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Received October 7, 1977

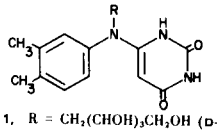
The acid-catalyzed reaction of 6-(*N*-D-ribityl-3,4-xylidino)uracil (**1**) with trimethyl orthoformate yields a bis(methoxymethylene) derivative (**2**), which is readily deprotected to give 5-deazariboflavin (**3**). Correspondingly, 5-methyl-5-deazariboflavin (**6**) is produced by cyclization of the tetraacetate of **1** with acetyl chloride in the presence of stannic chloride followed by deacetylation.

J. Heterocyclic Chem., 15, 489 (1978)

5-Deazariboflavin (**3**) (1) has generated considerable interest as a coenzyme analog in studies of flavin-mediated biochemical reactions (2-11). Furthermore, this laboratory has recently reported that 5-deazariboflavin is a riboflavin antagonist with potent, broad-spectrum activity against poultry coccidiosis (12). In order to resynthesize **3** on large scale and to prepare a series of analogs of **3**, we sought a general route to 5-deazaisoalloxazines which would be shorter and more economical than the one originally described (1).

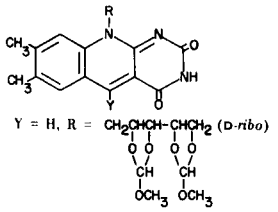
The reported cyclization of 6-(*N*-D-ribityl-3,4-xylidino)-uracil (**1**) to riboflavin N^5-oxide by nitrosation or nitration (13-15) suggested that treatment of **1** or a related derivative with an electrophilic carbon species in the proper oxidation state might yield a 5-deazariboflavin. Intermediate **1** was prepared by a modification of the literature procedures (13-16), which in our hands had failed to give the material in satisfactory yield and purity.

Reaction of **1** with trimethyl orthoformate in the presence of catalytic *p*-toluenesulfonic acid furnished the bis(methoxymethylene) derivative **2** (17), which was readily hydrolyzed to **3**. Corresponding treatment of **1** with trimethyl or triethyl orthoacetate failed to give any significant cyclization to a 5-deazariboflavin. However, **1** was converted to its tetraacetate (**4**), which could be cyclized under Friedel-Crafts conditions. Thus, treatment of **4** with acetyl chloride and stannic chloride yielded **5**, which was deprotected to give 5-methyl-5-deazariboflavin (**6**).



1, R = $CH_2(CHOH)_3CH_2OH$ (D-*ribo*)

4, R = $CH_2(CHOAc)_3CH_2OAc$



2, Y = H, R = $CH_2CHCH\text{-}CHCH_2$ (D-*ribo*)

3, Y = H, R = $CH_2(CHOH)_3CH_2OH$

5, Y = CH_3, R = $CH_2(CHOAc)_3CH_2OAc$

6, Y = CH_3, R = $CH_2(CHOH)_3CH_2OH$

Subsequent to the completion of this work, the synthesis of a series of 10-alkyl-5-deazaisoalloxazines from 6-(*N*-alkylanilino)uracils with phosphorus oxychloride and dimethylformamide was reported by Yoneda and Sakuma (18). The synthesis of 5-deazariboflavin (**3**) from **4** using similar treatment with the Vilsmeier reagent was announced by Janda and Hemmerich (19), although no details were given for the preparation of **4**. Expanding on their earlier work (18), the Yoneda group (20) reported the synthesis of **3** from **1** by reaction with triethyl orthoformate and dimethylformamide in the absence of an acid catalyst. In our hands, this last method failed to give **3** under the conditions stated.

EXPERIMENTAL

^{1}H Nmr spectra were obtained with a Varian T-60, T-60A, or A-60 spectrometer, using TMS as the internal standard. Signals due to the ribityl moiety are omitted here. Uv-visible spectra were recorded on a Cary 118C spectrophotometer. Mass spectra were obtained with a Varian MAT 731 instrument or an LKB 9000 gc-mass spectrometer. Melting points were determined in open capillary tubes with a Thomas Hoover apparatus and are uncorrected. All compounds showed satisfactory purity by tlc on silica gel GF plates in the solvents indicated.

6-(*N*-D-Ribityl-3,4-xylidino)uracil or 1-Deoxy-1-[(3,4-dimethylphenyl)(1,2,3,6-tetrahydro-2,6-dioxo-4-pyrimidinyl)amino]-D-ribitol (**1**).

A mixture of 47.0 g. (0.32 mole) of 6-chlorouracil (21), 245 g. (0.96 mole) of *N*-D-ribityl-3,4-xylidine (22), and 1.25 l. of water was mechanically stirred under reflux for 15 hours and then cooled in an ice bath, resulting in heavy crystallization. Cooling and stirring were continued as 275 ml. (0.69 mole) of 2.5 *N* sodium hydroxide was added. After stirring for an additional hour in the ice bath, the solid was removed by filtration and washed with water. The tan solid thus recovered amounted to 175.4 g. of virtually pure *N*-D-ribityl-3,4-xylidine. The combined filtrate and washings were acidified to *p*H 3 with concentrated hydrochloric acid and concentrated to dryness on a rotary evaporator under high vacuum. The residual semi-solid was extracted with 1.25 l. of boiling methanol. The insoluble solid (sodium chloride) was removed by filtration and washed with some additional hot methanol. The combined filtrate and washings were evaporated *in vacuo*, and the residual gum was crystallized from 300 ml. of water to give 70.1 g. (57%) of cream-colored crystals, m.p. 183-185° [lit. (15) m.p. 185°]; tlc in 40:10:1 chloroform-methanol-water; uv (methanol): λ max 277 (ε, 20,400); field desorption ms: m/e 365 (M^+); nmr (DMSO-d_6): δ 2.23 (s, 6H, $ArCH_3$), 7.00-7.34 (m, 3H, ArH).

Anal. Calcd. for $C_{17}H_{23}N_3O_6 \cdot H_2O$: C, 53.25; H, 6.57; N, 10.96. Found: C, 53.69; H, 6.41; N, 10.87.

2,3,4,5-Bis-*O*-methoxymethylene-1-deoxy-1-(3,4-dihydro-7,8-dimethyl-2,4-dioxopyrimido[4,5-*b*]quinolin-10(2*H*)yl)-D-ribitol (**2**).

A mixture of 3.65 g. (9.5 mmoles) of **1**, 30 ml. of trimethyl orthoformate, and 0.2 g. of *p*-toluenesulfonic acid monohydrate was refluxed with stirring under nitrogen. (On larger scale it was necessary to distill off the methanol as it was formed in order to achieve a satisfactory reflux temperature.) After 4 days, considerable crystallization had occurred, and the mixture was cooled. The solid was collected on a filter and washed with acetone to give 2.06 g. (47%) of fine yellow crystals, m.p. 276-278°; tlc in 9:1 chloroform-methanol (blue fluorescence); uv (methanol): λ max (ε) 226 (38,400), 263 (30,100), 330 (11,000), 400 (13,500); ms: m/e 458 (M^+-1); nmr (DMSO-d_6): δ 2.30, 2.44 (s, each 3H, $ArCH_3$), 3.14 (s, approximately 3H, OCH_3), 3.33, 3.41 (s, total approximately 3H, OCH_3), 5.97 (s, >1H, orthoformyl CH), 6.01 (s, <1H, orthoformyl CH), 7.71 (br, s, 2H, C^6,C^9-H), 8.60 (s, 1H, C^5-H), 10.98 (s, 1H, NH) (17).

Anal. Calcd. for $C_{22}H_{25}N_3O_8$: C, 57.51; H, 5.48; N, 9.15. Found: C, 57.24; H, 5.43; N, 9.30.

5-Deazariboflavin or 1-Deoxy-1-(3,4-dihydro-7,8-dimethyl-2,4-dioxopyrimido[4,5-*b*]quinolin-10(2*H*)yl)-D-ribitol (**3**).

A suspension of 23.4 g. (51 mmoles) of **2** in 500 ml. of 1 *N* hydrochloric acid was heated on a steam bath with intermittent stirring. Crystallization of product began before all the starting material had dissolved. After 45 minutes, by which time tlc indicated complete reaction, the mixture was cooled and neutralized with excess saturated sodium bicarbonate solution. The product was collected on a filter and washed with water and then acetone to give 19.4 g. (97%) of fluffy yellow crystals, m.p. 289-292° dec. [lit. (1) m.p. 286-288°]; tlc in 40:10:1 chloroform-methanol-water (blue fluorescence); uv (methanol); λ max (ε) 270 (27,800), 330 (10,500), 400 (12,200); uv (*p*H 7 aqueous buffer): λ max (ε) 227 (27,700), 255 (21,300), 273 (19,200), 339 (9,800), 396 (9,800); uv (0.1 *N* hydrochloric acid): λ max (ε) 224 (27,000), 263 (33,700), 348 (16,600); uv (0.1 *N* sodium hydroxide); λ max (ε) 224 (35,500), 263 (49,200), 335 (14,100), 400 (13,100); ms: m/e 376 (M^++1); nmr (DMSO-d_6): δ 2.31, 2.43 (s, each 3H, $ArCH_3$), 7.79, 7.89 (s, each 1H, C^6,C^9-H), 8.71 (s, 1H, C^5-H), 10.95 (br. s., 1H, exchangeable, NH).

Anal. Calcd. for $C_{18}H_{21}N_3O_6 \cdot H_2O$: C, 54.95; H, 5.89; N, 10.68. Found: C, 55.22; H, 5.78; N, 10.59.

1-Deoxy-1-[(3,4-dimethylphenyl)(1,2,3,6-tetrahydro-2,6-dioxo-4-pyrimidinyl)amino]-D-ribitol Tetraacetate (**4**).

A mixture of 3.83 g. (10 mmoles) of **1**, 2.00 g. of zinc chloride, and 50 ml. of acetic anhydride was stirred at room temperature under a drying tube. After 18 hours the solution was concentrated on a rotary evaporator (high vacuum) over a lukewarm water bath. The amber residual oil was dissolved in 100 ml. of ethyl acetate and shaken thoroughly with three 100-ml. portions of saturated sodium bicarbonate solution until very little effervescence was observed. Finally, the ethyl acetate phase was washed with 100 ml. of water plus 25 ml. of saturated sodium chloride solution. The separated ethyl acetate solution was dried over magnesium sulfate, filtered, and concentrated to give a residue which solidified on trituration with ether. After isolation and further washing with ether, there was obtained 3.27 g. of light yellow-tan solid which on tlc showed contamination from a slower-moving impurity. The bulk of this material (3.00 g.) was chromatographed on a column of 120 g. of silica gel. Gradient elution culminating with 99:1 chloroform-methanol led to isolation of 2.70 g. (55%) of white amorphous solid, m.p. indeterminate; tlc in 9:1 chloroform-methanol; ms: m/e 533 (M+); nmr (deuteriochloroform): δ 1.90 (s, 3H, $COCH_3$), 2.03 (s, 6H, $COCH_3$), 2.13 (s, 3H, $COCH_3$), 2.30 (s, 6H, $ArCH_3$), 6.93 (center of m, 2H, ArH), 7.27 (d, J = 8 Hz, 1H, ArH), 9.55 (br, s, 2H, NH).

Anal. Calcd. for $C_{25}H_{31}N_3O_{10}$: C, 56.28; H, 5.82; N, 7.88. Found: C, 56.48; H, 5.92; N, 7.61.

1-Deoxy-1-(3,4-dihydro-2,4-dioxo-5,7,8-trimethylpyrimido[4,5-*b*]-quinolin-10(2*H*)yl)-D-ribitol Tetraacetate (**5**).

A mixture of 1.00 g. (1.88 mmoles) of **4**, 0.22 g. (2.8 mmoles) of acetyl chloride, 1.56 g. (6.00 mmoles) of stannic chloride, and 30 ml. of 1,2-dichloroethane was stirred under reflux for 8 hours. The dark mixture was cooled, added to ice, and extracted 3 times with dichloromethane. The combined dichloromethane fractions were washed twice with water, then dried, and concentrated to dryness. The glassy residue was chromatographed on a silica gel column using a dichloromethane-methanol gradient elution. At 24:1 dichloromethane-methanol the product was eluted, yielding on evaporation 0.75 g. (74%) of yellow crystals, m.p. 246-248°; tlc in 9:1 chloroform-methanol (blue fluorescence); uv (methanol): λ max (ε) 271 (28,500), 330 (9,900), 397 (12,200); ms: m/e 556 (M^+-1); nmr (deuteriochloroform) δ 1.73, 2.06, 2.17, 2.25 (s, each 3H, $COCH_3$), 2.43, 2.53 (s, each 3H, C^7,C^8-CH_3), 3.20 (s, 3H, C^5-CH_3), 7.57, 7.84 (s, each 1H, C^6,C^9-H), 8.40 (br, s, 1H, NH).

Anal. Calcd. for $C_{27}H_{31}N_3O_{10}$: C, 58.16; H, 5.60; N, 7.54. Found: C, 57.82; H, 5.87; N, 7.12.

5-Methyl-5-deazariboflavin or 1-Deoxy-1-(3,4-dihydro-2,4-dioxo-5,7,8-trimethylpyrimido[4,5-*b*]quinolin-10(2*H*)yl)-D-ribitol (**6**).

A solution of 700 mg. (1.26 mmoles) of **5** in 6 ml. of methanol saturated with anhydrous hydrogen chloride was allowed to stand at room temperature for 16 hours. The solvent was then evaporated in a stream of nitrogen. Treatment of the residue with water furnished 420 mg. (87%) of fluffy yellow crystals, m.p. 261-262°; tlc in 40:10:1 chloroform-methanol-water (blue fluorescence); uv (*p*H 7 aqueous buffer): λ max (ε) 225 (24,300), 250 (18,000), 271 (18,600), 334 (7,300), 394 (7,300); uv (0.1 *N* hydrochloric acid): λ max (ε) 224 (21,800), 236 (17,800), 264 (35,300), 345 (13,300); uv (0.1 *N* sodium hydroxide): λ max (ε) 226 (27,100), 264 (35,300), 330 (9,800), 398 (9,200); field desorption ms: m/e 390 (M^++1); nmr (deuteriotrifluoroacetic acid): δ 2.63, 2.71 (s, each 3H, C^7,C^8-CH_3), 3.51 (s, 3H, C^5-CH_3), 8.16, 8.46 (s, each 1H, C^6,C^9-H).

Anal. Calcd. for $C_{19}H_{23}N_3O_6 \cdot 2H_2O$: C, 53.65; H, 6.35; N, 9.88. Found: C, 53.59; H, 6.19; N, 9.74.

Acknowledgments.

We would like to thank Mr. Jack Smith for obtaining the mass spectra, Mrs. Valorie Mayo for the uv spectra, Mr. Herman Flynn for some of the nmr spectra, and the staff of Mr. Jack Gilbert for the elemental analyses.

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