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Registry No. **2a**, 103149-79-7; **2b**, 103149-81-1; **3a**, 103149-80-0; **3b**, 103149-81-1; **6a**, 116205-38-0; **6b**, 116205-43-7; **7**, 4170-71-2; **8a**, 116205-42-6; **8b**, 116205-44-8; **9**, 124267-06-7; **10**, 83239-24-1; **11a**, 116205-47-1; **11b**, 116205-46-0; **11c**, 116205-45-9; **11d**, 116205-39-1; **12**, 14916-79-1; **13**, 63478-76-2; **14**, 119837-81-9; **15**, 432-25-7; **16**, 124267-07-8; **19a**, 124267-10-3; **19b**, 124267-11-4; **20**, 124267-08-9; **21**, 756-79-6; **22**, 83239-22-9; **24**, 58496-74-5; **25a**, 100-68-5; **25b**, 7205-91-6; **26**, 38066-16-9; **27**, 55264-89-6; **28a**, 124267-12-5; **28b**, 124267-13-6; **29**, 124267-09-0; **30**, 99647-15-1; **31a**, 83239-21-8; **31b**, 83290-11-3; **31c**, 124375-83-3; **31d**, 88165-98-4; **32a**, 2437-56-1; **32b**, 35953-53-8; **32c**, 35953-54-9; **32d**, 124267-14-7; **33**, 116205-40-4; DAPA, 54856-92-7; APA, 4726-85-6; *tert*-butyllithium, 594-19-4; methanol, 67-56-1; *n*-butyllithium, 109-72-8; *sec*-butyllithium, 598-30-1; *sec*-butyl alcohol, 78-92-2; methanol-*O*-d_1, 1455-13-6; phenylsulfenyl chloride, 931-59-9; dodecyl aldehyde, 112-54-9; *p*-chlorophenylsulfenyl chloride, 933-01-7; bis(*p*-chlorophenyl) disulfide, 1142-19-4; methyl phenyl sulfinate, 670-98-4; triethyl phosphite, 122-52-1; (*E*)-1-(*tert*-butylsulfinyl)-1-tridecene, 124267-15-8.

Supplementary Material Available: Spectral data and general experimental details (23 pages). Ordering information is given on any current masthead page.

Notes

New Synthesis of 1-Alkyl(aryl)-2,3-dihydro-2-thioxo-1*H*-imidazole-4-carboxaldehydes

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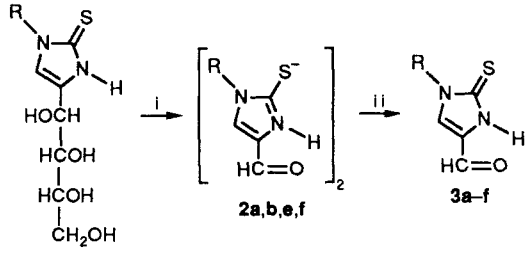
A general method for the synthesis of heterocyclic carboxaldehydes is the degradative oxidation of polyhydroxyalkylheterocycles with lead tetraacetate or sodium periodate.[1] We have reported[2,3] the utilization of this procedure for the preparation of 1,3-alkyl(aryl)-2,3-dihydro-2-thioxo-1*H*-imidazole-4-carboxaldehydes from 1,3-alkyl(aryl)-1,3-dihydro-4-(polyhydroxyalkyl)-2*H*-imidazole-2-thiones. We have also described[3-5] the synthesis of 1-aryl(H)-2-(benzylthio)-1*H*-imidazole-4-carboxaldehydes by oxidation of the corresponding 4-polyhydroxyalkyl derivatives. After acetalization of these aldehydes and reduction with Na/NH_3, 1-aryl(H)-2,3-dihydro-2-thioxo-1*H*-imidazole-4-carboxaldehydes were obtained.[3] However, this procedure requires several steps and the overall yields are low. We now report an improved method for the synthesis of carboxaldehydes **3** that avoids the use of protecting groups. This method employs the oxidation of 1-alkyl(aryl)-1,3-dihydro-4-(D-*arabino*-tetritol-1-yl)-2*H*-imidazole-2-thiones (**1**) to the corresponding 2,2′-dithiobis[1-alkyl(aryl)-1*H*-imidazole-4-carboxaldehydes] (**2**) followed by the reduction of the S–S bond. (Scheme I).

Scheme I[a]



a, R = C_4H_9; **b**, R = C_8H_{17}; **c**, R = $C_{12}H_{25}$; **d**, R = Ph; **e**, R = *p*-MeC_6H_4; **f**, R = *p*-$EtOC_6H_4$

[a] (i) $(AcO)_4Pb$; (ii) SO_2.

Compounds **3** are of interest because they are intermediates in the synthesis of imidazole derivatives with potential biological importance, such as thiolhistidines and thiolhistamines.

The oxidation of 1-alkyl(aryl)-1,3-dihydro-4-(D-*arabino*-tetritol-1-yl)-2*H*-imidazole-2-thiones (**1**) with 2.5 molar excess of lead tetraacetate in acetic acid benzene (1:2) gave a mixture of **2** and **3**, in which the disulfide was the major product.

Crystallization of the crude product of the reaction from ethyl acetate afforded the disulfides **2a,b,e,f** in 20–50% yield. In parallel experiments, the crude mixtures were reduced with SO_2, giving 1-alkyl(aryl)-2,3-dihydro-2-thioxo-1*H*-imidazole-4-carboxaldehydes (**3a–f**) in 50–70% yield from **1**.

The structures of compounds **2** and **3** were assigned on the basis of analytical, UV, IR, ^1H and ^{13}C NMR (Table I), and mass spectroscopic data, and in the case of **2e** X-ray data.

The IR,[3-5] ^1H NMR,[3] and ^{13}C NMR[6-8] spectroscopic data

(1) Garcia González, F.; Fernández-Bolaños, J.; López Aparicio, F. J. *ACS Symp. Ser.* **1977**, *39*, 207–226.
(2) Garcia González, F.; Fernández-Bolaños, J.; Fuentes Mota, J.; Pradera de Fuentes, M. A. *Carbohydr. Res.* **1973**, *26*, 427–430.
(3) Fernández-Bolaños, J.; Giménez Gracia, M. P.; Trujillo Pérez-Lanzac, M.; Fuentes Mota, J.; Viguera Rubio, F. J. *An. Quím.* **1985**, *81C*, 227–231.
(4) García-González, F.; Fernández-Bolaños, J.; Fuentes Mota, J. *Carbohydr. Res.* **1972**, *22*, 436–440.
(5) Fernández-Bolaños, J.; Heredia Moreno, A.; Saez de Buruaga J. *An. Quím.* **1973**, *69*, 933–935.
(6) Galbis Pérez, J. A.; Areces Bravo, P.; Rebolledo Vicente, F.; Fernández García-Hierro, J. I.; Fuentes Mota, J. *Carbohydr. Res.* **1988**, *176*, 97–106.

0022-3263/90/1955-0750$02.50/0

Table I. NMR Data of 2 and 3 in Me_2SO-d_6

	2a	2b	2e	2f	3a	3b	3c	3d	3e	3f
δ(CHO)	9.57 s	9.70 s	9.88 s	9.76 s	9.36 s	9.37 s	9.36 s	9.42 s	9.43 s	9.41 s
δ(H-5)	8.34 s	8.37 s	8.49 s	8.37 s	8.18 s	8.20 s	8.18 s	8.35 s	8.30 s	8.27 s
δ NH	–	–	–	–	13.04 br s	13.06 br s	13.05 br s	13.18 br s	13.02 br s	13.25 br s
δ(C=O)	185.1	185.1	185.1	185.1	177.2	177.0	177.0	177.4	177.3	177.3
δ(C-2)	142.2[a]	142.0[a]	141.9[a]	141.9[a]	165.6	165.6	165.6	166.3	166.3	166.5
δ(C-4)	141.5[a]	141.5[a]	141.2[a]	141.8[a]	128.1	128.0	128.0	128.6	128.5	128.4
δ(C-5)	130.9	132.6	131.9	132.2	131.4	131.3	131.3	132.0	131.9	132.2

[a] Assignments may be reversed.

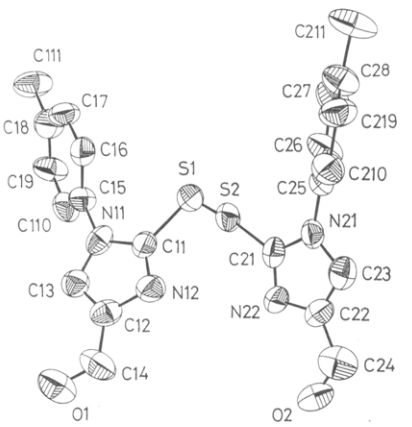


Figure 1.

of compounds **2** and **3** were in agreement with those reported for related compounds. The mass spectra of both types of compounds **2** and **3** showed molecular peaks, losses of sulfur and SH. Additionally **2** gave rupture of S–S bond (peak B), B + 1 (compounds **3**), B + 1 – formyl radical, and B + 1 – SH, whereas compounds **3** gave losses of hydrogen and formyl radical. The spectra of **3a,b,e,f** were contained in the spectra of the corresponding compounds **2**.

Compounds **3** are formulated in the thioxo form on the basis of their NMR data (δ HC=, NH, C-2, C-4, C-5) and bibliographic data on the thiol–thione equilibrium in imidazoline-2-thione.[9,10] The main differences between NMR spectra of **2** and **3** are indicated in Table I.

In order to corroborate the structure of these compounds, an X-ray analysis was carried out on **2e**. A perspective view of the molecule **2e** in the solid state, showing the relative configuration and the atomic numbering scheme, is given in Figure 1, bond lengths and bond angles in Table II. The molecule is a disulfide; the S1–S2 bond is 2.068 (6) Å. The two imidazole rings are planar, and the maximum deviations from the best plane are 0.012 and 0.009 Å, respectively. The sustituents S1, C14, and C15, and S2, C24 and C25 are at 0.027, –0.055 and –0.070, and –0.051, –0.002 and 0.019 Å from the respective ring best plane. The values of S–C, C–C, and C–N and C_{ring}–(C=O) bonds indicate some electronic delocalization in the imidazole and the carboxaldehyde group, and it is a normal feature of these compounds. The average interring angles C–N–C, N–C–C, and N–C–N are 105 (1), 109 (1), and 113 (1)°. The C14–O1 and C24–O2 distances of 1.225 (22) and 1.233 (22) Å also confirm an aldehyde structure. The two phenyl groups are planar, maximum deviation from the best planes –0.012 and –0.018 Å, with average C–C bond 1.384 (22) and 1.392 (24) Å. The sustituents N11, C111, N21, and C211 are at –0.007, 0.031, –0.001, and –0.036 Å from the respective phenyl planes. The C18–C111 and C28–C211 distances of 1.512 (22) and 1.518 (23) Å and the interring distances N11–C15 and N21–C25 of 1.440 (16) and 1.423 (17) Å agree well with those in analogous compounds.[11] The angles of the phenylimidazole planes are 51.3 (5) and 123.4 (5)°. The crystal packing is determined by van der Waals contacts.

Table II

Bond Lengths, Å			
S1–S2	2.068 (6)		
S1–C11	1.760 (14)	S2–C21	1.748 (14)
O1–C14	1.225 (22)	O2–C24	1.233 (22)
N11–C11	1.374 (15)	N21–C21	1.390 (16)
N11–C13	1.365 (19)	N21–C23	1.346 (20)
N11–C15	1.440 (17)	N21–C25	1.423 (17)
N12–C11	1.326 (18)	N22–C21	1.318 (19)
N12–C12	1.368 (18)	N22–C22	1.374 (17)
C12–C13	1.376 (19)	C22–C23	1.382 (22)
C12–C14	1.447 (21)	C22–C24	1.428 (25)
C15–C16	1.381 (20)	C25–C26	1.387 (23)
C15–C110	1.380 (19)	C25–C210	1.383 (22)
C16–C17	1.389 (20)	C26–C27	1.385 (25)
C17–C18	1.421 (21)	C27–C28	1.388 (24)
C18–C111	1.511 (22)	C28–C211	1.518 (24)
C18–C19	1.354 (22)	C28–C29	1.393 (23)
C19–C110	1.377 (21)	C29–C210	1.420 (22)
Bond Angles, deg			
C11–S1–S2	102.9 (5)	S1–S2–C21	100.6 (5)
C13–N11–C15	126.6 (11)	C23–N21–C25	126.2 (12)
C11–N11–C15	127.3 (11)	C21–N21–C25	127.8 (11)
C11–N11–C13	106.1 (11)	C21–N21–C23	106.0 (12)
C11–N12–C12	103.8 (11)	C21–N22–C22	103.6 (11)
N11–C11–N12	112.8 (11)	N21–C21–N22	112.8 (11)
S1–C11–N12	123.5 (10)	S2–C21–N22	124.6 (10)
S1–C11–N11	123.7 (10)	S2–C21–N21	122.5 (11)
N11–C13–C12	105.7 (12)	N21–C23–C22	106.2 (13)
N12–C12–C13	111.5 (13)	N22–C22–C23	111.3 (14)
C13–C12–C14	126.9 (14)	C23–C22–C24	125.4 (15)
N12–C12–C14	121.6 (14)	N22–C22–C24	123.3 (14)
O1–C14–C12	124.0 (16)	O2–C24–C22	124.0 (16)
N11–C15–C110	118.7 (12)	N21–C25–C210	118.5 (12)
N11–C15–C16	119.8 (12)	N21–C25–C26	120.9 (13)
C16–C15–C110	121.4 (13)	C26–C25–C210	120.6 (14)
C15–C16–C17	118.5 (14)	C25–C26–C27	119.7 (15)
C16–C17–C18	120.7 (13)	C26–C27–C28	121.4 (16)
C17–C18–C19	117.8 (14)	C27–C28–C29	118.8 (15)
C17–C18–C111	117.2 (14)	C27–C28–C211	121.2 (15)
C111–C18–C19	125.0 (15)	C211–C28–C29	120.0 (15)
C18–C19–C110	122.7 (15)	C28–C29–C210	120.2 (14)
C15–C110–C19	118.8 (14)	C25–C210–C29	119.2 (14)

Experimental Section

General Methods. Melting points were taken on a Gallenkamp melting point apparatus and are uncorrected. UV spectra (EtOH) were measured with a Perkin-Elmer 545 spectrophotometer. IR spectra (KBr discs) were recorded on a Perkin-Elmer 299 spectrophotometer. ^1H and ^{13}C NMR spectra were registered

(7) Fuentes Mota, J.; Pradera Adrián, M. A.; Ortiz Mellet, C.; García Fernández, J. M.; Babiano Caballero, R. *Carbohydr. Res.* **1988**, *173*, 1–16.
(8) Fuentes Mota, J.; Fernández García-Hierro, J. I.; Areces Bravo, P.; Rebolledo Vicente, F.; Galbis Pérez, J. A. *Nucleosides Nucleotides* **1988**, *7*, 457–477.
(9) Kjellin, K.; Sandstrom, J. *Acta Chem. Scand.* **1969**, *23*, 2888–2899.
(10) Elguero, J.; Harzin, C.; Katritzky, A. R.; Linda, P. The Tautomerism of heterocycles *Adv. Heterocycl. Chem. Sup.* **1976**, *1*, 400.
(11) Moreno, E.; López-Castro, A.; Márquez, R. *Acta Crystallogr.* **1985**, *C41*, 767–769.

at 200 and 50.3 MHz, respectively, on a Varian XL-200 instrument with Me_4Si as the internal standard and Me_2SO-d_6 as solvent. Chemical shifts are given in ppm from internal Me_4Si, and coupling constants are given in hertz. Assignments of NH were confirmed by H/D exchange experiments, and proton-decoupled APT spectra[12] were obtained to assist in carbon signal assignments. The EI mass spectra were realized at 70 eV, with an ion-source temperature of 200 °C, using a MS-80 RFA Kratos instrument.

General Procedure for the Preparation of 2,2′-Dithiobis[1-alkyl(aryl)-1*H*-imidazole-4-carboxaldehydes] (2). To a stirred mixture of 1-alkyl(aryl)-1,3-dihydro-4-(D-*arabino*-tetritol-1-yl)-2*H*-imidazole-2-thione (1) (15 mmol) and 1:2 acetic acid–benzene (300 mL) was added lead tetraacetate (40 mmol). The suspension was just dissolved, and the solution was left to stand for 30 min at room temperature. Then water (300 mL) was added, and the organic layer was washed with a saturated solution of $NaHCO_3$ and with water, dried (Na_2SO_4), and evaporated. The dark yellow residue was a mixture of **2** (R_f 0.13, ether–hexane, 5:1) and **3** (R_f 0.41, ether–hexane, 5:1), which crystallized from ethyl acetate, yield **2**. The following compounds were prepared in this manner.

2,2′-Dithiobis(1-*n*-butyl-1*H*-imidazole-4-carboxaldehyde) (2a): 0.97 g (29%); mp 118–120 °C; UV λ_{max} 209, 264 nm; IR ν_{max} 3090, 2950, 2930, 2820, 2710, 1690, 1670, 1600 cm^{-1}; ^1H NMR Table I and δ 4.09 (t, 2 H, ^3J = 7.1, NCH_2), 1.76 (m, 2 H, CH_2), 1.36 (m, 2 H, CH_2), 0.99 (t, 3 H, ^3J = 7.1, CH_3); ^{13}C NMR Table I and 47.0 (C-1′), 32.1 (C-2′), 19.2 (C-3′), 13.5 (C-4′); MS *m/z* 366 (2%, M^+), 334 (M − S), 333 (M − SH), 305 (M − S − CHO), 183 (B), 184 (B + H), 155 (B + 1 − CHO), 151 (100%, B + 1 − SH). Anal. Calcd for $C_{16}H_{22}N_4O_2S_2$: C, 52.43; H, 6.05; N, 15.23. Found: C, 52.42; H, 6.26; N, 15.52.

2,2′-Dithiobis(1-*n*-octyl-1*H*-imidazole-4-carboxaldehyde) (2b): 1.30 g (37%); mp 119–121 °C; UV λ_{max} 208, 264 nm; IR ν_{max} 3095, 2930, 2860, 1690, 1675 cm^{-1}; ^1H NMR Table I and δ 3.92 (t, 2 H, ^3J = 7.0, NCH_2), 2.52 (m, 2 H, CH_2), 1.42 (m, 2 H, CH_2), 1.20 (m, 8 H, 4 CH_2), 0.87 (t, 3 H, ^3J = 7.0, CH_3); ^{13}C NMR Table I and δ 47.3 (C-1′), 31.2 (C-2′), 30.1 (C-3′), 28.6 (C-4′), 28.5 (C-5′), 25.9 (C-6′), 22.2 (C-7′), 14.0 (C-8′); MS *m/z* 478 (4%, M^+), 445 (M − SH), 239 (B), 240 (B + 1), 211 (B + 1 − CHO), 207 (100%, B + 1 − SH). Anal. Calcd for $C_{24}H_{38}N_4O_2S_2$: C, 60.21; H, 8.00; N, 11.70. Found: C, 59.74; H, 7.89; N, 11.64.

2,2′-Dithiobis[1-*p*-tolyl-1*H*-imidazole-4-carboxaldehyde] (2e): 1.75 g (50%); mp 205–207 °C; UV λ_{max} 210, 260 nm; IR ν_{max} 3130, 3090, 3030, 2920, 2830, 1685, 1605, 1580 cm^{-1}; ^1H NMR Table I and δ 7.45–7.24 (m, 4 H, C_6H_4), 2.48 (s, 3 H, CH_3); ^{13}C NMR Table I and δ 139.1, 133.7 (C-1″, C-4″), 129.7 (C-3″ and C-5″), 125.9 (C-2″ and C-6″), 20.8 (CH_3); MS *m/z* 434 (50%, M^+), 402 (M − S), 401 (M − SH), 373 (M − S − CHO), 217 (B), 218 (100%, B + 1), 189 (B + 1 − CHO), 185 (B + 1 − SH), 91 (tropylium ion). Anal. Calcd for $C_{22}H_{18}N_4O_2S_2$: C, 60.81; H, 4.17; N, 12.89. Found: C, 60.80; H, 4.48; N, 12.58.

2,2′-Dithiobis[1-(*p*-ethoxyphenyl)-1*H*-imidazole-4-carboxaldehyde] (2f): 0.76 g (21%); mp 149–151 °C; UV λ_{max} 204, 226, 267 nm; IR ν_{max} 3130, 3090, 2900, 2920, 2830, 1685, 1610, 1585 cm^{-1}; ^1H NMR Table I and δ 7.32–6.92 (m, 4 H, C_6H_4), 4.08 (q, 2 H, ^3J = 7.0, OCH_2), 1.36 (t, 3 H, ^3J = 7.0, CH_3); ^{13}C NMR Table I and 128.5 (C-1″), 158.9 (C-4″), 114.7 (C-3″ and C-5″), 127.6 (C-2″ and C-6″), 63.6 (OCH_2), 14.7 (CH_3); MS *m/z* 494 (1%, M^+), 462 (M − S), 247 (B), 248 (100%, B + 1), 219 (B + 1 − CHO), 215 (B + 1 − SH). Anal. Calcd for $C_{24}H_{22}N_4O_4S_2$: C, 58.28; H, 4.48; N, 11.30. Found: C, 57.97; H, 4.40; N, 11.19.

General Procedure for the Preparation of 1-Aryl(alkyl)-2,3-dihydro-2-thioxo-1*H*-imidazole-4-carboxaldehyde (3). To a solution of crude **2** (15 mmol) in dioxane (75 mL) was bubbled a steady stream of SO_2 for 1 h. The reaction mixture was concentrated to dryness under diminished pressure, and the residue was crystallized from ethanol–water. The following compounds were prepared in this manner.

1-*n*-Butyl-2,3-dihydro-2-thioxo-1*H*-imidazole-4-carboxaldehyde (3a): 1.92 g (58% from **1a**); mp 117–119 °C; UV λ_{max} 216, 261, 329 nm; IR ν_{max} 3130, 2950, 2930, 2860, 2720, 1640, 1585 cm^{-1}; ^1H NMR Table I and δ 4.00 (t, 2 H, ^3J = 7.0, NCH_2), 1.76 (m, 2 H, CH_2), 1.36 (m, 2 H, CH_2), 0.90 (t, 3 H, ^3J = 7.0, CH_3); ^{13}C NMR Table I and δ 46.2 (C-1′), 30.5 (C-2′), 19.2 (C-3′), 13.7 (C-4′); MS *m/z* 184 (100%, M^+), 183 (M − H), 155 (M − CHO), 152 (M − S), 151 (M − SH), 123 (M − S − CHO). Anal. Calcd for $C_8H_{12}N_2OS$: C, 52.14; H, 6.56; N, 15.20. Found: C, 52.03; H, 6.50; N, 15.32.

1-*n*-Octyl-2,3-dihydro-2-thioxo-1*H*-imidazole-4-carboxaldehyde (3b): 2.15 g (60% from **1b**); mp 130–131 °C; UV λ_{max} 216, 261, 329 nm; IR ν_{max} 3180, 2960, 2920, 2850, 2700, 1675, 1650, 1590 cm^{-1}; ^1H NMR Table I and δ 3.99 (t, 2 H, ^3J = 7.0, NCH_2), 1.72 (m, 2 H, CH_2), 1.27 (m, 10 H, 5 CH_2), 0.86 (t, 3 H, ^3J = 7.0, CH_3); ^{13}C NMR Table I and δ 46.4 (C-1′), 31.3 (C-2′), 28.6 (C-3′ and C-4′), 28.3 (C-5′), 25.8 (C-6′), 22.2 (C-7′), 14.1 (C-8′); MS *m/z* 240 (M^+), 239 (M − H), 211 (M − CHO), 208 (M − S), 207 (100%, M − SH), 179 (M − S − CHO). Anal. Calcd for $C_{12}H_{20}N_2OS$: C, 59.90; H, 8.38; N, 11.65. Found: C, 59.49; H, 8.29; N, 11.54.

1-*n*-Dodecyl-2,3-dihydro-2-thioxo-1*H*-imidazole-4-carboxaldehyde (3c): 2.61 g (69% from **1c**); mp 128–129 °C; UV λ_{max} 216, 261, 329 nm; IR ν_{max} 3080, 3050, 2960, 2920, 2850, 2700, 1680, 1650, 1590 cm^{-1}; ^1H NMR Table I and δ 3.98 (t, 2 H, ^3J = 7.0, NCH_2), 1.70 (m, 2 H, CH_2), 1.23 (m, 18 H, 9 CH_2), 0.85 (t, 3 H, ^3J = 7.0, CH_3); ^{13}C NMR Table I and δ 46.4 (C-1′), 31.4 (C-2′), 29.2 (C-3′ and C-4′), 29.1 (C-5′), 29.0 (C-6′), 28.8 (C-7′), 28.6 (C-8′), 28.3 (C-9′), 25.9 (C-10′), 22.2 (C-11′), 14.07 (C-12′); MS *m/z* 296 (M^+), 295 (M − H), 267 (M − CHO), 264 (M − S), 263 (100%, M − SH), 235 (M − S − CHO). Anal. Calcd for $C_{16}H_{28}N_2OS$: C, 64.81; H, 9.52; N, 9.45. Found: C, 65.08; H, 9.54; N, 9.66.

1-Phenyl-2,3-dihydro-2-thioxo-1*H*-imidazole-4-carboxaldehyde (3d): 1.77 g (51% from **1d**); mp 219–221 °C; UV λ_{max} 250, 352 nm; IR ν_{max} 3140, 3095, 3040, 2910, 2850, 2820, 1680, 1590, 1500, 1480 cm^{-1}; ^1H NMR Table I and δ 7.40–7.65 (m, 5 H, C_6H_5); ^{13}C NMR Table I and δ 137.0 (C-1″), 128.8 (C-4″), 129.1 (C-3″ and C-5″), 126.5 (C-2″ and C-6″); MS *m/z* 204 (100%, M^+), 203 (M − H), 175 (M − CHO), 172 (M − S), 171 (M − SH), 143 (M − S − CHO), 77 (C_6H_5). Anal. Calcd for $C_{10}H_8N_2OS$: C, 58.80; H, 3.94; N, 13.71. Found: C, 58.59; H, 3.74; N, 13.38.

1-*p*-Tolyl-2,3-dihydro-1*H*-imidazole-4-carboxaldehyde (3e): 1.98 g (56% from **1e**); mp 238–240 °C (lit.[3] yield 9% from **1e**, mp 236–238 °C); UV λ_{max} 214, 281, 331 nm; IR ν_{max} 3130, 3030, 2920, 2830, 2720, 1680, 1610, 1580 cm^{-1}; ^1H NMR Table I and δ 7.31–7.50 (m, 4 H, C_6H_4), 2.37 (s, 3 H, CH_3); ^{13}C NMR Table I and δ 138.4, 134.5 (C-1″, C-4″), 129.5 (C-3″ and C-5″), 126.2 (C-2″ and C-6″), 20.8 (CH_3); MS *m/z* 218 (100%, M^+), 217 (M − H), 189 (M − CHO), 186 (M − S), 185 (M − SH), 157 (M − S − CHO), 91 (tropylium ion).

1-(*p*-Ethoxyphenyl)-2,3-dihydro-2-thioxo-1*H*-imidazole-4-carboxaldehyde (3f): 0.82 g (52% from **1f**); mp 230–232 °C (lit.[3] yield 24% from **1f**, mp 230–232 °C); UV λ_{max} 274, 332 nm; IR ν_{max} 3120, 3040, 2930, 2830, 2730, 1650, 1600, 1580 cm^{-1}; ^1H NMR Table I and δ 7.02–7.48 (4 H, m, C_6H_4), 4.1 (q, 2 H, ^3J = 7.0, OCH_2), 1.35 (t, 3 H, ^3J = 7.0, CH_3); ^{13}C NMR Table I and δ 129.7 (C-1″), 158.6 (C-4″), 114.6 (C-3″ and C-5″), 127.8 (C-2″ and C-6″), 63.6 (OCH_2), 14.7 (CH_3); MS *m/z* 248 (100%, M^+), 247 (M − H), 219 (M − CHO), 216 (M − S), 215 (M − SH), 187 (M − S − CHO).

X-ray Analysis. A crystal of **2e** was mounted on a CAD4 Enraf-Nonius automated diffractometer. Crystal size: 0.20 × 0.11 × 0.23 mm. Unit cell dimensions (Table III, supplementary material) were determined by least-squares refinement of the best angular positions for 25 independent reflections in the range $5 < \theta < 10°$ using MoKα radiation (λ = 0.710 69 Å). Data (3326 reflections) were collected at room temperature, using $\omega/2\theta$ scan mode to a maximum 2θ value of 60°. The intensities of two standard reflections were measured every 100 reflections, and as the intensities of these reflections showed less than 5% variation, corrections for decomposition were deemed unnecessary. Intensities were corrected for Lorentz and polarization effects, but no absorption correction was made. A total of 1659 reflections were considered observed [$I > 2.0\sigma(I)$]. The structure was solved by using MULTAN 80[13] to locate 28 of the 30 non-hydrogen atoms

(12) Patt, S. L.; Shoolery, J. N. *J. Magn. Reson.* **1982**, *48*, 323–327.

(13) Main, P.; Fiske, S. J.; Hull, S. E.; Lessinger, L.; Germain, G.; Declerco, J. P.; Woolfson, M. M. MULTAN 80, A. System of Computer Programs for the Automatic solution of Crystal Structures from X-ray Diffractions Data; Universities of York, England, and Louvain, Belgium, 1980.

having the structure. Successive cycles of least-squares full matrix refinements, followed by difference Fourier synthesis, allowed location of the remainder non-H atoms. Refinements of scale factor, positional, and anisotropic thermal parameters for all non-hydrogen atoms was carried out to convergence, minimizing the function $\sum w(|F_o| - |F_c|)^2$. Some hydrogen atoms were located at geometric positions and the others from a final difference Fourier and isotropic thermal parameters. H atoms were not refined. The final cycle of refinements led to a final agreement factor, $R = 0.06$, $R = \sum(|F_o| - |F_c|)/\sum|F_o|$, using unit weight $R_w = 0.06$.

Atomic scattering factors from *International Tables for X-ray Crystallography*,[14] all calculations carried out with the XRAY system;[15] maximum residual density in the final difference map = ±0.3 eA.

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Registry No. **1a**, 16885-21-5; **1b**, 93125-33-8; **1c**, 93125-35-0; **1d**, 24580-90-3; **1e**, 24916-29-8; **1f**, 14965-56-1; **2a**, 123540-53-4; **2b**, 123540-54-5; **2c**, 123540-55-6; **2f**, 123540-56-7; **3a**, 123540-57-8; **3b**, 123540-58-9; **3c**, 123540-59-0; **3d**, 123540-60-3; **3e**, 107127-16-2; **3f**, 107127-18-4.

Supplementary Material Available: Table III listing crystallographic data (1 page). Ordering information is given on any current masthead page. [A listing of calculated and observed structure factors is available from A.L.]

(14) *International Tables for X-ray Crystallography*; Kynoch Press: Birmingham, 1974; Vol. IV, pp 202-207 (Present distributor D. Reidel, Dordrecht).

(15) Stewart, J. M.; Kundell, F. A.; Baldwin, J. C. *The* XRAY *System*; Computer Science Center, University of Maryland: College Park, MD, 1970.

Ab Initio Study of the Protonation and the Tautomerism of the 7-Aminopyrazolopyrimidine Molecule

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Introduction

7-Aminopyrazolo[4,3-*d*]pyrimidine[1] (see compound Ia in Scheme I) is an aromatic moiety present in several nucleosides of both biological and synthetic origins. Among them, formycin (7-amino-3β-D-ribofuranosyl pyrazolo[4,3-*d*]pyrimidine) is of particular interest (see compound Ib in scheme I). Formycin is a C-nucleoside analogue of adenosine, which was first isolated from cultures of Norcardia Interforma.[1b] This nucleoside has been extensively studied due to its antiviral,[2-4] antibiotic,[1b] immunodepressant,[5] antitumor,[5,6] and antimetabolic[4] properties. Nevertheless, its clinical use is hampered by its ease of deamination by adenosine deaminase (E.C.3.5.4.4),[7] the enzyme catalyzing the hydrolytic conversion of adenosine (and analogues) to inosine (and analogues).

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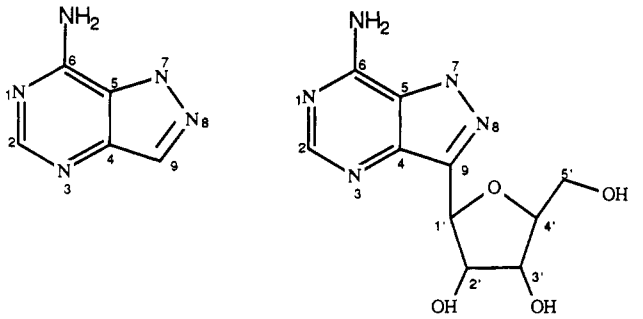
Scheme I. Schematic Representation of the 7-Aminopyrazolopyrimidine (IA) and Formycin (IB) Molecules[a]



I A I B

[a] Atom numbering follows the purine nomenclature system.

From an structural point of view, formycin is very similar to adenosine, but two differences exist: (i) The N-ribose bond of adenosine is replaced by a C-ribose bond in formycin; (ii) The imidazole ring of adenosine is replaced by a pyrazolo ring in formycin. The presence of a C-ribose bond instead of the N-ribose bond has consequences for the conformation of formycin, which have been discussed elsewhere (see ref 8 and references therein). Moreover, the existence of a pyrazolo ring in formycin leads to the existence of possible N7-H—N8-H tautomerism, an interesting phenomenon that cannot occur for adenosine.

The biological relevance of the N7H-N8H tautomerism has been recently pointed out by our laboratory.[9] Our theoretical results suggest that the N8-H tautomer of formycin can be deaminated by adenosine deaminase, while the N7-H tautomer is not a substrate for the enzyme. Since the deamination reaction is one of the most important interfering reactions accompanying the in vivo pharmacological use of formycin, accurate analysis of the pyrazolo tautomerism seems to be of major importance.

Several experimental (spectrophotometric, NMR, and X-ray) results have been reported in the literature concerning the structure, tautomerism, and protonation of pyrazolo pyrimidines. Thus Prusiner[10] reported the X-ray structure of formycin, Koyama et al.[11] that of formycin hydrobromide, and McKenna et al.[7] that of 3'-deoxy-

(1) (a) In this paper (although the rigourous IUPAC name of the aminopyrazolopyrimidine molecule is used) atom numbering has been done according to the purine nomenclature system. This is preferred to the use of the specific IUPAC nomenclature for pyrazolopyrimidine rings, in order to clarify the discussion. The purine nomenclature system has been used extensively in several studies about pyrazolopyrimidine derivatives, which are referenced and discussed in this paper. (b) Hori, M.; Ito, E.; Takita, T.; Koyama, T.; Takeuchi, T.; Umezawa, A. J. *J. Antibiot. Ser. A* **1964**, *17*, 96.

(2) Ishida, N.; Honiura, K.; Ksmegui, Y.; Schimizu, Y.; Matsumoto, S.; Izawa, A. *J. Antibiot. Ser. A* **1967**, *20*, 49.

(3) Takeuchi, T.; Iwanaga, J.; Aogaiad, T.; Umezawa, H. *J. Antibiot. Ser. A* **1966**, *19*, 286.

(4) Giziewicz, J.; De Clerq, M.; Luczak, M.; Shugar, D. *Biochem. Pharmacol.* **1975**, *24*, 1813.

(5) Odaka, T.; Takizawa, K.; Yamaura, K.; Yamamoto, T. *Jpn. J. Exp. Med.* **1969**, *39*, 327.

(6) Suhadolnik, R. J. In *Nucleosides as Biological Probes*; Willey: New York, 1979.

(7) McKenna, R.; Neidle, S.; Serafinowski, P. *Acta Crystallogr.* **1987**, *C43*, 2358.

(8) Birnbaum, G. I.; Shugar, D. In *Topics in Nucleic Acids Structure*; Macmillan Press: London, 1987; Part III, Chapter 1.

(9) Orozco, M.; Canela, E. I.; Franco, R. *Mol. Pharmacol.* **1989**, *35*, 257-264.

(10) Prusiner, P.; Brennan, T.; Sundaralingam, M. *Biochemistry* **1973**, *12*, 1196.

(11) Koyama, G.; Umezawa, H.; Iitaka, Y. *Acta Crystallogr.* **1974**, *B30*, 1511.

0022-3263/90/1955-0753$02.50/0