Synthesis and Structural Characterization of Substituted Thieno[2,3-*b*]pyridines from *o*-Chloroformyl-1,4-dihydropyridines

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Novel 4,7-dihydrothieno[2,3-*b*]pyridines **10a-d** have been prepared in a one step procedure from the readily available *o*-chloroformyl substituted 1,4-dihydropyridines **9a-d** and ethyl mercaptoacetate in good yields. Semiempirical calculations reveal a favoured geometry with a boat conformation in the dihydropyridine system and a planar thieno ring. The calculated charge density values for the olefinic carbons (C5 and C6) are in agreement with the experimental *push-pull* effect observed in the ^{13}C nmr.

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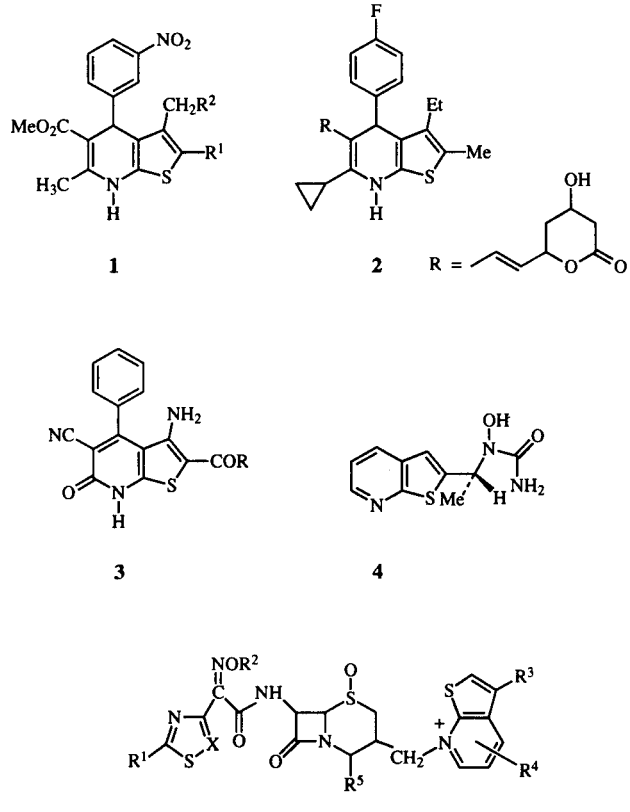
Thieno[2,3-*b*]pyridines are very attractive heterocyclic systems due mainly to their biological activity, useful for multiple pharmacological applications. Thus, dihydrothieno[2,3-*b*]pyridines **1** show effects as calcium antagonists [1] and have been also used in treatment of epilepsy, Alzheimer's disease, and Huntington's chorea [2].

Recently, the activity of the two enantiomers of compound **1** (R^1 = H, R^2 = $CHMe_2$) and its interaction with 1,4-dihydropyridine binding sites has been thoroughly investigated [3]. Other thieno[2,3-*b*]pyridines showing a different substitution pattern have shown interesting antiatherosclerotic (**2**) [4] or antimicrobial (**3**) [5] effects. The enantioselective synthesis of thieno[2,3-*b*]pyridine **4** as 5-LO inhibitor has been recently reported [6], and other thieno[2,3-*b*]pyridines have been also found as subunits of more complex structures as **5** which behave as antibacterial agent [7] (Chart 1).

Chart 1

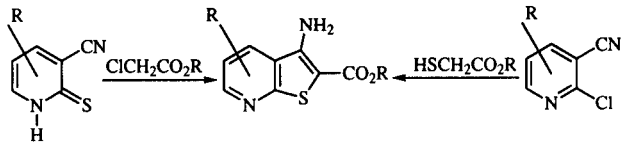


Thieno[2,3-*b*]pyridines have been previously obtained in a multistep procedure from either a thiophene or a pyridine ring and further ring closure leading to the other heterocyclic fused system [8].

With regard to the preparation of thieno[2,3-*b*]pyridines from appropriately 2,3-substituted pyridines, the reaction of 2-chloro-3-cyanopyridine **7** or 3-cyanopyridin-2-thione **6** with alkyl mercaptoacetate or alkyl chloroacetate, respectively, affording 3-amino-2-alkoxycarbonylthieno-[2,3-*b*]pyridines **8** is one of the most general and successful procedures for the preparation of this heterocyclic fused systems [9,10] (Scheme 1).

Recently, we have reported a general and expeditious procedure for the synthesis of pyrazolo[3,4-*b*]pyridines by reaction of the novel *o*-chloroformyl substituted methyl 1,4-dihydropyridine-5-carboxylates **9** with hydrazine [11]. 1,4-Dihydropyridine **9** proved to be an excellent candidate for further transformations into other heterocyclic-fused 1,4-dihydropyridines.

Scheme 1

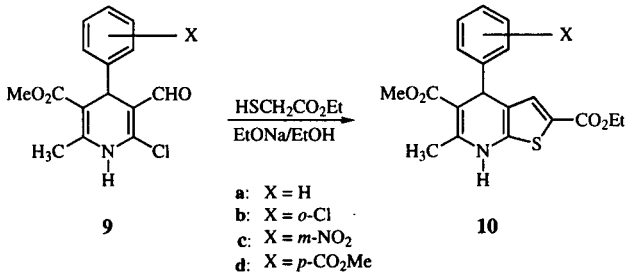


6 8 7

Thieno[2,3-*d*]pyrimidines have been recently obtained by following a similar synthetic approach from 6-chloro-5-formyl-1,3-dimethyluracil [12].

The synthesis of the novel 4,7-thieno[2,3-*b*]pyridines **10a-d** was accomplished by refluxing *o*-chloroformyl substituted 1,4-dihydropyridines **9** with an equimolecular amount of ethyl mercaptoacetate in the presence of sodium ethoxide and dry ethanol under an inert atmosphere. The reaction takes place by nucleophilic attack of the anion of the mercaptoacetate, generated in the basic medium, at the carbon bearing the chlorine atom, followed by 5-*exo-trig* cyclization and dehydration [13] to afford compounds **10a-d** as stable crystaline solids in good yields (55-62%) (Scheme 2).

Scheme 2



a: X = H
b: X = *o*-Cl
c: X = *m*-NO_2
d: X = *p*-CO_2Me

9 10

The starting compound **9** was prepared from the corresponding methyl 2-oxo-1,2,3,4-tetrahydropyridine-5-carboxylate by the Vilsmeier-Haack reaction [11] and provided an appropriately functionalized 1,4-dihydropyridine ring for further heterocyclizations yielding bicyclic systems.

Thieno[2,3-*b*]pyridines **10a-d** now prepared were fully characterized by their analytical and spectroscopic data. Thus, compounds **10a-d** showed the presence of the NH group in the ir spectra (3280-3300 cm^{-1}). In the ^1H nmr spectra the NH group appears at 10.0-10.2 ppm as a broad singlet. The 1,4-dihydropyridine proton on C-4 appears as a singlet at δ 5.2-5.6 and the singlet of the vinylic proton on C-3 at δ 7.3-7.4. The assignement of this signal was ascertained with the HC-COSY spectrum for compounds **10a-d** (see Experimental).

The ^{13}C nmr spectra showed the signals of carbons C-5 and C-6 at 98 and 148 ppm respectively, thus indicating the *push-pull* effect due to the electronic effects of the carboxylic and the NH groups attached to the olefinic double bond. These results are in agreement with those previously observed for other related molecules [11,14]. The ^{13}C nmr assignement was supported by DEPT 135°, DEPT 90° and COLOC experiments.

The mass spectral data showed the presence of the respective molecular ions with an appreciable intensity, the base peak appearing in all cases at m/z = 280, corresponding to the loss of the aryl group ($M^{+\cdot}$- aryl) to form a stable ion.

Table 1

Relevant Bond Distances, Bond Angles and Dihedral Angles (Å,°) for Compounds **10a-d**

	10a	**10b**	**10c**	**10d**
Bond Distances				
C5-C6	1.371	1.374	1.370	1.370
C3a-C7a	1.405	1.405	1.405	1.405
C2-S	1.687	1.684	1.685	1.686
S-C7a	1.684	1.685	1.684	1.685
N7-C7a	1.386	1.386	1.386	1.386
N7-C6	1.402	1.399	1.401	1.402
C4-C5	1.509	1.504	1.509	1.509
C4-C3a	1.486	1.487	1.484	1.484
C3a-C3	1.418	1.417	1.418	1.418
C2-C3	1.388	1.390	1.387	1.389
Bond Angles				
C6-N7-C7a	118.00	118.10	118.11	117.83
C2-S-C7a	93.06	93.13	93.12	93.06
C5-C4-C3a	110.32	110.55	110.66	110.54
Dihedral Angles				
N7-C6-C5-C4	-1.41	-0.88	-1.58	-0.73
C6-C5-C4-C3a	19.03	13.43	15.20	15.04
C5-C4-C3a-C7a	-17.54	-13.49	-13.89	-14.22
C4-C3a-C7a-N7	0.78	0.56	-0.76	-0.58
C3a-C7a-N7-C6	16.83	14.24	15.91	16.40
C7a-N7-C6-C5	-15.47	-13.92	-14.69	-15.68
C2'-C1'-C4-C3a	-63.88	-82.14	-40.33	-37.69
S-C7a-C3a-C3	0.87	0.70	0.67	0.84
C7a-C3a-C3-C2	-0.57	-0.54	-0.72	-0.73
C4a-C3-C2-S	0.02	0..15	0.46	0.29
C3-C2-S-C7a	0.41	0.22	-0.06	0.16
C2-S-C7a-C3a	-0.74	-0.54	-0.35	-0.58

The relationship between the conformation of the biologically active 1,4-dihydropyridines and their pharmacological effects have previously been well-established. X-Ray data and theoretical calculations have been used as evidence to support these structure-activity findings [15].

We have carried out quantum chemical calculations for all compounds by using the AM1 method in order to obtain the favoured conformation of these dihydrothieno-[2,3-*b*]pyridines **10a-d**. The geometrical features of AM1 calculation for compounds **10a-d** are listed in Table 1.

The structure of these compounds show a boat-type conformation for the 1,4-dihydropyridine ring with the C-4 and the nitrogen atoms out of the plane defined by the

olefinic carbons of the pyridine ring, both atoms being displaced in the same direction from the ring and form the apexes of the boat. This conformation is best described in terms of torsion angles about the intra-ring bonds (see Table 1). The phenyl substituent on C4 is in a pseudoaxial position and is orthogonal to the plane of the pyridine ring (see Figure 1). The thiophene ring is essentially planar and forms a dihedral angle with the pyridine ring as shown in Table 1. In these compounds the conjugated alkoxycarbonyl group at C5 is coplanar with the endocyclic double bond, exhibiting a *trans* disposition.

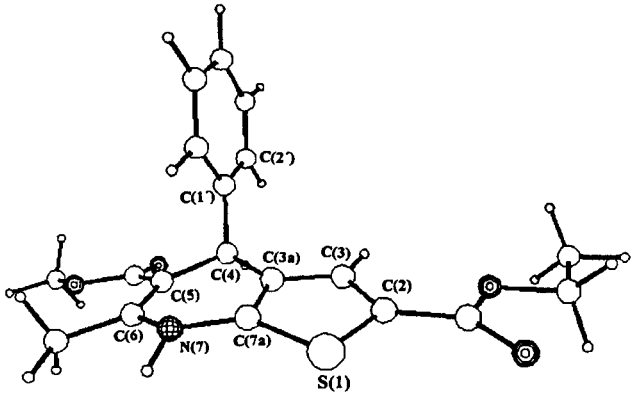


Figure. Minimum Energy Conformation for Compound **10a**.

The calculated heat of formation and theoretical dipole moments are collected in Table 2. Compound **10c** bearing the strong electron-withdrawing nitro group on the phenyl substituent on C4 exhibits a higher dipole moment in comparison with the chloro compound **10b** or alkoxycarbonyl compound **10d**.

Table 2

Heat of Formation and Dipole Moments for the Favoured Conformation for Compounds **10a-d**

Compound	Heat of Formation Kcal/mol [a]	Dipole Moment Debyes [b]
10a	-100.40	3.23
10b	-106.67	4.09
10c	- 97.73	7.69
10d	-108.71	4.14

[a] 1 cal = 4.184 J; [b] 1 D ≈ 3.33564 x 10^{-30} cm.

Finally, the charge density values have also been calculated for the most relevant atoms and are shown in Table 3. These values confirm the electronic *push-pull* effect of the substituents on C5 and C6 observed in the ^{13}C nmr spectra.

In conclusion, we carried out the synthesis of novel 4,7-dihydrothieno[2,3-*b*]pyridines **10a-d** from *o*-chloroformyl substituted 1,4-dihydropyridines **9** and ethyl mercaptoacetate in good yield. Semiempirical calculations reveal a favoured geometry with a flatened boat conformation in the dihydropyridine system and a planar thieno moiety.

EXPERIMENTAL

Melting points were determinated in capillary tubes in an Electrothermal 9100 apparatus and are uncorrected. The nmr spectra were recorded on a Bruker AC spectrometer [250 MHz (^1H) and 62.0 MHz (^{13}C)]. Chemical shifts are given as δ values with tetramethylsilane as the internal standard. The ir spectra were measured with a Bruker IRS48 instrument as potassium bromide pellets. Mass spectra were obtained with a Hewlett Packard 5890 spectrometer. Microanalyses were performed by the Servicio de Microanálisis of Universidad Complutense de Madrid. The reactions were monitored by tlc performed on silica-gel plates (Merck $60F_{250}$) and using benzene:methanol (8:2) as the eluent. Meldrum's acid, methyl acetoacetate, ammonium acetate, *N,N*-dimethylformamide, phosphorus oxychloride, sodium acetate, and ethyl 2-mercaptoacetate were obtained from commercial sources (Aldrich and Merck) and were used without further purification. Aromatic aldehydes were distilled before use. The geometry optimization was carried out with the semiempirical AM1 method by using the MOPAC molecular orbitals set. Previously, the molecular geometry was optimized by using Allinger's Molecular Mechanics with PCMODEL program. Calculations were performed on a PC 486/33 computer.

Methyl 4-Aryl-6-chloro-5-formyl-2-methyl-1,4-dihydropyridine-3-carboxylates **9a-d**.

These compounds were obtained by following the method previously reported in the literature [11].

4-Aryl-2-ethoxycarbonyl-5-methoxycarbonyl-6-methyl-4,7-dihydrothieno[2,3-*b*]pyridines **10a-d**.

General Procedure.

A mixture of the appropriate pyridine **9** (1.3 mmoles) and ethyl 2-mercaptoacetate (1.8 mmoles) in ethanolic sodium ethoxide [prepared from sodium (0.04 g) in dry ethanol (20 ml)]

Table 3

Net Atomic Charges (in e) Calculated for the Most Relevant Atoms in Compounds **10a-d**

Compound	N	C6	C5	C4	C3a	C3	C2	S	C7a
10a	-0.217	0.112	-0.217	0.062	-0.161	-0.027	-0.449	0.628	-0.238
10b	-0.221	0.111	-0.224	0.074	-0.161	-0.029	-0.449	0.627	-0.236
10c	-0.217	0.120	-0.226	0.065	-0.173	-0.030	-0.448	0.639	-0.239
10d	-0.214	0.117	-0.221	0.059	-0.168	-0.028	-0.448	0.633	-0.238

was refluxed for 10 hours. The reaction solution was evaporated to dryness under reduced pressure. The residue was triturated with water (20 ml) and the solid was collected by filtration Further purification was accomplished by recrystallization from methanol.

2-Ethoxycarbonyl-5-methoxycarbonyl-6-methyl-4-phenyl-4,7-dihydrothieno[2,3-*b*]pyridine **10a**.

Following the general procedure gave **10a** (68%), mp 201-202°; ir (potassium bromide): 3280 (NH), 1720 (C=O), 1670 (C=O), 1625 (C=C), 1510, 1450 and 1420 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 10.03 (1H, s, NH), 7.31 (1H, s, H-3), 7.27-7.08 (5H, m, Ph), 5.16 (1H, s, H-4), 4.16 (2H, q, CH_2), 3.45 (3H, s, OCH_3), 2.37 (3H, s, CH_3) and 1.19 (3H, t, CH_3-CH_2); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 167.5 ($COOCH_3$), 161.6 ($COOCH_2CH_3$), 148.2 (C6), 146.8 (C1'), 143.3 (C7a), 133.3 (C3), 128.4 (C3', C5'), 126.8 (C2', C6'), 126.1 (C4'), 122.0 (C3a), 119.6 (C2), 98.7 (C5), 60.4 (CH_2), 50.5 (OCH_3), 40.9 (C4), 19.3 (CH_3) and 14.2 (CH_3-CH_2); ms: m/z (intensity %) 357 (M^+, 16%), 355 (20%), 342 (10), 324 (15), 298 (15), 280 (100), 252 (46), 222 (10), 192 (12), 152 (5), 115 (7) and 59 (12).

Anal. Calcd. for $C_{19}H_{19}NO_4S$ (357.42): C, 63.85; H, 5.36; N, 3.92. Found: C, 63.45; H, 5.62; N, 3.22.

4-(2-Chlorophenyl)-2-ethoxycarbonyl-5-methoxycarbonyl-6-methyl-4,7-dihydrothieno[2,3-*b*]pyridine **10b**.

Following the general procedure gave **10b** (70%), mp 216-217°; ir (potassium bromide): 3300 (NH), 1720 (C=O), 1670 (C=O), 1637 (C=C), 1510 and 1450 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 10.09 (1H, s, NH), 7.37 (1H, H-3'), 7.29 (1H, H-4'), 7.25 (1H, s, H-5), 7.22 (1H, H-6'), 7.14 (1H, H-5'), 5.61 (1H, s, H-4), 4.16 (2H, q, CH_2), 3.40 (3H, s, OCH_3), 2.38 (3H, s, CH_3) and 1.20 (3H, t, CH_3-CH_2); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 167.0 ($COOCH_3$), 161.4 ($COOCH_2CH_3$), 147.8 (C6), 145.4 (C1'), 143.5 (C7a), 132.0 (C3), 130.0 (C2'), 129.7 (C6'), 129.2 (C3'), 127.9 (C4'), 127.8 (C5'), 120.6 (C3a), 119.8 (C2), 97.7 (C5), 60.5 (CH_2), 50.6 (OCH_3), 37.8 (C4), 19.3 (CH_3) and 14.2 (CH_3-CH_2); ms: m/z (intensity %) 393 (M+2, 4%), 391 (M^+, 10), 355 (16), 354 (68), 332 (11), 326 (17), 280 (100), 252 (38), 222 (11), 220 (10) and 192 (11).

Anal. Calcd. for $C_{19}H_{18}ClNO_4S$ (391.87): C, 58.24; H, 4.63; N, 3.57. Found: C, 57.91; H, 4.72; N, 3.23.

2-Ethoxycarbonyl-5-methoxycarbonyl-6-methyl-4-(3-nitrophenyl)-4,7-dihydrothieno[2,3-*b*]pyridine **10c**.

Following the general procedure gave **10c** (80%), mp 165.5-167°; ir (potassium bromide): 3300 (NH), 1710 (C=O), 1670 (C=O), 1640 (C=C), 1530 (N=O), 1450, 1350 (N=O) and 1410 cm^{-1}, ^1H nmr (dimethyl sulfoxide-d_6): δ 10.21 (1H, s, NH), 8.05 (1H, d, Ph), 7.71 (1H, s, Ph), 7.61 (2H, m, Ph), 7.41 (1H, s, H-3), 5.40 (1H, s, H-4), 4.18 (2H, q, OCH_2), 3.50 (3H, s, OCH_3), 2.40 (3H, s, CH_3) and 1.21 (3H, t, CH_3-CH_2); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 167.1 ($COOCH_3$), 161.8 ($COOCH_2CH_3$), 150.2 (C3'), 147.8 (C6), 146.6 (C1'), 143.5 (C7a), 133.7 (C6'), 133.2 (C3), 129.9 (C5'), 121.2 (C2'), 121.2 (C2), 120.8 (C3a), 120.4 (C4'), 97.7 (C5), 60.5 (OCH_2), 50.6 (OCH_3), 40.6 (C4), 19.4 (CH_3) and 14.2 (CH_3-CH_2); ms: m/z (intensity %) 402 (M^+, 7%), 383 (11), 370 (10), 338 (8), 280 (100), 252 (44), 220 (11), 192 (15), 148 (7), 104 (5) and 59 (19).

Anal. Calcd. for $C_{19}H_{18}N_2O_6S$ (402.42): C, 56.71; H, 4.51; N, 6.96. Found: C, 56.47; H, 4.68; N, 6.70.

2-Ethoxycarbonyl-5-methoxycarbonyl-4-(4-methoxycarbonylphenyl)-6-methyl-4,7-dihydrothieno[2,3-*b*]pyridine **10d**.

Following the general procedure gave **10d** (62%), mp 222-223°; ir (potassium bromide): 3300 (NH), 1720 (C=O), 1670 (C=O), 1637 (C=C), 1510 and 1450 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 10.11 (1H, s, NH), 7.85 (2H, d, H-3', H-5'), 7.35 (2H, d, H-2', H-6'), 7.30 (1H, s, H-3), 5.23 (1H, s, H-4), 4.16 (2H, q, CH_2), 3.80 (3H, s, OCH_3), 3.43 (3H, s, OCH_3), 2.36 (3H, s, CH_3) and 1.20 (3H, t, CH_3-CH_2); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 167.2 ($COOCH_3$), 166.1 ($COOCH_3$), 161.5 ($COOCH_2CH_3$), 153.2 (C1'), 147.4 (C6), 143.4 (C7a), 133.3 (C3), 129.5 (C3', C5'), 127.8 (C4'), 127.2 (C2', C6'), 121.1 (C3a), 119.8 (C2), 97.9 (C5), 60.5 (OCH_2), 52.0 (OCH_3), 50.6 (OCH_3), 41.0 (C4), 19.4 (CH_3) and 14.2 (CH_3-CH_2); ms: m/z (intensity %) 415 (M^+, 15%), 400 (20), 356 (58), 344 (11), 280 (100), 252 (40), 222 (15), 192 (15) and 59 (12).

Anal. Calcd. for $C_{21}H_{21}NO_6S$ (415.46): C, 60.71; H, 5.09; N, 3.37. Found: C, 60.39; H, 4.49; N, 3.09.

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REFERENCES AND NOTES

[1] M. Masui, M. Kawakami, M. Nakajima, S. Hara, H. Ito and M. Ueda, *Drug Dev. Res.*, **20**, 453 (1990); Y. Adachi, T. Yamamori, Y. Hiramatsu, K. Sakai, S. Mihara, M. Kavakami, M. Masui, O. Uno and M. Veda, *Chem. Pharm. Bull.*, **36**, 4389 (1988).

[2] M. Veda, T. Gemba, M. Eigyo and Y. Adachi, European Patent Appl; EP 519,602 (1992); *Chem. Abstr.*, **118**, 94335t, (1993).

[3] Ch. Dessy, S. Salomone, N. Morel and T. Godfraind, *Eur. J. Pharmacol.*, **231**, 435, (1993).

[4] Y. Saito, M. Yasushi, M. Sakashita, K. Toyoda and T. Shibazalti, European Patent Appl; EP 535,548 (1993); *Chem. Abstr.*, **119**, 117112e (1993).

[5] M. Z. A. Badr, S. A. Mahgoub, F. F. Abdel-Latif and A. A. A. El-Hafez, *Phosphorus, Sulfur, Silicon Relat. Elem.*, **55**, 175 (1991).

[6] J. C. Rohloff, T. V. Alfredson and M. A. Schwartz, *Tetrahedron Letters*, **35**, 1011, (1994).

[7] K. Tanaka, M. Sutani, M. Komatsu, K. Tsuchida, A. Saito, K. Hayashi, H. Kanna, A. Goto, S. Minami and Y. Watanabe, Japan Kokai Tokkyo Koho JP 05,331,175 [93,331,175] (1993); *Chem. Abstr.*, **121**, 108362a (1994).

[8] G. P. Ellis, Synthesis of Fused Heterocycles, Wiley Interscience, Vol **47**, Part **1**, pp 171 and 185, Part **2**, pp 742, 103 and 1309, 1992.

[9] K. Gwal, M. Hentschel and L. Illgen, *J. Prakt. Chem.*, **316**, 878 (1974).

[10] F. Yoneda, H. Yomato and M. Ono, *J. Am. Chem. Soc.*, **103**, 5943 (1981).

[11] Y. Verdecia, M. Suárez, A. Morales, E. Rodriguez, E. Ochoa, L. González, N. Martín, M. Quinteiro, C. Seoane and J. L. Soto, *J. Chem. Soc., Perkin Trans 1*, 947 (1996).

[12] K. Hirota, M. Shirahashi and S. Senda, *J. Heterocyclic Chem.*, **27**, 717, (1990).

[13] The Baldwin nomenclature for classifying ring closures is used here. See J. E. Baldwin, *J. Chem. Soc., Chem. Commun.*, 734 (1976); J. E. Baldwin and M. J. Lusch, *Tetrahedron*, **38**, 2939 (1982).

[14] N. Martín, L. Segura, C. Seoane, J. L. Soto, M. Morales and M. Suárez, *Liebigs Ann. Chem.*, 827 (1991); N. Martín, M. Quinteiro, C. Seoane, J. L. Soto, A. Mora, M. Suárez, E. Ochoa, A. Morales and J. R. del Bosque, *J. Heterocyclic Chem.*, **32**, 235, (1995); R. Rodríguez, M. Suárez, E. Ochoa, A. Morales, L. González, N. Martín, M. Quinteiro, C. Seoane and J. L. Soto, *J. Heterocyclic Chem.*, **33**, 45 (1996); A. Morales, E. Ochoa, M. Suárez, Y. Verdecia, L. González, N. Martín, M. Quinteiro, C. Seoane and J. L. Soto, *J. Heterocyclic Chem.*, **33**, 103, (1996).

[15] S. Goldman, L. Born, S. Kazda, B. Pittel and M. Schramm, *J. Med. Chem.*, **33**, 1413 (1990); R. Fossheim, K. Suarteng, A. Mostad, C. Romming, E. Shefter and D. T. Triggle, *J. Med. Chem.*, **25**, 1229 (1982); R. Fossheim, A. Joslyn, A. L. Solo, E. Luchowski, A. Rutledge and D. T. Triggle, *J. Med. Chem.*, **31**, 300 (1988).