Substituted 5-(D,L-*erythro*-1',2'-Dihydroxypropyl)pyrazines. Potential Precursors for the Synthesis of Biopterin Derivatives

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A convenient synthesis of substituted 5-(D,L-*erythro*-1',2'-dihydroxypropyl)pyrazines from crotonic acid **4** is described. The anomalous behavior during decarboxylation of functionalized 2-oximino-3-oxoesters **8a,b** is noted. The structures of prepared compounds were determined by spectroscopic methods.

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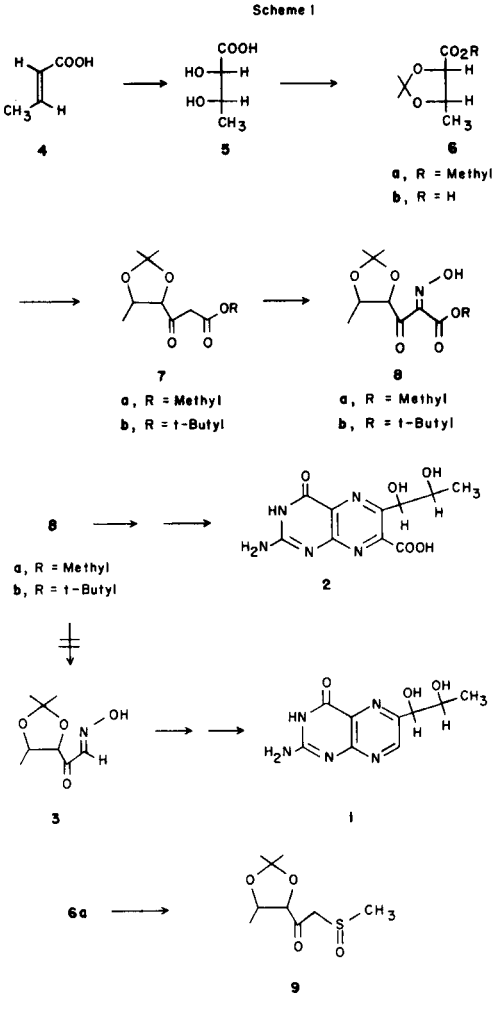
The pteridine ring system has been the subject of numerous synthetic efforts due to its ubiquitous occurrence in nature [2]. Biopterin **1** occurs universally throughout nature, having been identified in microorganisms, insects, algae, amphibia, mammals, and man [2a,3,4]. Recently, Taylor *et al.* have developed an elegant unequivocal synthesis of **1** and other 6-substituted pterins from *o*-aminocyano (or carboalkoxy)pyrazines [5-11]. Although neither biopterin-7-carboxylic acid **2** nor its derivatives have been reported, several pterin-6-carboxylic acids have been reported to possess biological activity [12,13].

Scheme I

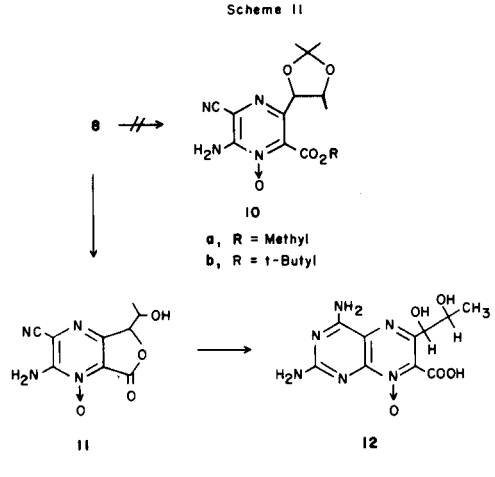


Prior synthetic methods directed towards **1** which did not start from naturally occurring precursors gave mixtures of **1** and its 7-isomer requiring tedious chromatographic workup. To alleviate this situation, we considered a totally synthetic approach to the D,L-*erythro*-esters **8a,b**. In principle, the methodology developed by Taylor *et al.* could be utilized to convert **8a,b** into derivatives of **2**, whereas prior decarboxylation to **3** should provide a fascile route to **1**. Although this approach would lead to pterins possessing 50 percent of the activity of the naturally occurring pterin, the possibility of preparing copious quantities of **1** and esters of **2** without resorting to sugar chemistry would attenuate this drawback.

Results and Discussion.

Epoxidation of **4** by the method of Viscontini *et al.* [14] gave **5** in 34 percent recrystallized yield (Scheme I). The conversion of **5** to **6a** with a 56 percent yield in two steps

Scheme II



has been reported in the literature [15]. We anticipated that this conversion could be accomplished in one step by treatment of **5** with 2,2-dimethoxypropane catalyzed by acidic ion-exchange resin [16-21]. In fact, treatment of **5** with 2,2-dimethoxypropane catalyzed by DOWEX-50 acid ion-exchange resin gave **6a** in 70 percent distilled yield. A higher boiling fraction was identified by ^{1}H nmr as the free acid **6b**, which was converted to **6a** on treatment with 2,2-dimethoxypropane.

The methyl **7a** and *t*-butyl **7b** esters were prepared by the condensation of **6a** with methyl and *t*-butyl acetate respectively, using lithium bis(trimethylsilyl)amide [22] as a non-nucleophilic condensation catalyst.

Oximination of **7a,b** with sodium nitrite-aqueous acetic acid [23] gave **8a,b** as white crystalline solids. The ^{1}H nmr spectra of **8a** and **8b** exhibited two sharp singlets integrating to three protons each which were assigned to the protons of two magnetically non-equivalent isopropylidene methyl groups. The C-6 methyl protons were observed as a sharp doublet. The ^{1}H nmr spectra are indicative of a *single* isomer, since a *threo:erythro* mixture should exhibit increased multiplicity barring fortuitous equivalence of chemical shifts.

A further indication of *erythro* stereochemistry was ascertained from the ^{1}H nmr spectrum of **9**, prepared from **6a** by treatment with sodium methylsulfinylmethide [24]. The isopropylidene methyl group protons were observed as two sharp singlets. The accidental equivalence of the isopropylidene methyl protons for *erythro:threo* isomers in both **8a,b** and **9** seems unlikely.

In a decoupling experiment, the C-5 methyl protons were irradiated leading to the collapse of the complex centered at 4.48 ppm into a sharp AB quartet with $^3J_{HCCH}$ = 8 Hz.

The sharp AB quartet observed for the C-3 and C-4 methine protons with lack of further splitting lends further evidence that **9** is not an *erythro-threo* mixture. Comparison of reported couplings for a dioxalane ring (J_{cis} = 7.3 Hz; J_{trans} = 6.0 Hz) was a further indication of *erythro* stereochemistry [25].

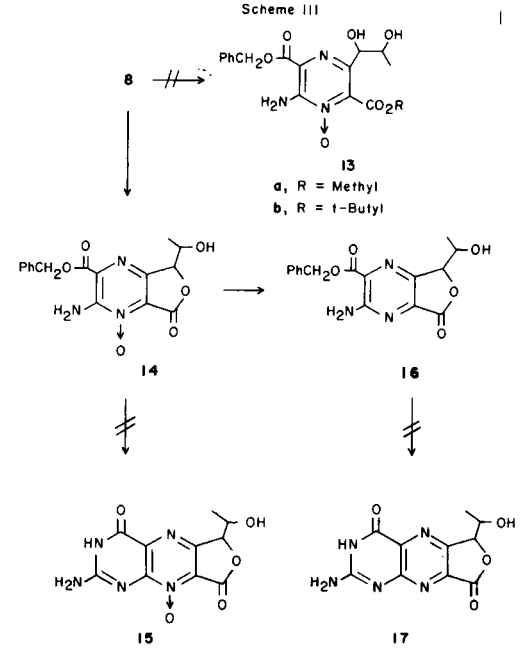
Ample precedent exists in the literature for the hydroxylysis and decarboxylation of 2-oximino-3-oxoesters to keto-aldoximes [26]. Hydrolysis and decarboxylation of **8a** or **8b** to **3** were expected to provide a fascile synthesis of **1** by the method of Taylor and Jacobi [5,6]. However, attempted hydrolysis-decarboxylation of **8a** under the usual conditions with aqueous sodium hydroxide followed by acidification, lithium iodide in dimethylformamide [27] alcoholic potassium hydroxide, or trimethylsilyl iodide [28-31] gave complex mixtures containing none of the desired product by ^{1}H nmr spectral analysis of the reaction product. Equally disappointing, treatment of **8b** with *p*-toluenesulfonic acid in toluene [32], thermal decomposition in refluxing methanol [33], or trifluoroacetic acid at low temperature [34] gave no detectable product. During the course of our work, Taylor and Dumas reported a similar unsuccessful attempt to decarboxylate a functionalized 2-oximino-3-oxoester [35].

A more promising approach appeared to be the conversion of **8** to esters of **2** (Scheme II). The condensation of **8b** with aminomalononitrile *p*-toluenesulfonic acid salt [36] in 2-propanol was expected to give **10b**. A bright yellow solid was obtained whose spectral characteristics were not consistent with **10b**. The ir spectrum showed a carbonyl absorption at 1770 cm^{-1}, while no evidence for a *t*-butyl ester or acetonide protecting group was observed in the ^{1}H nmr spectrum. Closer scrutiny revealed that the condensation product of **8a** or **8b** with aminomalononitrile were identical in every respect. Elemental analysis and spectral data were fully in accord with the *gamma*-lactone **11**. The formation of **11** suggested that lactonization occurred due to the instability of the acetonide protecting group under the acidic reaction conditions.

The condensation of **11** with guanidine in methanol with sodium methoxide gave a small quantity of material for which satisfactory elemental analysis could not be obtained. The ir and mass spectrum of the product suggested the presence of the pteridine *N*-oxide **12** as a major component [37]. Repeated attempts to optimize the yield and obtain satisfactory analysis were unsuccessful.

An alternate approach investigated was the replacement of the 3-cyano substituent in **11** with a carbobenzyloxy group (Scheme III). The condensation of benzyl *alpha*-aminocyanoacetate methanesulfonic acid salt [6] with **8a,b** did not give **13a,b**, but analogous to the aminomalononitrile series gave the *gamma*-lactone **14**. Attempts to con-

Scheme III



dense **14** with guanidine to obtain **15** under a variety of conditions were unsuccessful.

One possibility for the failure of **14** to condense with guanidine in the expected manner, was the increased acidity of the 2-amino substituent due to the *N*-oxide functionality [35]. The deoxypyrazine **16** was synthesized by reduction of **14** with sodium dithionite [6,35] in aqueous *p*H 7 buffered solution or a hetergeneous methanol suspension in isolated yields of 49 and 67 percent respectively. The reduction of **14** with triethyl phosphite [35,38] also gave **16**, albeit in poor yield.

The condensation of **16** under a variety of reaction conditions gave uncharacterizable products from which **17** could not be isolated. Elemental analysis of an isolated product showed a high percentage of nitrogen, suggesting a competing reaction of the lactone functionality with guanidine (tlc showed complete disappearance of starting **16**). Indeed, Taylor and LaMattina reported that competing acylation of guanidine occurred during preparation of a pteridine from a 5-(2-carboethoxyethyl) substituted pyrazine, although the nature of the products were not elucidated [39].

EXPERIMENTAL

All melting points were determined in open capillary tubes on a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra (1% solution in chloroform, potassium bromide cells) were recorded on a Perkin-Elmer 710 spectrophotometer. The ^{1}H nmr spectra were taken on Varian Model XL-100, T-60 or CFT-20 spectrometers. All ^{1}H chemical shifts are reported in ppm relative to tetramethylsilane. Unless otherwise indicated, all reagents were purchased from Aldrich Chemical Company. All solvents were dried prior to use. Reactions were carried out in flame-dried apparatus under a dry-nitrogen atmosphere.

Methyl D,L-*erythro*-*O*-Isopropylidene-2,3-dihydroxybutanoate (**6a**) and *O*-Isopropylidene-2,3-dihydroxybutanoic Acid (**6b**).

A mixture of 39.8 g (0.33 mole) of **5**, 132.0 g (1.23 moles) of 2,2-dimethoxypropane, and 8.0 g DOWEX-50 acid in ion-exchange resin was stirred 24 hours. The reaction mixture was filtered and the excess 2,2-dimethoxypropane was removed *in vacuo*. The residue was distilled under vacuum to give 25.1 g (44%) of a clear liquid, bp 54° at 0.2 mm Hg; ^{1}H nmr (deuteriochloroform): δ 1.24 (d, 3H, methyl), 1.40 and 1.64 (two s, 3H each, isopropylidene), 3.74 (s, 3H, methoxy), 4.54 (complex, 2H, methine).

Anal. Calcd. for $C_8H_4O_4$: C, 55.2; H, 8.1. Found: C, 55.4; H, 8.2.

A higher boiling fraction was distilled and to it was assigned structure **6b**, bp 84-90° at 0.2 mm Hg; ^{1}H nmr (deuteriochloroform): δ 1.31 (d, 3H, methyl), 1.64 and 1.56 (two s, 3H, each, isopropylidene), 4.55-3.25 (complex, 2H, methine), 6.0 (br s, 1H, $-CO_2H$).

Methyl D,L-*erythro*-*O*-Isopropylidene-4,5-dihydroxy-3-oxohexanoate (**7a**).

To a solution of 11.9 g (71 mmoles) of lithium bis(trimethylsilyl)amide [22] in 100 ml dry tetrahydrofuran at −50° was added dropwise 5.0 g (68 mmoles) of methyl acetate. The reaction mixture was stirred an additional 15 minutes and then it was treated with 5.9 g (34 mmoles) of **6a** at −50°. The reaction mixture was allowed to warm to ambient temperature. The reaction mixture was cooled to 0° and was treated with 4.20 g (71 mmoles) of acetic acid. To the reaction mixture was added 250 ml of diethyl ether and the mixture was extracted sequentially with 5% aqueous sodium bicarbonate and saturated aqueous sodium chloride. The organic phase was dried over anhydrous sodium sulfate, and the solvent was removed *in vacuo*. The residue was distilled to give 5.06 g (69%) as a clear liquid, bp 79-81° at 0.4 mm Hg; ^{1}H nmr (deuteriochloroform): δ 1.21 (d, 3H, methyl), 1.58 and 1.37 (two s, 3H each, isopropylidene), 3.58 (d, 1H, H-4), 3.74 (s, 3H, methoxy), 4.2-4.72 (complex, 1H, H-5).

Anal. Calcd. for $C_{10}H_{16}O_5$: C, 55.6; H, 7.5. Found: C, 55.9; H, 7.6.

t-Butyl D,L-*erythro*-*O*-Isopropylidene-4,5-dihydroxy-3-oxohexanoate (**7b**).

By the procedure used to prepare compound **7a**, compound **7b** was prepared from 11.3 g (103 mmoles) of lithium bis(trimethylsilyl)amide, 12.0 g (103 mmoles) of *t*-butyl acetate, and 18.0 g (103 mmoles) of **6a**. The residue was distilled under vacuum to give 3.5 g (49% corrected for recovered **6a**) of clear liquid, bp 90-95° at 0.4 mm Hg; ^{1}H nmr (deuteriochloroform): δ 1.21 (d, 3H, methyl), 1.45 (s, 9H, *t*-butyl), 1.50 (two s, 3H each, isopropylidene), 3.50 (d, 1H, H-4), 4.35-4.83 (complex, 1H, H-5).

Anal. Calcd. for $C_{13}H_{22}O_5$: C, 60.5; H, 8.6. Found: C, 60.2; H, 8.8.

Methyl D,L-*erythro*-*O*-Isopropylidene-4,5-dihydroxy-2-oximino-3-oxohexanoate (**8a**).

To a solution of 10.2 g (47 mmoles) of **7a** in 5 g of glacial acetic acid at 10° was added dropwise a solution of 3.2 g (47 mmoles) of sodium nitrite in 3 ml of water. The reaction was stirred an hour at ice-bath temperature and then 5 ml of water was added. The reaction mixture was stirred an additional hour at ambient temperature. To the reaction mixture was added 250 ml of diethyl ether and the ether layer was separated. The organic phase was sequentially extracted with 5% sodium bicarbonate and water, and then it was dried over anhydrous sodium sulfate. The solvent was removed *in vacuo* and the residue was recrystallized from cyclohexane/toluene to give 8.9 g (77%) of a white crystalline solid, mp 148-150°; ir (1% in dichloromethane, potassium bromide cell): 1745 cm^{-1} (ester), 1710 cm^{-1} (ketone); ^{1}H nmr (deuteriochloroform): δ 1.22 (d, 3H, methyl), 1.52 (two s, 3H each, isopropylidene), 3.90 (s, 3H, methoxy), 4.42-4.92 (complex, 1H, H-5), 5.41 (d, 1H, H-4), 10.00 (br s, 1H, oxime OH).

Anal. Calcd. for $C_{10}H_{15}NO_6$: C, 49.0; H, 6.2; N, 5.7. Found: C, 48.9; H, 6.4; N, 5.6.

t-Butyl D,L-*erythro*-*O*-Isopropylidene-4,5-dihydroxy-2-oximino-3-oxohexanoate (**8b**).

By the procedure used to prepare compound **8a**, compound **8b** was prepared from 2.19 g (8.5 mmoles) of **7b** and 0.59 (8.5 mmoles) of sodium nitrite. Recrystallization from cyclohexane/toluene gave 1.32 g (54%) of a white crystalline solid, mp 124-127°; ir (1% dichloromethane, potassium bromide cells): 1745 cm^{-1} (ester), 1710 cm^{-1} (ketone); ^{1}H nmr (deuteriochloroform): δ 1.19 (d, 3H, methyl), 1.49 (two s, 3H each, isopropylidene), 1.59 (s, 9H, *t*-butyl), 4.45-4.80 (complex, 1H, H-5), 5.35 (d, 1H, H-4), 10.40 (br s, 1H, oxime OH).

Anal. Calcd. for $C_{13}H_{21}NO_6$: C, 54.3; H, 7.4; N, 4.9. Found: C, 54.5; H, 7.5; N, 4.7.

D,L-*erythro*-*O*-Isopropylidene-3,4-dihydroxy-1-methylsulfinylpentan-2-one (**9**).

To a solution of sodium methylsulfinylmethide [24] prepared from 1.32 g (55 mmoles) of sodium hydride and 39 g of dimethyl sulfoxide in 40 ml of tetrahydrofuran at 5° was added dropwise 4.35 g (25 mmoles) of **6a**. The mixture was stirred thirty minutes at room temperature and it was poured into 180 ml of water. The mixture was acidified with dilute hydrochloric acid and it was extracted three times with chloroform. The combined chloroform extracts were dried over sodium sulfate, and the solvent was removed *in vacuo*. The residue was recrystallized from diethyl ether to give 0.74 g (13%) of a white solid. Sublimation gave an analytical sample, mp 107-109°; ^{1}H nmr (deuteriochloroform): δ 1.24 (d, 3H, methyl), 1.40 and 1.64 (two s, 3H each), 2.72 (s, 3H, methylsulfinyl), 4.04 (s, 2H, methylene), 4.40 (complex, 2H, methine).

Anal. Calcd. for $C_9H_{16}O_4S$: C, 49.1; H, 7.3; S, 14.6. Found: C, 49.4; H, 7.2; S, 14.6.

2-Amino-3-cyano-5-(D,L-*erythro*-1',2'-dihydroxypropyl)pyrazine-6-carboxylic Acid *gamma*-Lactone 1-Oxide (**11**).

Method A.

A suspension of 0.70 g (24 mmoles) of **8b** and 0.89 g (24 mmoles) of aminomalononitrile *p*-toluenesulfonic acid salt in 5 ml of 2-propanol was stirred for six days. The yellow precipitate was filtered washing with cold 2-propanol. The solid was recrystallized from ethanol/toluene to give 0.43 g (69%) of a bright yellow solid, mp 100° dec; ir (potassium bromide): 1770 cm^{-1} (C=O); ^1H nmr (dimethylsulfoxide-d_6): δ 1.22 (d, 3H, methyl), 4.16 (complex, 1H, H-2), 4.88 (br s, 1H, OH), 5.36 (d, 1H, H-1), 8.22 (br s, 2H, amine).

Anal. Calcd. for $C_9H_{10}N_4O_5$: C, 42.5; H, 4.0; N, 22.0. Found: C, 42.1; H, 3.9; N, 22.1.

Method B.

The above procedure was repeated using 9.8 g (40 mmoles) of **8a** and 11.6 g (46 mmoles) of aminomalononitrile *p*-toluenesulfonic acid salt to give 5.7 g (74%) product, identical in every respect to that prepared from **8b**.

2-Amino-3-(carbobenzyloxy)-5-D,L-*erythro*-1',2'-dihydroxypropyl)pyrazine-6-carboxylic Acid *gamma*-Lactone 1-Oxide (**14**).

Method A.

A suspension of 2.0 g (8.2 mmoles) of **8a** and 2.3 g (8.2 mmoles) of benzyl *alpha*-aminocyanoacetate methanesulfonic acid salt in 15 ml ethanol was stirred for seven days. The reaction mixture was cooled and the precipitate was filtered washing with cold ethanol. The solid was recrystallized from ethanol/toluene to give 1.1 g (39%) as bright yellow needles, mp 213° dec; ir (potassium bromide): 1770 cm^{-1} (lactone C=O) 1710 cm^{-1} (ester C=O); ^1H nmr (dimethylsulfoxide-d_6): δ 1.23 (d, 3H, methyl), 3.80-5.26 (complex, 3H, =CHCHOH-), 5.46 (s, 2H, benzylic H), 7.46 (s, 5H, aromatic), 8.00 (br s, 2H, amine).

Anal. Calcd. for $C_{16}H_{15}N_3O_6$: C, 55.7; H, 4.4; N, 12.2. Found: C, 55.9; H, 4.6; N, 12.0.

Method B.

The above procedure was repeated using 0.2 g (0.7 mmole) of **8b** and 0.2 g (0.7 mmole) of benzyl *alpha*-aminocyanoacetate methanesulfonic acid salt to give 0.8 g (33%) of product identical in every respect to that prepared from **8a**.

2-Amino-3-(carbobenzyloxy)-5-(D,L-*erythro*-1',2'-dihydroxypropyl)pyrazine-6-carboxylic Acid *gamma*-Lactone (**16**).

Method A.

To a suspension of 0.15 g (0.43 mmole) of **14** in 7 ml of buffer solution (1 ml of concentrated *p*H 7 buffer in 24 ml water) was added 0.30 g of sodium dithionite. The reaction temperature was raised to 90-95° and the now homogeneous reaction mixture was placed in a refrigerator overnight. The precipitate was filtered washing with cold water and was recrystallized from ethanol/toluene to give pale yellow needles, mp 207-209°; ir (potassium bromide): 1760 cm^{-1} (lactone C=O) 1710 cm^{-1} (ester C=O); ^1H nmr (dimethylsulfoxide-d_6): δ 1.33 (d, 3H, methyl), 4.30-5.13 (complex, 3H, =CHCHOH-), 5.53 (s, 2H, benzylic H), 7.53 (s, 5H, aromatic), 7.90 (br s, 2H, amine).

Anal. Calcd. for $C_{16}H_{15}N_3O_5$: C, 58.4; H, 4.6; N, 12.8. Found: C, 58.2; H, 4.6; N, 12.5.

Method B.

A suspension of 0.35 g (1 mmole) of **14** and 0.35 g (2 mmoles) of sodium dithionite in 15 ml methanol was stirred for 24 hours. The reaction mixture was taken up in chloroform and it was extracted with water. The solvent was removed *in vacuo*. The residue was recrystallized from ethanol/-toluene to give 0.20 g (61%) product identical in every respect to that prepared by Method A.

Method C.

A mixture of 0.1 g (0.29 mmole) of **14** and 2.0 g (21 mmoles) of triethyl phosphite was stirred at 70° for 15 hours. The excess triethyl phosphite was removed *in vacuo* and the residue was triturated with 2-propanol to give 0.017 g (17%) of product identical in every respect to that prepared by Method A.

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