mixture was stirred at room temperature for 36 hr. Dilution with ether and cooling and filtering then gave, as the final crystalline product of this series of *in situ* conversions, 0.46 g (47% yield from **6**) of 2-amino-3-benzyloxycarbonyl-5-(L-*erythro*-1′,2′-dihydroxypropyl)pyrazine 1-oxide (**8**), mp 165–166° (nmr (DMSO-d_6) δ 8.32(1)(s)(C_7–H), 7.53(2)(br s)(NH_2), 7.35(5)(s)(C_6H_5), 5.31(2)(s)(CH_2-C_6H_5), 4.53–3.22(4)(m)(CHOH–CHOH), 0.91(3)(d)(CH_3). *Anal.* Calcd for $C_{15}H_{17}N_3O_5$: C, 56.42; H, 5.37; N, 13.16. Found: C, 56.32; H, 5.28; N, 13.07). A suspension of 0.35 g of **8**, 0.22 g of guanidine hydrochloride, and 0.32 g of freshly prepared sodium methoxide in 4 ml of DMF was heated for 12 hr at 70–75° and diluted with 6 ml of water and the pH adjusted to 3–4 to give 0.21 g (76%) of biopterin 8-oxide (**9**), mp >300° (R_f 0.31 on Whatman No. 1, 30-cm path, butanol–acetic acid–water (50:15:35). *Anal.* Calcd for $C_9H_{11}N_5O_4$: C, 42.69; H, 4.38; N, 27.67. Found: C, 42.41; H, 4.41; N, 27.92). Heating a solution of 100 mg of **9** with a slight excess (70 mg) of sodium dithionite in a buffered aqueous (pH 7) solution for 30 min, followed by cooling and filtering, then gave 78 mg (81%) of pure L-*erythro*-biopterin; mass spectral, uv, nmr, and chromatographic behavior were identical with the authentic natural product. *Anal.* Calcd for $C_9H_{11}N_5O_3$: C, 45.56; H, 4.68; N, 29.53. Found: C, 45.49; H, 4.63; N, 29.65.

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(23) This reaction was monitored by conversion of the osone to iminodeoxyascorbic acid, followed by titration with iodine.[24] This is the poorest step in the overall conversion of **2** to **1**; maximum yields achieved thus far in this oxidation have averaged 40–45%.

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Edward C. Taylor,* Peter A. Jacobi
Department of Chemistry, Princeton University
Princeton, New Jersey 08540
Received June 13, 1974

Transition Metal Ion Inhibition of Enzyme-Catalyzed Phosphate Ester Displacement Reactions

Sir:

The action of oxovanadium(IV) and vanadium(V) ions and their uridine complexes led Lienhard and his colleagues[1] to suggest that they may act as possible transition state analogs. We have reached similar conclusions for the even more potent inhibition of acid phosphatases by transition metal oxyanions. Moreover, our results lead to significant conclusions about the potential utility of early transition metal oxyanions as structural and mechanistic probes of enzymatic reactions involving displacement reactions on phosphate esters.

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