

Ring-Ring Interconversions. Part 3 [1]. On the Effect of the Substituents on the Thiazole Moiety in the Ring-Opening/Ring-Closing Reactions of Nitrosoimidazo[2,1-*b*][1,3]thiazoles with Hydrochloric Acid

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The reaction of 6-(4-chlorophenyl)-5-nitrosoimidazo[2,1-*b*][1,3]thiazole **1b**, 6-(4-chlorophenyl)-2-methyl-5-nitrosoimidazo[2,1-*b*][1,3]thiazole **1c**, 6-(4-chlorophenyl)-2,3-dimethyl-5-nitrosoimidazo[2,1-*b*][1,3]thiazole **1d** and 2-(4-chlorophenyl)-3-nitrosobenzo[*d*]imidazo[2,1-*b*][1,3]thiazole **1e** with hydrochloric acid has been carried out in order to investigate the effect of substituents on the thiazole ring in a recently reported ring-ring interconversion reaction. In every case the corresponding [1,4]-thiazino[3,4-*c*][1,2,4]oxadiazol-3-ones **2b-e** have been obtained. In particular, the benzoderivative **1e** furnished the 4-(4-chlorophenyl)-4-hydroxy-4*H*-benzo[5,6][1,4]thiazino[3,4-*c*][1,2,4]oxadiazol-1-one **2e**, containing a new tricyclic system with a quasi-planar geometry whose pharmacological potentialities appear promising.

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Recently we reported [2] on a novel ring-ring interconversion which furnishes a new heterocyclic system characterized by the [1,4]thiazino[3,4-*c*][1,2,4]oxadiazol-3-one moiety. Thus, 8-(4-chlorophenyl)-8-hydroxy-5-methyl-8*H*-[1,4]thiazino[3,4-*c*][1,2,4]oxadiazol-3-one **2a** was obtained in high yield from 6-(4-chlorophenyl)-3-methyl-5-nitrosoimidazo[2,1-*b*][1,3]thiazole **1a** (Scheme 1) simply by reflux in ethanol in the presence of hydrochloric acid. Afterwards we extended the scope of the reaction to several *meta*- and *para*-substituted (H, F, Cl, Br, Me, OMe, CN, CF₃, NO₂, Ph) 6-arylnitrosoimidazothiazoles [1] enlightening the effect of the substituent on the yield of the interconversion. Moreover we gained an interesting insight into the reaction mechanism [1] carrying out the reaction at room temperature in dioxane; thus, we were able to isolate a reaction intermediate (**A**) which can evolve to **2a** via several possible intermediates (e.g. **B**, formed by an acyclic

nucleophilic substitution with the cleavage of the feeble carbonyl-sulphur bond).

In order to evaluate any effect of substituents in the thiazole ring, we have herein carried out the reaction on nitroso derivatives containing different substitution patterns.

Thus, we tested the reactivity of 6-(4-chlorophenyl)-5-nitrosoimidazo[2,1-*b*][1,3]thiazole (**1b**; R¹ = R² = H), 6-(4-chlorophenyl)-2-methyl-5-nitrosoimidazo[2,1-*b*][1,3]thiazole (**1c**; R¹ = Me, R² = H), 6-(4-chlorophenyl)-2,3-dimethyl-5-nitrosoimidazo[2,1-*b*][1,3]thiazole (**1d**; R¹ = R² = Me) and 2-(4-chlorophenyl)-3-nitrosobenzo[*d*]imidazo[2,1-*b*][1,3]thiazole (**1e**; R¹-R² = C₆H₄) with hydrochloric acid (Scheme 2).

The results of the reactions, carried out in the same conditions adopted [1,2] for the ring-ring interconversion of **1a** (as well as of its derivatives of *meta*- and *para*-substitution in the 6-phenyl moiety), are reported in Table 1, together with those for **1a** itself for homogeneity sake. The crude products **2b-e** were purified by column chromatography and their structures were easily identified by comparison with the spectra (¹H and ¹³C NMR as well as MS) of **2a** [2].

Scheme 1

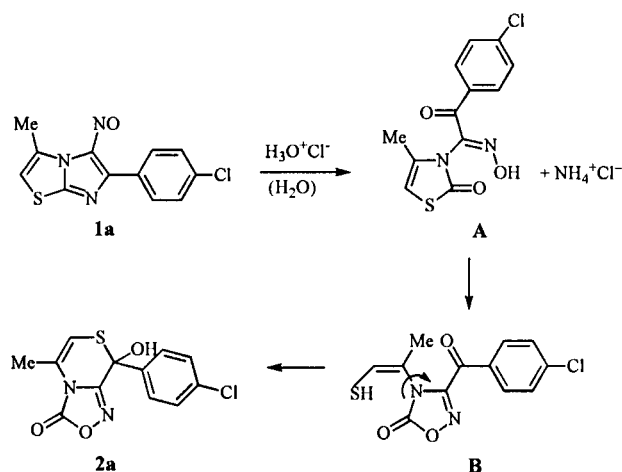
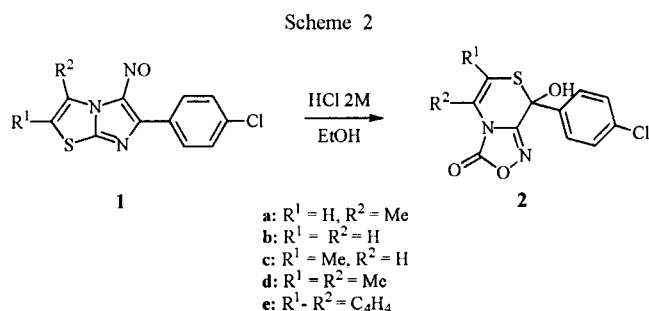


Table 1

Results for the Ring-Ring Interconversion of Compounds **1a-e** in EtOH/2*M* HCl

Substrate	Reaction time [a]	Yield [b]
1a [c]	1 hour	2a : 65%
1b	1 hour	2b : 26%
1c	1 hour	2c : 37%
1d	11 hours	2d : 26% [d]
1e	1 hour	2e : 38%

[a] At reflux. [b] After chromatography. [c] From Ref [2]. [d] Unreacted substrate (20%) also recovered.



The determination of the structure of **2e** requires some comments. The ^1H NMR spectrum shows resonances regarding both protons of *para*-disubstituted benzene and the exchangeable proton very similar to those of the spectrum of compound **2a** [2]. The ^{13}C NMR spectrum shows resonances at 155.73, 155.19 and 77.41 ppm for C-3a, C-1 and C-4 and at 135.24, 128.90, 128.38 and 134.28 ppm for those of C-1', C-2', C-3' and C-4' of the disubstituted *para*-chlorophenyl moiety strictly recalling those observed for **2a** [2] (at 155.55, 154.81 and 76.31 for C-8a, C-3 and C-8 and at 135.87, 128.99, 128.17 and 133.94 ppm for C-1', C-2', C-3' and C-4', respectively). In the mass spectrum the M^+-1 and the M^+-44 peaks were observed.

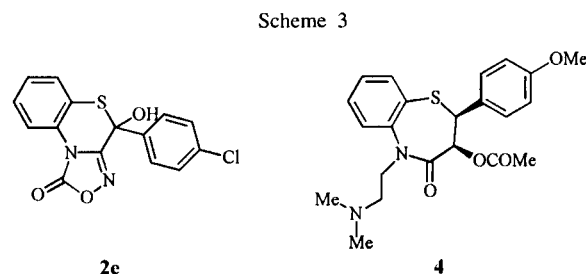
The data of Table 1 clearly show that, against the good yield of **2a** (65% after chromatography) [2], the ring-ring interconversion of **1b-e** lead to modest yields of the desired thiazinooxadiazolones **2b-e**, which were found to be accompanied by several unidentified by-products. Thus, the presence of a methyl at C-3 (as in **1a**) seems essential to guarantee a significant yield increase (65%) with respect to the unsubstituted **1b** (26%), while a methyl at C-2 (as in **1c**) proves less effective (37%). As far as **1d** is concerned, the contemporaneous presence of a methyl at both C-2 and C-3 plays a negative effect (most likely of steric origin), mirrored by a very slow reaction. Thus, after 11 hours of reflux some substrate (20%) could be recovered unreacted while the prolonged reaction time itself could well be responsible for the low yield of **2d** (26%): as a matter of fact a further increase of the reaction time was observed to cause a significant increase of decomposition products.

In order to better understand the influence of factors that affect the reactivity of **1d** we attempted to identify the stage at which they operate by separating the two steps of the reaction (formation of the **A**-like intermediate and ring closure to **2d**, see Scheme 1). Thus, we carried on the reaction of **1d** with hydrochloric acid in dioxane at room temperature, *i.e.* in the same experimental conditions used for **1a**, and were able to isolate an intermediate (5-Me-A) whose spectroscopic data (^1H NMR and MS) strictly resemble those of compound **A** of Scheme 1 [1]. The isolated

1-(4-chlorophenyl)-2-[4,5-dimethyl-2-oxo-2*H*-1,3-thiazol-3-yl]-1,2-ethandione-2-oxime furnished **2d** after a prolonged reflux (11 hours) in ethanol in the presence of hydrochloric acid while the **A** $\rightarrow$ **2a** conversion requires only 15 minutes [1].

These experiments allow to conclude that **1a** and **1d** have analogous reactivity in the imidazole ring-opening step (formation of **A** and 5-Me-A, respectively); by contrast, the following ring closure to **2a** and **2d** requires different reaction times, pointing to a significant retarding effect (probably of steric origin) in the second case.

In conclusion the study herein has confirmed the general applicability of the ring-ring interconversion of Scheme 1 to substrates characterized by a variously substituted thiazole moiety, pointing out the effects of the substituents on the yield of the reaction. We have also realised the first synthesis of the benzo[5,6][1,4]thiazino[3,4-*c*][1,2,4]oxadiazol-1-one nucleus (see **2e**), a tricyclic quasi-planar structure recalling that of diltiazem **4**, which shows an interesting therapeutic activity in the treatment of angina and hypertension [3]. Biological assays on several [1,4]thiazino[3,4-*c*][1,2,4]oxadiazol-3-ones are in progress. Preliminary tests have shown for **2e** a moderate activity against gram-positive bacteria and an interesting negative inotropic effect coupled with a high negative inotropic effect [4].



EXPERIMENTAL

Melting points are uncorrected. The mass spectra were recorded with a VG70 70E apparatus. ^1H and ^{13}C NMR spectra were determined in dimethyl- d_6 sulfoxide with a Varian Gemini 300 Instrument in the Fourier transform mode at $21 \pm 0.5^\circ$. Chemical shifts are reported in parts per million (δ) high frequency from tetramethylsilane and coupling constants are in hertz (Hz). Silica gel plates (Merck F₂₅₄) and silica gel 60 (Merck 230-400 mesh) were used for analytical thin-layer chromatography (tlc) and for column chromatography, respectively. Solvents were removed under reduced pressure.

Compounds **1b** and **1c** were synthesized as already reported [5], by nitrosation of the corresponding substituted imidazothiazoles. The same methodology was applied to the synthesis of **1d** and **1e**, which were prepared by nitrosation of 6-(4-chlorophenyl)-2,3-dimethylimidazo[2,1-*b*][1,3]thiazole **3d** and

2-(4-chlorophenyl)benzo[d]imidazo[2,1-b][1,3]thiazole **3e**, respectively.

2-(4-Chlorophenyl)benzo[d]imidazo[2,1-b][1,3]thiazole (**3e**).

Mp 158–160° (lit. [6] mp 160°). ¹H nmr: δ 8.83 (s, 1H, 3-H), 8.04 (dd, 1H, *J* = 7.5, 1.0, 5-H or 8-H), 7.97 (dd, 1H, *J* = 7.5, 1.0, 8-H or 5-H), 7.89 (AA' part of AA'XX' system, 2H, 2'-H and 6'-H), 7.58 (ddd, 1H, *J* = 7.5, 7.5, 1.0, 7-H or 6-H), 7.50 (XX' part of AA'XX' system, 2H, 3'-H and 5'-H), 7.44 (ddd, 1H, *J* = 7.5, 7.5, 1.0, 6-H or 7-H); ¹³C nmr: δ 147.08, 145.03, 132.73, 131.65, 131.48, 129.16, 128.72, 126.67, 126.24, 125.21, 124.99, 113.29, 109.50; ms: *m/z* 286 (M⁺+2, 35%), 284 (M⁺, 100%), 249 (6), 248 (8), 228 (8), 150 (9), 142 (9), 136 (5), 125 (6) and 114 (4).

6-(4-Chlorophenyl)-2,3-dimethyl-5-nitrosoimidazo[2,1-b][1,3]thiazole (**1d**).

A solution of NaNO₂ (0.53 g, 7.7 mmol) in water (10 ml) was added dropwise to a previously cooled (0°) solution of 6-(4-chlorophenyl)-2,3-dimethylimidazo[2,1-b][1,3]thiazole **3d** [7] (1.00 g, 3.4 mmol) in acetic acid (20 ml). The mixture was allowed to warm to room temperature and stirred for 2 hours. After this time water (100 ml) was added and the green precipitate was collected by filtration and recrystallized from ethanol (0.59 g, 60%), mp 210° dec; ¹H nmr: δ 8.38 (AA' part of AA'BB' system, 2H, 3'-H and 5'-H), 7.64 (BB' part of AA'BB' system, 2H, 2'-H and 6'-H), 2.47 (s, 3H, 3-Me), 2.36 (s, 3H, 2-Me); ¹³C nmr: δ 159.15, 157.69, 155.98, 136.01, 131.60, 130.61, 128.85, 128.54, 123.83, 14.17, 12.89; ms: *m/z* 293 (M⁺+2, 4%), 291 (M⁺, 12%), 275 (60), 274 (30), 208 (10), 44 (9), 32 (100). HRMS (Cl-35 isotope): found 291.02400, C₁₃H₁₀ClN₃OS requires 291.02331.

Anal. Calcd. for C₁₃H₁₀ClN₃OS: C, 53.52; H, 3.45; N, 14.40. Found: C, 53.65; H, 3.42; N, 14.51.

2-(4-Chlorophenyl)-3-nitrosobenzo[d]imidazo[2,1-b][1,3]thiazole (**1e**).

Operating as described for the nitrosation of **3d**, 2-(4-chlorophenyl)benzo[d]imidazo[2,1-b][1,3]thiazole **3e** afforded the nitroso derivative **1e** (1.05 g, 96%), mp (from ethanol) 203–208° dec; ¹H nmr: δ 8.76 (dd, 1H, *J* = 7.8, 1.1, 5-H or 8-H), 8.50 (AA' part of AA'XX' system, 2H, 2'-H and 6'-H), 8.18 (dd, 1H, *J* = 7.9, 1.1, 8-H or 5-H), 7.70 (XX' part of AA'XX' system, 2H, 3'-H and 5'-H), 7.67 (m, 1H, 7-H or 6-H), 7.58 (m, 1H, 6-H or 7-H); ¹³C nmr: δ 159.76, 159.20, 156.90, 136.71, 132.21, 131.94, 130.35, 130.26, 129.14, 126.77, 126.60, 124.72, 117.55; ms: *m/z* 315 (M⁺+2, 35%), 313 (M⁺, 99%), 297 (51), 296 (75), 285 (19), 284 (52), 283 (19), 278 (22), 271 (10), 262 (26), 248 (76), 245 (13), 160 (13), 146 (66), 139 (100), 135 (12), 134 (18), 123 (17), 114 (12), 111 (30), 108 (32), 102 (16), 90 (18), 82 (12), 76 (10), 75 (24), 69 (30), 63 (25), 51 (14), 50 (18), 45 (17), 44 (13), 39 (18). HRMS (Cl-35 isotope): found 313.00704, C₁₅H₈ClN₃OS requires 313.00766.

Anal. Calcd. for C₁₅H₈ClN₃OS: C, 57.42; H, 2.57; N, 13.39. Found: C, 57.55; H, 2.63; N, 13.52.

8-(4-Chlorophenyl)-8-hydroxy-8H-[1,4]thiazino[3,4-c]-[1,2,4]oxadiazol-3-one (**2b**).

A suspension of **1b** (0.25 g; 1 mmol) in ethanol (40 ml) was refluxed under stirring with HCl 2M (1 ml) for 1 hour. Removal of the solvent left a solid which was purified by chromatography (petroleum ether-ethyl acetate 3:1 as eluant) to give the colourless **2b** (0.07 g, 26%), mp 209° dec; ¹H nmr: δ 8.45 (br s, exch.

1H, OH), 7.70 (AA' part of AA'BB' system, 2H, 3'-H and 5'-H), 7.54 (BB' part of AA'BB' system, 2H, 2'-H and 6'-H), 7.27 (d, 1H, *J* = 7.6, 5-H), 6.60 (d, 1H, *J* = 7.6, 6-H); ¹³C nmr: δ 154.65 (s, C-3), 154.06 (m, C-8a), 135.90 (t, *J* = 7.4, C-1'), 134.05 (tt, *J* = 10.7, 3.1, C-4'), 128.94 (dd, *J* = 164.9, 6.6, C-2' and C-6'), 128.18 (dd, *J* = 168.6, 5.0, C-3' and C-5'), 116.14 (dd, *J* = 195.0, 5.4, C-5), 109.73 (dd, *J* = 187.7, 7.1, C-6), 76.91 (dt, *J* = 3.7, 3.7, C-8); ms: *m/z* 282 (M⁺, 1%), 238 (7), 224 (1), 189 (60), 139 (100), 111 (46), 100 (12), 75 (27), 58 (29), 50 (13), 44 (93).

Anal. Calcd. for C₁₁H₇ClN₂O₃S: C, 46.73; H, 2.50; N, 9.91. Found: C, 46.85; H, 2.61; N, 10.00.

8-(4-Chlorophenyl)-8-hydroxy-6-methyl-8H-[1,4]thiazino[3,4-c]-[1,2,4]oxadiazol-3-one (**2c**).

With the same general procedure described for **1b**, compound **1c** (0.28 g; 1 mmol) afforded the colourless **2c** (0.11 g, 37%), mp 160° dec; ¹H nmr: δ 8.49 (br s, exch., 1H, OH), 7.69 (AA' part of AA'BB' system, 2H, 2'-H and 6'-H), 7.54 (BB' part of AA'BB' system, 2H, 3'-H and 5'-H), 7.16 (q, 1H, *J* = 1.5, 5-H), 2.08 (d, 3H, *J* = 1.5, Me); ¹³C nmr: δ 154.66 (d, *J* = 1.2, C-3), 153.79 (dd, *J* = 4.2, 4.2, C-8a), 135.68 (t, *J* = 7.6, C-1'), 134.06 (tt, *J* = 10.8, 3.1, C-4'), 128.91 (dd, *J* = 165.0, 6.5, C-2'), 128.19 (dd, *J* = 168.6, 5.2, C-3'), 120.74 (dq, *J* = 6.7, 6.7, C-6), 112.09 (dq, *J* = 192.5, 6.9, C-5), 77.53 (dt, *J* = 3.6, 2.2, C-8), 19.03 (qd, *J* = 130.1, 4.2, Me); ms: *m/z* 298 (M⁺+2, 2%), 296 (M⁺, 5%), 263 (4), 252 (15), 236 (8), 220 (4), 209 (2), 165 (2), 139 (100), 111 (41), 75 (25), 59 (19), 50 (11), 44 (43). HRMS (Cl-35 isotope): found 296.00229, C₁₂H₉ClN₂O₃S requires 296.00224.

Anal. Calcd. for C₁₂H₉ClN₂O₃S: C, 48.57; H, 3.06; N, 9.44. Found: C, 48.75; H, 3.15; N, 9.51.

4-(4-Chlorophenyl)-4-hydroxy-4H-benzo[5,6][1,4]thiazino[3,4-c]-[1,2,4]oxadiazol-1-one (**2e**).

With the same general procedure described for **1b**, compound **1e** (0.31 g; 1 mmol) gave the colourless **2e** (0.13 g, 38%), mp 210° dec; ¹H nmr: δ 8.60 (br s, exch., 1H, OH), 8.22 (m, 1H, 6-H or 9-H), 7.72 (AA' part of AA'BB' system, 2H, 3'-H and 5'-H), 7.58 (BB' part of AA'BB' system, 2H, 2'-H and 6'-H), 7.52 (m, 2H), 7.40 (m, 1H, H-7 or H-8); ¹³C nmr: δ 155.73 (d, *J* = 3.9, C-3a), 155.19 (s, C-1), 135.24 (t, *J* = 7.6, C-1'), 134.28 (tt, *J* = 10.8, 3.0, C-4'), 129.70 (dd, *J* = 166.1, 8.3, C-6), 129.04 (dddd, *J* = 10.2, 8.4, 1.8, 1.8, C-9a), 128.90 (dd, *J* = 164.6, 6.9, C-2' and C-6'), 128.28 (dd, *J* = 168.9, 4.9, C-3' and C-5'), 127.91 (dd, *J* = 164.8, 8.0, C-8), 127.32 (dd, *J* = 165.1, 7.9, C-7), 122.83 (ddd, *J* = 9.0, 7.1, 1.7, C-5a), 118.01 (ddd, *J* = 167.1, 8.1, 2.7, C-9), 77.41 (t, *J* = 4.0, C-4); ms: *m/z* 331 (M⁺+1, 1%); 288 (17), 150 (11), 139 (100), 111 (36), 75 (14), 44 (26).

Anal. Calcd. for C₁₅H₉ClN₂O₃S: C, 54.14; H, 2.73; N, 8.42. Found: C, 54.26; H, 2.65; N, 8.40.

8-(4-Chlorophenyl)-8-hydroxy-5,6-dimethyl-8H-[1,4]thiazino[3,4-c]-[1,2,4]oxadiazol-3-one (**2d**).

A suspension of **1d** (0.29 g; 1 mmol) in ethanol (20 ml) was refluxed (11 hours) under stirring with HCl 2M (1 ml). Removal of the solvent left an orange solid which still contained some starting material. A column chromatography of the mixture (petroleum ether-ethyl acetate 3:1 as eluant) allowed the elution of **1d** (0.06 g) followed by the colourless **2d** (0.06 g, 26%), mp 149° dec; ¹H nmr: δ 8.32 (br s, exch., 1H, OH), 7.65 (AA' part of AA'BB' system, 2H, 2'-H and 6'-H), 7.53 (BB' part of AA'BB' system, 2H, 3'-H and 5'-H), 2.37 (s, 3H, 6-Me), 2.01 (s, 3H, 5-Me); ¹³C nmr: δ 156.07

(d, $J = 4.6$, C-8a), 155.04 (s, C-3), 135.44 (t, $J = 7.7$, C-1'), 133.91 (tt, $J = 10.8$, 3.4, C-4'), 128.85 (dd, $J = 164.8$, 6.7, C-2'), 128.14 (dd, $J = 168.4$, 5.3, C-3'), 123.32 (m, C-5), 115.19 (m, C-6), 76.39 (dt, $J = 3.7$, 2.2, C-8), 18.31 (q, $J = 131.8$, 5-Me), 12.87 (q, $J = 132.6$, 6-Me); ms: m/z 312 ($M^{+}+2$, 1%), 310 (M^{+} , 3%), 277 (3), 266 (6), 251 (5), 234 (21), 219 (5), 206 (20), 165 (5), 139 (100), 111 (42), 75 (21), 59 (8), 44 (35). HRMS (Cl-35 isotope): found 310.01796, $C_{13}H_{11}ClN_2O_3S$ requires 310.01792.

Anal. Calcd. for $C_{13}H_{11}ClN_2O_3S$: C, 50.25; H, 3.57; N, 9.01. Found: C, 50.32; H, 3.64; N, 9.21.

Reaction of **1d** at Room Temperature in Dioxane: Isolation of 1-(4-Chlorophenyl)-2-[4,5-dimethyl-2-oxo-2H-1,3-thiazol-3-yl]-1,2-ethandione-2-oxime (**5-Me-A**).

To a stirred suspension of **1d** (0.29 g; 1 mmole) in 10 ml of dioxane was added 2M HCl (0.75 ml) at room temperature. After 1 hour removal of the solvent gave a colourless solid (0.30 g). 1H nmr: δ 10.04 (br s, exch., 1H, OH), 8.13 (AA' part of AA'XX' system, 2H, 2'-H and 6'-H), 7.69 (XX' part of AA'XX' system, 2H, 3'-H and 5'-H), 2.23 (s, 3H, 6-Me), 1.92 (s, 3H, 5-Me). MS m/z 293 ($M^{+} - 17$, 2), 291 ($M^{+} - 19$, 2), 165 (40), 139 (100), 111 (36), 75 (29), 74 (13), 60 (17), 59 (19), 50 (21).

Anal. Calcd. for $C_{13}H_{11}ClN_2O_3S$: C, 50.25; H, 3.57; N, 9.01. Found: C, 50.34; H, 3.68; N, 9.18.

By prolonged reflux (11 hours) in ethanol in the presence of hydrochloric acid **5-Me-A** gave **2d** (0.09 g, 30%).

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REFERENCES AND NOTES

- [1] For Part 2, see: R. Billi, B. Cosimelli, D. Spinelli and M. Rambaldi, *Tetrahedron*, **55**, 5433 (1999).
- [2a] A. Andreani, R. Billi, B. Cosimelli, A. Mugnoli, M. Rambaldi and D. Spinelli, *J. Chem. Soc., Perkin Trans.2*, 2407 (1997); [b] D. Spinelli, A. Mugnoli, A. Andreani, M. Rambaldi and S. Frascari, *J. Chem. Soc., Chem. Commun.*, 1394 (1992).
- [3a] M. Fujita, S. Ito, A. Ota, N. Kato, K. Yamamoto, Y. Kawashima, H. Yamauchi and J. Iwao, *J. Med. Chem.*, **33**, 1898 (1990); [b] H. Kugita, H. Inoue, M. Ikezaki, M. Konda and S. Takeo, *Chem. Pharm. Bull.*, **19**, 595 (1971); [c] T. Nagao, M. Sato, H. Nakajima and A. Kiyomoto, *Chem. Pharm. Bull.*, **21**, 92 (1973).
- [4] B. Cosimelli, R. Budriesi, A. Chiarini, M. Rossi and D. Spinelli, work in progress.
- [5] A. Andreani, M. Rambaldi, F. Andreani, P. Hrelia and G. Cantelli Forti, *Arch. Pharm. Chem. Sci. Ed.*, **15**, 41 (1987).
- [6] H. Alper, *J. Chem. Ed.*, **47**, 223 (1970).
- [7] A. Andreani, M. Rambaldi, A. Leoni, A. Locatelli, R. Bossa, A. Fraccari, I. Galatulas and G. Salvatore, *J. Med. Chem.*, **39**, 2852 (1996).