Tetrahedron Letters No. 30, pp 2551 - 2554, 1977. Pergamon Press. Printed in Great Britain.

DEAZA ISOSTERES OF RIBOFLAVINE AND LUMICHROME

Wallace T. Ashton, Donald W. Graham, Ronald D. Brown, and Edward F. Rogers*
Merck Sharp & Dohme Research Laboratories, P.O. Box 2000, Rahway, N.J. 07065

(Received in USA 19 April 1977; received in UK for publication 8 June 1977)

5-Deazariboflavine (1a), made by Cheng and coworkers[1] in 1967, has proved to be a valuable tool in flavine biochemistry.[2] In the course of studies on riboflavine antagonists,[3] we have synthesized several new deaza isosteres of the vitamin, namely 1-deaza- (2a), 3-deaza- (3a), 1,5-dideaza- (4a), 1,3,5-trideaza- (5), and 9-aza-5-deazariboflavine (1b). The syntheses of these compounds and certain methylated and desribityl analogs are described below.

Reaction of 6a with diethyl 2-bromo-3-oxoglutarate[4] (K_2CO_3/DMF, 25°, 18 hr) accompanied by spontaneous air oxidation afforded a 20% yield of the quinoxaline diester 7: mp 105-106°; MS m/e 316 (M^+); NMR ($CDCl_3$) δ 1.26 (t, 3H, J = 7 Hz, $CH_2\underline{CH_3}$), 1.48 (t, 3H, J = 7 Hz, $CH_2\underline{CH_3}$), 2.51 (s, 6H, $ArCH_3$), 4.23 (q, 2H, J = 7 Hz, $O\underline{CH_2}CH_3$), 4.45 (s, 2H, $ArCH_2CO_2$-), 4.56 (q, 2H, J = 7 Hz, $O\underline{CH_2}CH_3$), 7.90, 8.06 (s, each 1H, ArH).[5] Treatment of 7 with saturated methanolic NH_3 at 25° for 40 hr yielded 93% of 2b·NH_3 as purple crystals: mp ∤ 360°. Dissolution in anhydrous CF_3CO_2H at 25° followed by precipitation with MeOH after several min gave 89% of free 1-deazalumichrome (2b) as purple crystals: mp ∤ 360°; MS m/e 241 (M^+); UV λ_{max} (MeOH) 231 nm (ε19,200), 248 (sh, 14,100), 299 (25,800), 540 (5,900). The complex 2b·NH_3 had a comparable UV spectrum. Whereas lumichrome has an alloxazine (1H) structure, NMR data indicate that 2b exists as a mixture of the 10H and 1H tautomers in a variable ratio, with the 10H form predominating: NMR (300 MHz, DMSO-d_6) δ 2.29, 2.34 (s, each 3H, $ArCH_3$), 4.28 (s, ~0.6-0.8H, exchangeable, -CH_2- at 1-position), 5.15 (s, ~0.6-0.7H, exchangeable, =CH- at 1-position), 7.06, 7.62 (s, each 1H, C^6,C^9-H), 11.02, 12.24 (s, each ≤ 1H, exchangeable, NH). A comparable tautomeric relationship exists with 2c and 4b, which are described below.

Similar treatment of 7 with $MeNH_2$ furnished 82% of 2c·$MeNH_2$: purple crystals; mp >345° dec; MS m/e 255 (M^+ for free 2c). Removal of $MeNH_2$ with CF_3CO_2H as for 2b provided a 93% yield of 2c as a purple solid: mp >295° dec, NMR (300 MHz, DMSO-d_6) δ 2.29, 2.35 (s, each 3H, $ArCH_3$), 4.36 (s, ~0.3H, exchangeable, -CH_2- at 1-position), 5.30 (s, ~0.85H, exchangeable, =CH- at 1-position), 7.06, 7.65 (s, each 1H, C^6,C^9-H), 12.30 (s, ≤ 1H, exchangeable, NH); UV λ_{max} (MeOH) 256 nm (ε11,200), 297 (20,300), 540 (4,650).

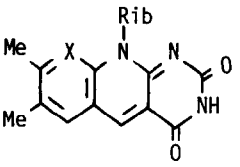
Reaction of 2b with Ac_2O in pyridine (steam bath, 2 hr) followed by treatment with hot H_2O gave 79% of a monoacetylated derivative identified as the C^1-acetyl compound 2f: reddish orange crystals: mp >340° dec; MS m/e 283 (M^+); NMR (300 MHz, DMSO-d_6) δ 2.48, 2.51 (s, each

3H, $ArCH_3$), 2.65 (s, 3H, $COCH_3$), 7.96, 8.00 (s, each 1H, C^6,C^9-H), 11.38 (s, 1H, exchangeable, N^3-H), 16.53 (s, 1H, exchangeable, N^{10}-H); UV λ_{max} (MeOH) 235 nm (ε21,200), 258 (12,200), 311 (16,800), 480 (5,300). The corresponding acetylation of 2c (30 min, no H_2O treatment) yielded 72% of 2g as a dark red-orange solid: mp 300-303° dec (preliminary softening); MS m/e 297 (M^+); NMR (300 MHz, DMSO-d_6) δ 2.50, 2.54 (s, each 3H, $ArCH_3$), 2.70 (s, 3H, $COCH_3$), 8.01, 8.06 (s, each 1H, C^6,C^9-H), 16.62 (s, 1H, exchangeable, NH); UV λ_{max} (MeOH) 233 nm (ε32,700), 258 (20,000), 310 (30,800), 480 (7,200). Consistent with their representation as C-acylated rather than N-acylated derivatives, 2f and 2g are strikingly resistant to base hydrolysis.

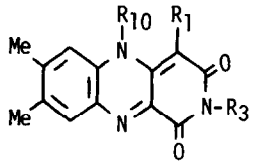
Reaction of 6b[6] with diethyl 2-bromo-3-oxoglutarate under conditions similar to those used for 6a but without purification of intermediate bicyclic diesters yielded, on treatment with NH_3, 14% of purple 1-deazariboflavine (2a); mp 300-305° dec; MS (field desorption) m/e 375 (M^+); NMR[7] (100 MHz, DMSO-d_6) δ 2.29, 2.36 (s, each 3H, $ArCH_3$), 5.50 (s, 1H, C^1-H), 7.54, 7.58 (s, each 1H, C^6,C^9-H), 8.14 (s, 1H, NH); UV λ_{max} (MeOH) 230 nm (ε19,200), 305 (24,300), 356 (3,500), 530 (7,100). Similarly obtained from the crude bicyclic diesters on $MeNH_2$ treatment was the N^3-methyl derivative 2d in 13% overall yield: purple crystals; mp 289-294° dec; MS (field desorption) m/e 389 (M^+); NMR[7] (100 MHz, DMSO-d_6) δ 2.30, 2.37 (s, each 3H, $ArCH_3$), 3.22 (s, 3H, NCH_3), 5.69 (s, 1H, C^1-H), 7.63, 7.69 (s, each 1H, C^6,C^9-H); UV λ_{max} (MeOH) 230 nm (ε20,400), 296 (27,100), 355 (4,100), 536 (7,800).

An alternative route to 1-deazariboflavine (2a), which corroborates the assigned structure, was found during the synthesis of 3-deazariboflavine (3a). Condensation of 6c[8] with 2,4,6-trioxopiperidine[9] (2 eq) in AcOH (95°, 30 min)[10,11] was followed by evaporation *in vacuo* and chromatography on silica gel (eluent 2-10% MeOH/CH_2Cl_2). First eluted was 1-deazariboflavine tetraacetate (2e) (14%) as a red-purple glass: NMR ($CDCl_3$) δ 1.82, 2.07 (s, each 3H, $COCH_3$), 2.23 (s, 6H, $COCH_3$), 2.32, 2.45 (s, each 3H, $ArCH_3$), 5.50 (s, 1H, C^1-H), 7.20, 7.74 (s, each 1H, C^6,C^9-H), 8.90 (broad s, 1H, NH); UV λ_{max} (MeOH) 285 nm (ε22,200), 303 (23,200), 351 (5,300), 518 (8,600). On further elution, 3-deazariboflavine tetraacetate (3b) (36%) was obtained as a yellow-brown glass: NMR[7] ($CDCl_3$) δ 1.71, 2.04, 2.20, 2.27 (s, each 3H, $COCH_3$), 2.42, 2.53 (s, each 3H, $ArCH_3$), 6.39 (s, 1H, C^3-H), 7.55, 7.77 (s, each 1H, C^6,C^9-H); UV λ_{max} (MeOH) 265 nm (ε25,100), 436 (15,300).[12] Hydrolysis of 2e (6N HCl, MeOH, 50°, 2 hr) gave 2a identical (mp, UV, TLC) with material prepared by the other route. Hydrolysis (same conditions) of 3b gave 3-deazariboflavine (3a) (80%) as yellow-brown crystals: mp 220-222° (recrystd from H_2O); MS (field desorption) m/e 375 (M^+); NMR[7] (CF_3CO_2D) δ 2.71, 2.82 (s, each 3H, $ArCH_3$), 6.72 (s, 1H, C^3-H), 8.35 (s, 2H, C^6,C^9-H); UV λ_{max} (H_2O, pH 7) 265 nm (ε27,400), 400 (14,800).[12]

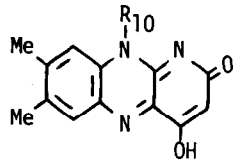
Condensation of 6d[1] with glutazine (8)[9] (or alternatively with 2,4,6-trioxopiperidine[9]) in 1:10 AcOH-H_2O on the steam bath for 1.5 hr furnished an 89% yield of 1,5-dideazariboflavine (4a) as red-orange crystals: mp 285-290° dec (preliminary softening); MS m/e 374 (M^+); NMR (DMSO-d_6) δ 2.26, 2.36 (s, each 3H, $ArCH_3$), 5.48 (s, 1H, C^1-H), 7.56, 7.66 (s, each 1H, C^6,C^9-H), 8.47 (s, 1H, C^5-H), 10.73 (broad s, 1H, NH); UV λ_{max} (MeOH) 234 nm (ε38,700), 254 (13,400), 267 (13,200), 306 (34,700), 340 (3,800), 480 (10,600). From 6e[1] the corresponding 1,5-dideazalumichrome (4b) was obtained in 24% yield as a dark red or red-violet solid: mp ≠ 360°; MS m/e 240 (M^+); NMR (300 MHz, DMSO-d_6) δ 2.27, 2.35 (s, each 3H, $ArCH_3$), 4.74 (s, ~0.3H, exchangeable, $-CH_2-$ at 1-position), 5.10 (s, ~0.85H, exchangeable, =CH- at 1-position),



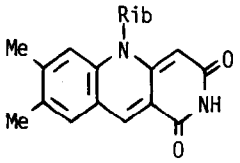
1a X = CH
b X = N
Rib = $CH_2(CHOH)_3CH_2OH$
$RibAc_4$ = $CH_2(CHOAc)_4CH_2OAc$



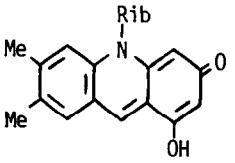
	R_1	R_3	R_{10}
2a	H	H	Rib
b	H	H	H
c	H	Me	H
d	H	Me	Rib
e	H	H	$RibAc_4$
f	Ac	H	H
g	Ac	Me	H



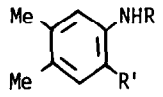
3a R_{10} = Rib
b R_{10} = $RibAc_4$



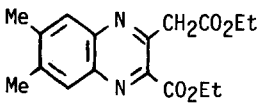
4a R_{10} = Rib
b R_{10} = H



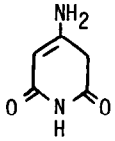
5



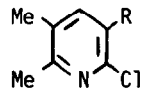
	R	R'
6a	H	NH_2
b	Rib	NH_2
c	$RibAc_4$	$N_2C_6H_4NO_2(4)$
d	Rib	CHO
e	H	CHO



7



8



9a R = CN
b R = CHO

7.14, 7.64 (s, each 1H, C^6,C^9-H), 8.48 (s, 1H, C^5-H), 10.69 (s, ≤ 1H, exchangeable, NH), 11.33 (broad s, ≤ 1H, exchangeable, NH); UV λ_{max} (MeOH) 233 nm (ε13,400), 289 (9,000), 305 (10,000), 480 (2,900).[13]

Pronounced shifts in the longest wavelength UV spectral bands are observed when the N^1 or N^5 atoms of riboflavine, 1- or 5-deazariboflavine and 1- or 5-deazalumichrome are replaced by methenyl. Substitution of CH for N^1 produces bathochromic shifts of 80-90 nm, while replacement at N^5 produces 45-60 nm shifts to shorter wavelengths. In contrast to the flavines, the 1-deaza and 1,5-dideaza analogs (2a-e; 4a,b) are not fluorescent, but fluorescence [λ_{max} (MeOH) ~620 nm; excitation λ 480 nm] is observed in 1-acetyl derivatives 2f and 2g.

1,3,5-Trideazariboflavine (5) [red crystals; mp 311-314° dec (recrystd from DMF); MS (field desorption) m/e 373 (M^+); NMR[7] (CF_3CO_2D) δ 2.62, 2.75 (s, each 3H, $ArCH_3$), 6.85 (s, 1H, C^3-H), 8.05, 8.26 (s, each 1H, C^6,C^9-H) 9.65 (s, 1H, C^5-H);[14] UV λ_{max} 289 nm (ε17,600), 370 (5,300), 498 (3,300)][12] was prepared in 35% yield by condensation of 6d with phloroglucinol (dil NaOH, EtOH, reflux, 18 hr).[15]

Treatment of 9a[16] with Raney Ni-HCO_2H analogous to a reported procedure for 2-chloronicotinaldehyde[17] gave 31% of aldehyde 9b: mp 72.5-73°; MS m/e 169 (M^+); NMR ($CDCl_3$) δ 2.33, 2.55

(s, each 3H, $ArCH_3$), 7.91 (s, 1H, ArH), 10.38 (s, 1H, CHO). Condensation of 9b with 6-D-ribitylaminouracil[18] in DMF at reflux for 5 min yielded 43% of 9-aza-5-deazariboflavine (1b): orange-tan solid; mp >260° dec (recrystd, DMF-MeOH); MS (field desorption) m/e 376 (M^+) NMR[7] (100 MHz, DMSO-d_6), 2.38, 2.64 (s, each 3H, $ArCH_3$), 7.98 (s, 1H, NH), 8.22 (s, 1H, C^6-H), 8.55 (s, 1H, C^5-H); UV λ_{max} (H_2O, pH 7) 260 nm (ϵ30,500), 306 (4,600), 393 (18,400).

Biological data for these and related compounds will be published elsewhere.

Acknowledgments. We wish to thank Dr. Byron Arison for obtaining and assisting in interpretation of many of the NMR spectra and Dr. James Steffens for determining fluorescence spectra.

References and Notes

1. D. E. O'Brien, L. T. Weinstock, and C. C. Cheng, Chem. Ind. (London), 2044 (1967); J. Heterocycl. Chem., 7, 99 (1970).
2. M. S. Jorns and L. B. Hersh, J. Am. Chem. Soc., 96, 4012 (1974); J. Fisher and C. T. Walsh, *ibid.*, 4345 (1974); B. A. Averill, A. Schonbrunn, R. Abeles, L. T. Weinstock, C. C. Cheng, J. Fisher, R. Spencer, and C. T. Walsh, J. Biol. Chem., 250, 1603 (1975); L. B. Hersh and M. S. Jorns, *ibid.*, 8728 (1975); L. B. Hersh, M. S. Jorns, J. Peterson, and M. Currie, J. Am. Chem. Soc., 98, 865 (1976); R. Spencer, J. Fisher, and C. T. Walsh, Biochemistry, 15, 1043, 1054 (1976).
3. D. W. Graham, J. E. Brown, W. T. Ashton, R. D. Brown, and E. F. Rogers, submitted for publication.
4. I. Ito, T. Mitsuzaki, and A. Murakami, Japanese Patent 68 07,932 (1968); Chem. Abstr., 70, 19599 (1969).
5. All new compounds gave acceptable elemental analyses and showed satisfactory purity by TLC. All reported NMR data are at 60 MHz unless otherwise indicated.
6. P. Karrer, Helv. Chim. Acta, 30, 2105 (1947).
7. Signals from protons in the ribityl group are omitted.
8. M. Tishler, J. M. Wellman, and K. Ladenburg, J. Am. Chem. Soc., 67, 2165 (1945).
9. H. N. Stokes and H. von Pechmann, Chem. Ber., 19, 2694 (1886); V. Niementowski and U. Sucharda, J. Prakt. Chem., 94, 193 (1916).
10. M. Tishler, K. Pfister, R. D. Babson, K. Ladenburg, and A. J. Fleming, J. Am. Chem. Soc., 69, 1487 (1947).
11. Dr. George B. Payne studied this reaction in our laboratories in 1951.
12. Data are also consistent with an alternative tautomer in which the 2-carbonyl rather than the 4-carbonyl is enolized.
13. Apparent ϵ values are probably low due to incomplete solubility.
14. No signal was observed for C^1-H, indicating exchange at this position in strong acid.
15. G. K. Hughes and E. Ritchie, Aust. J. Sci. Res., A4, 423 (1951).
16. R. P. Mariella and J. L. Leech, J. Am. Chem. Soc., 71, 331 (1949).
17. A. Taurins and V. Tan Khouw, Can. J. Chem., 51, 1741 (1973).
18. G. F. Maley and G. W. E. Plaut, J. Biol. Chem., 234, 641 (1959).