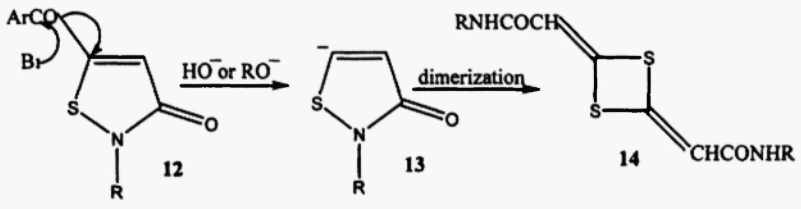
CEPHEM AND PYRROLO[2,1-b][1,3]THIAZINE-4,6-DIONE RING SYSTEMS CONSTRUCTION FROM 6 BENZOYL-2,3-DIHYDRO-4H-1,3-THIAZINE-4-ONES PREPARED VIA REARRANGEMENT OF 5-BENZOYL-3(2H)-ISOTHIAZOL-3-ONES

Georgia Tsolomiti, Kyriaki Tsolomiti and Athanase Tsolomitis*
The Laboratory of Organic Chemistry, The School of Chemical Engineering, The National Technical University of Athens, Athens157 80, Greece

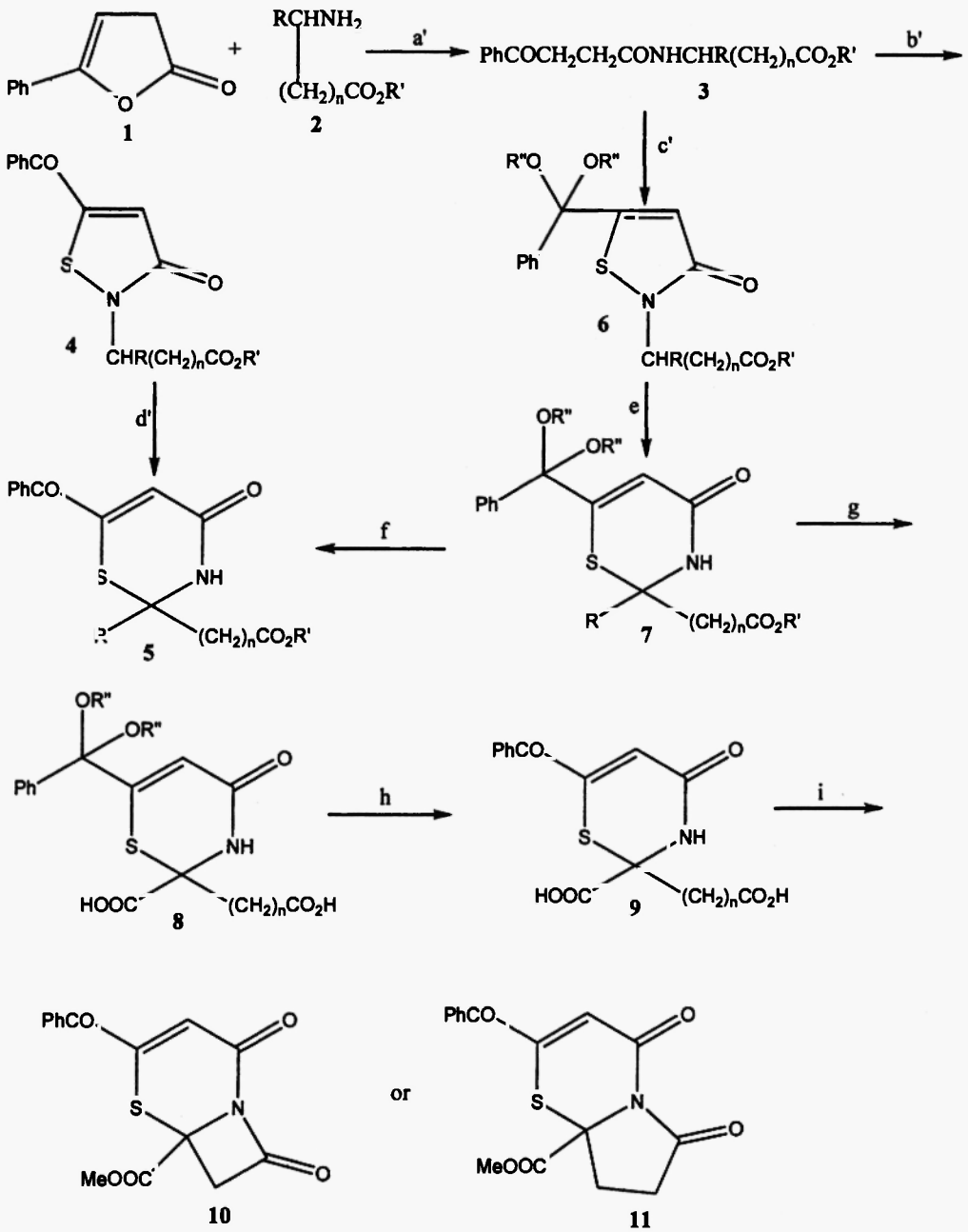
Abstract : Cephem and Pyrrolo[2,1-b][1,3]thiazine-4,6 dione ring systems' construction from 6-benzoyl-2,3-dihydro-1,3-thiazine-4-ones prepared from properly designed 5-benzoyl-3(2H)-isothiazol-3-ones through experimental simple reactions, is described here.
Key words : 5-Benzoyl-3(2H)-isothiazol-3-ones; 6-Benzoyl-2,3-dihydro-1,3-thiazine-4-ones; Cephems; Pyrrolo[2,1-b][1,3]thiazine-4,6 diones.

The unique structural and chemotherapeutic properties of β-lactam antibiotics continue to attract the attention of the synthetic community since they present variety of synthetic challenges. The susceptibility of β-lactam antibiotics to the hydrolytic activity of β-lactamase enzymes is known, and is the most common and growing form of bacterial resistance to the normally lethal action of these antibacterial agents.[1] One way of overcoming this problem is to alter the substituents of the cephalosporin nucleus thus that the compounds are more resistant to attack by lactamases. From the other hand the pyrrolo[2,1-b][1,3]thiazine-4,6-dione ring system is at least studied,[2] exhibiting activity in the amnesia reversal screen. While isomeric pyrrolo-thiazinediones were prepared as antihypertensives and angiotensin converting enzyme inhibitors,[3a] and as antibacterial agents.[3b]
In this communication we wish to report the synthesis of some new 5-benzoyl-3(2H)-isothiazol-3-ones **4**, according to the previously reported procedure,[4] and their rearrangement to 1,3-thiazin-4-ones **5**, followed by the construction of cephem and pyrrolothiazinedione derivatives **10** and **11** respectively (Scheme-1). For the preparation of isothiazolones **4** we used as nitrogen insertion moieties the α-amino acid esters bearing active C-H bonds such as, methyl glycinate and the optically inactive methyl phenylglycinate, diethyl aspartate and diethyl glutamate.

Rearrangements of 5-aroyl-3(2H)-isothiazol-3-ones have been also reported,[5] the analogue reaction of isothiazolones **4** to the thiazinones **5** needs the abstraction, by a base, of a proton from the α-positioned carbon to the heterocyclic nitrogen. But since 5-aroyl-3(2H)-isothiazol-3-ones **12** have been found[6] to be debenzoylated readily by nucleophilic bases such as alkoxides or hydroxides, it was shown that the thus formed 5-anions of isothiazolones **13**, proceeded, through attack on the S-N bond of a second isothiazolone molecule, to 1,3-dithietanes **14** formation, (Scheme 2).



Scheme-2



(a): R=H, R'=CO_2Me, n=0; (b); R=Ph, R'=CO_2Me, n=0; (c); R=R'=CO_2Et, n=1; (d): R=R'=CO_2Et, n=2. For **5d** and **7d:** R'=COOH. R"=Et or Me.

a′: EtOH or MeOH, AcONa/H_2O, rfx; b′: $SOCl_2$; c′: $SOCl_2$/EtOH or MeOH; d′: 1,8-bis-(dimethylamino)naphthalene/p-xylene, rfx; e: NaH/C_6H_6, r.t.; f: c.H_2SO_4, r.t.; g: 5 % KOH, r.t. ; h: 50 % H_2SO_4, r.t.; i: $SOCl_2$, then abs. MeOH

Scheme-1

For this reason the rearrangement of isothiazolones **4b-d** was succeeded using the non nucleophilic 1,8-bis(dimethylamino)naphthalene, as base, although the respective rearrangement of isothiazolone **4a** was unsuccessful under the same conditions owing to the lower acidity of the methylene's *alfa* to the nitrogen protons.

Since we experienced difficulties in the direct hydrolysis of esters **5c, d→9c, d**, the thiazinones **9c, 9d**, were prepared through the also prepared acetal-isothiazolones **6c, 6d**, hence protecting the sensitive to nucleophilic attack, benzoyl carbonyl group. The rearrangement of acetal-isothiazolones **6c, 6d** to the corresponding thiazinones **7c, 7d** was performed using sodium hydride/benzene, whereas for the rearrangement of acetal-isothiazolone **6a→7a**, sodium methylate/methanol was used.

It is worth noting that the thiazinones **5d** and **7d** were isolated as monoester-primary acid derivatives, analogues regioselective diesters hydrolyses have been reported.[7]
Cephem **10** was prepared through the reaction sequence **7c→8c→9c** followed by treatment with $SOCl_2$ and then with absolute methanol to give the desired product. Pyrrolothiazinedione **11**, was prepared from thiazinone-diacid **9d** by an analogue to the cephem **10** procedure.

In conclusion, we have presented a novel approach to the synthesis of a cephem core system from available starting materials followed by a convenient reaction sequence which includes the preparation of 5-benzoyl-3(2H)-isothiazol-3-ones, their rearrangement to 6-benzoyl-2,3-dihydro-1,3-thiazine-4-ones, which depended on 2-positioned substituents transformed to the cephem or to a pyrrolo[2,1-b][1,3]thiazine-4,6 dione derivative. This methodology could be useful to medicinal chemists engaged in the field of cephalosporin chemistry as well as to those of least studied pyrrolo[2,1-b][1,3]thiazine-4,6-dione ring system.

Experimental

General. NMR spectra were recorded at ambient temperature using a Varian Gemini 2000 300 MHz spectrometer. The data are reported as follows: chemical shift are quoted in ppm on the δ scale, multiplicity (br=broad, s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet), coupling constants are given in (Hz). Micro analyses were performed by microanalytical laboratory of CNRS (France). Melting points are reported uncorrected. IR spectra were obtained at a Nicolet Magna 560 spectrometer, as Nujol mulls, and were calibrated against the polystyrene 1600 cm^{-1} band, and given in reciprocal centimeters..

General procedure for the preparation of γ-keto amides **3**. To a mixture of 5-phenylfuran-2(3H)-one, **1**, 33.33 mmol and an equimolar quantity of amino ester hydrochloride **2**, in 20 ml of alcohol, (ethyl or methyl alcohol in the case of ethyl or methyl esters respectively), a solution of sodium acetate 8.20 g, (100 mmol), in water 12 ml was added, and the mixture was refluxed for an hour. The resulted solution was then concentrated on the half of its volume and water 5-10 ml was added, the new solution, or slurry, was extracted few times with ethyl acetate, the combined extracts were washed with a solution of sodium bicarbonate 5 %, and then with water. The organic phase was dried ($MgSO_4$), and the solvent was evaporated under vacuum. The solid residue obtained was proved to be an almost pure sample, ^1H NMR, of γ–keto amide **3**. After recrystallization, from the appropriate solvent, an analytical sample was obtained, in yields 78-84 %.
Glycine-*N*(1,4-dioxo-4-phenylbutyl)-methyl ester, 3a: yield 84%, mp 102-103 ^0C, (from benzene), lit.[3] mp 98.9-100.8 ^0C. IR (Nujol mull): 3390, 1745, 1658, 1590. ^1H NMR ($CDCl_3$): 2.65 (t, J=7 Hz,

2H, CH_2), 3.31 (t, J=7Hz, 2H, CH_2), 3.67 (s, 3H, CH_3), 3.98 (d, J=7.5 Hz, 2H, CH_2CO_2Me), 6.54 (br m, 1H, NH, exchangeable), 7.32-7.61 (m, 3H, m,p-arom.), 7.81-8.16 (m, 2H, o-arom.).^{13}C NMR ($CDCl_3$): 29.81, 33.90, 41.36, 52.36, 128.27, 128.81, 133.50, 136.73, 170.75, 172.70, 199.24.

dl-Phenylglycine-*N*(1,4-dioxo-4-phenylbutyl)-methyl ester, 3b. yield 82%, mp 126-127 ^{0}C, (from methanol). Anal. Calcd for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.88; N, 4.30. Found: C, 69.87; H, 5.61; N, 4.38. IR (Nujol mull): 3380, 1751, 1660, 1580. ^{1}H NMR ($CDCl_3$): 2.72 (t, J=7 Hz, 2H, CH_2), 3.33 (t, J=7Hz, 2H, CH_2), 3.68 (s, 3H, CH_3), 5.55 (d, J=7Hz, 1H, CH), 7.12 (d, J=7 Hz, NH, exchangeable), 7.25-7.66 (m, 3H, m, p-arom.), 7.87-8.15 (m, 2H, o-arom.).^{13}C NMR ($CDCl_3$): 30.06, 34.78, 52.58, 56.65, 127.61, 128.73, 128.85, 129.27, 129.71, 133.23, 136.69, 170.44, 172.56, 199.63.

dl-Aspartic acid-*N*(1,4-dioxo-4-phenylbutyl)-diethyl ester, 3c: yield 78%, mp 72-73 ^{0}C, (from ethyl acetate/ethyl ether). Anal. Calcd for $C_{18}H_{23}NO_6$: C, 61.88; H, 6.63; N, 4.01. Found: C, 61.96; H, 6.57; N, 4.28. IR (Nujol mull): 3385, 1746, 1662, 1590. ^{1}H NMR ($CDCl_3$): 1.10 (t, J=7 Hz, 6H, two CH_3), 2.70 (t, J=7Hz, 2H, CH_2), 2.86-3.05 (**dd**, J=2.5 Hz, 2H, CH_2CO_2Et), 3.95-4.45 (m, 4H, two OCH_2Me), 4.66-5.05 (m, 1H, CH), 6.90 (br d, J=8 Hz, 1H, NH, exchangeable), 7.33-7.63 (m, 3H, m, p-arom.), 7.85-8.16 (m, 2H, o-arom.). ^{13}C NMR ($CDCl_3$): 14.05, 14.11, 30.02, 33.83, 36.42, 48.74, 61.10, 61.90, 128.27, 128.80, 133.42, 136.81, 171.03, 171.27, 172.17, 198.92.

dl-Glutamic acid-*N*(1,4-dioxo-4-phenylbutyl)-diethyl ester, 3d: yield 81%, mp 80-81 ^{0}C, (from ethyl ether). Anal. Calcd for $C_{19}H_{25}NO_6$: C, 62.80; H, 6.93; N, 3.85. Found: C, 63.01; H, 6.77; N, 4.00. IR (Nujol mull): 3392, 1745, 1660, 1587. ^{1}H NMR ($CDCl_3$): 1.25 and 1.28 (two t, J=7 Hz, 6H, two CH_3), 1.83-2.52 (m, 4H, $CH_2CH_2CO_2Et$), 2.70 and 3.36 (two t, J=7Hz, 4H, $COCH_2CH_2CO$), 3.93-4.42 (m, 4H, two OCH_2Me), 4.45-4.82 (m, 1H, CH), 6.75 (br m, 1H, NH, exchangeable), 7.30-7.66 (m, 3H, m, p-arom.), 7.85-8.12 (m, 2H, o-arom.). ^{13}C NMR ($CDCl_3$): 14.04, 14.13, 26.65, 28.23, 30.34, 35.14, 52.21, 61.32, 61.51, 128.71, 128.83, 133.21, 136.67, 169.49, 171.31, 172.45, 199.20

General procedure for the preparation 5-benzoyl-3(2H)-isothiazol-3-ones **4**: A mixture of γ-keto amide **3**, 18.50 mmol and an excess of thionyl chloride, 50 ml, was stirred at room temperature for an hour. The excess of thionyl chloride was then removed under vacuum, (without heating), and the greenish residue, (usually solid), was recrystallized from methanol or ethanol, (methyl ester or ethyl ester derivatives, respectively), to give yellow crystals of an analytical sample of isothiazolone **4**, in yields 76-87%.

5-Benzoyl-3(2H)-isothiazol-3-one-2-acetic acid methyl ester 4a: yield 76%, (from methanol), mp 108-109 ^{0}C. Anal. Calcd for $C_{13}H_{11}NO_4S$: C, 56.31; H, 4.00; N, 5.05; S, 11.56. Found: C, 56.47; H, 4.13; N, 5.11; S, 11.30. IR (Nujol mull): 1740, 1661, 1640, 1595, 1543. ^{1}H NMR ($CDCl_3$): 3.83 (s, 3H, CH_3), 4.63 (s, 2H, CH_2), 6.83 (s, 1H, =CH-), 7.42-7.87 (m, 3H, m, p-arom.), 7.88-8.16 (m, 2H, o-arom.). ^{13}C NMR ($CDCl_3$):): 44.54, 52.90, 119.55, 129.23, 129.50, 134.50, 135.50, 135.46, 155.36, 167.93, 168.56, 187.30.

5-Benzoyl-3(2H)-isothiazol-3-one-2-[(1dl)-phenylacetic acid] methyl ester, 4b: yield 85%, mp 96-97 ^{0}C, (from methanol). Anal. Calcd for $C_{19}H_{15}NO_4S$: C, 64.57; H, 4.28; N, 3.96; S, 9.07. Found: C, 64.71; H, 4.31; N, 4.19; S, 9.21. . IR (Nujol mull): 1744, 1640, 1618, 1595, 1545. ^{1}H NMR ($CDCl_3$): 3.92 (s, 3H, CH_3), 6.28 (s, 1H, CH), 6.77 (s, 1H, =CH-), 7.43-7.83 (m, 3H, m, p-arom.), 7.83-8.13 (m, 2H, o-arom.). ^{13}C NMR ($CDCl_3$): 52.80, 56.54, 119.10, 128.58, 128.80, 134.20, 135.63, 155.06, 167.75, 171.30, 187.23.

5-Benzoyl-3(2H)-isothiazol-3-one-2-[(2dl)-butandioic acid] diethyl ester 4c: yield 81%, mp 114-115 ^{0}C, (from ethyl ether). Anal. Calcd for $C_{18}H_{19}NO_6S$: C, 57.28; H, 5.07; N, 3.71; S, 8.50. . Found: C, 57.42; H, 5.13; N, 3.85; S, 8.64. IR (Nujol mull): 1745, 1647, 1590, 1540. ^{1}H NMR ($CDCl_3$): 1.27 and 1.30 (two t, J=7 Hz, 6H, two CH_3), 3.17 (apparent d, J=6.5 Hz, 2H, CH_2CO_2Et), 3.97-4.51 (m, 4H, two OCH_2Me), 5.57 (apparent t, J=6.5 Hz, 1H, CH), 6.88 (s, 1H, =CH-), 7.40-7.78 (m, 3H, m, p-arom.), 7.83-8.05 (m, 2H, o-arom.). ^{13}C NMR ($CDCl_3$): 14.04, 14.10, 34.09 54.21, 61.23, 61.37, 119.61, 129.32, 129.87, 134.56, 135.62, 154.90, 167.85, 168.65, 187.47.

5-Benzoyl-3(2H)-isothiazol-3-one-2-[2(dl)-pentandioic acid] diethyl ester 4d: yield 77%, mp 109-111 ^{0}C, (from ethanol/ethyl ether). Anal. Calcd for $C_{19}H_{21}NO_6S$: C, 58.30; H, 5.41; N, 3.58; S, 8.19. Found: C, 58.41; H, 5.60; N, 3.47; S, 8.35. IR (Nujol mull): 1745, 1642, 1595, 1543. ^{1}H NMR ($CDCl_3$): 1.26 and 1.30 (two t, J=7 Hz, 6H, two CH_3), 2.03-2.72 (m, 4H, $CH_2CH_2CO_2Et$), 3.90-4.50 (m, 4H, two OCH_2Me), 5.10-5.57 (m, 1H, CH), 6.77 (s, 1H, =CH-), 7.33-7.77 (m, 3H, m, p-arom.), 7.78-8.12 (m, 2H, o-arom.). ^{13}C NMR ($CDCl_3$): 14.06, 14.13, 23.34, 27.78, 58.48, 61.27, 61.41, 120.11, 129.87, 134.56, 135.87, 135.43, 155.07, 168.31, 171.44, 172.11, 187.46.

General procedure for the preparation of isothiazolone aketals 6: Following the general procedure described above, for the preparation of isothiazolones **4**, and the same reagents' quantities, 18.50mmol, until the step of the concentration of excess of thionyl chloride, except of 5-7 ml, (from the initial quantity of 50 ml used). To this concentrated solution ,almost pure isothiazolone **4**, as was assigned by ^{1}H NMR, absolute alcohol, 40 ml, (methanol or ethanol for the methyl or ethyl esters respectively), was added, through a dropping funnel, keeping under control the reflux. When the exothermic reflux was ceased the solution was additionally refluxed for two hours, and then was concentrated under vacuum to give a resinous mass which proved, ^{1}H NMR, to be almost pure isothiazolone aketal 6. After trituration with ethyl ether the resulted solid was recrystallized from ethyl ether/hexane to give an analytical sample of isothiazolone aketal 6:

5-[Benzene-(1,1-dimethoxymethyl)]-3(2H)-isothiazol-3-one-2-acetic acid methyl ester, 6a: yield 78%, mp 117-118 ^{0}C. Anal. Calcd for $C_{15}H_{17}NO_5S$: C, 55.72; H, 5.30; N, 4.33; S, 9.91. Found: C, 55.57; H, 5.41; N, 4.43; S, 10.07. IR (Nujol mull): 1747, 1620, 1540, 1490. ^{1}H NMR ($CDCl_3$): 3.22 (s, 6H, two OCH_3), 3.72 (s, 3H, CO OCH_3), 4.55 (s, 2H, CH_2), 6.03 (s, 1H, =CH-), 6.93-7.63 (m, 5H, arom.). ^{13}C NMR ($CDCl_3$): 44.50, 50.04, 50.10, 52.81, 116.11, 120.15, 128.41, 128.90, 129.67, 138.65, 152.70, 167.83, 169.16.

5-[Benzene-(1,1-diethoxymethyl)]-3(2H)-isothiazol-3-one-2-[(2dl)-butandioic acid] diethyl ester, 6c: yield 72%, mp 122-123 ^{0}C. Anal. Calcd for $C_{22}H_{29}NO_7S$: C, 58.52; H, 6.47; N, 3.10; S, 7.10. Found: C, 58.71; H, 6.31; N, 3.22; S, 7.34. IR (Nujol mull): 1745, 1637, 1550, 1490. ^{1}H NMR ($CDCl_3$): 1.23 (t, J=7 Hz, 12H, four CH_3), 3.03 (apparent d, J=6.5 Hz, 2H, CH_2CO_2Et), 3.20-4.42 (m, 8H, four OCH_2Me), 5.42 (apparent t, J=6.5 Hz, 1H, CH), 5.95 (s, 1H, =CH-), 7.20-7.68 (m, 5H, arom.). ^{13}C NMR ($CDCl_3$): 13.80, 14.12, 15.85, 15.91, 34.10, 54.48, 58.78, 58.90, 61.29, 61.35, 114.13, 120.09, 127.35, 127.76, 128.67, 135.80, 154.15, 168.33, 171.65, 171.90.

5-[Benzene-(1,1-diethoxymethyl)]-3(2H)-isothiazol-3-one-2-[(2dl)-pentandioic acid] diethyl ester, 6d: yield 76%, mp 131-132 ^{0}C. Anal. Calcd for $C_{23}H_{31}NO_7S$: C, 59.34; H, 6.71; N, 3.01; S, 6.89. Found: C, 59.47; H, 6.60; N, 3.25 S, 6.65. IR (Nujol mull): 1743, 1641, 1540, 1490. ^{1}H NMR ($CDCl_3$): 1.03-1.58 (m, 12H, four CH_3), 2.08-2.63 (m, 4H, $CH_2CH_2CO_2Et$), 3.23-4.46 (m, 8H, four OCH_2Me), 5.00-5.46 (m, 1H, CH), 5.95 (s, 1H, =CH-), 7.13-7.73 (m, 5H, arom.). ^{13}C NMR ($CDCl_3$): 13.95, 14.07, 15.67, 15.90, 23.31, 27.78, 54.64, 58.60, 58.81, 61.23, 61.28, 116.28, 120.12, 127.39, 127.81, 128.63, 134.66, 154.21, 168.09, 171.55, 171.87.

General procedure for the preparation of 6-benzoylthiazinones **5**: An equimolar mixture, 8.54 mmol of each, 5-benzoylisothiazolone **4** and 1,8-bis-(dimethylamino)naphthalene, in p-xylene, 50 ml, was refluxed for five and half an hour. The resulting green-brown solution after cooling to room temperature was washed few times with a solution of hydrochloric acid 10%, after usual workup and condensation under vacuum. The solid residue thus obtained proved to be almost pure, ^{1}H NMR, the desired thiazinone **5**. After recrystallization from benzene/hexane an analytical sample of thiazinone **5** was received.

2H-1,3-Thiazine-2-carboxylic acid-2-phenyl-6-benzoyl-3,4-dihydro-4-oxo methyl ester, 5b: yield 84%, mp 144-145 ^{0}C. Anal. Calcd for $C_{19}H_{15}NO_4S$: C, 64.57; H, 4.28; N, 3.96; S, 9.07. Found: C, 64.44; H, 4.31; N, 4.07; S, 9.11. IR (Nujol mull): 3150, 1745, 1655, 1590. ^{1}H NMR ($CDCl_3$): 3.88 (s, 3H, CH_3), 6.47 (d, J=1.2 Hz, 1H, =CH-, become singlet by irradiation on NH- signal), 7.33-7.77 (m, 11H, 10H, arom. plus NH). ^{13}C NMR ($CDCl_3$): 51.21, 58.11, 125.31, 129.21, 129.85, 134.55, 134.86, 145.43, 164.55, 168.65, 192.18.

2H-1,3-Thiazine-2-carboxylic acid-2-acetic acid-6-benzoyl-3,4-dihydro-4-oxo diethyl ester, 5c: yield 77%, mp 133-134 ^{0}C. Anal. Calcd for $C_{18}H_{19}NO_6S$: C, 57.28; H, 5.07; N, 3.71; S, 8.50. Found: C, 57.31; H, 4.96; N, 3.90; S, 8.45. IR (Nujol mull): 3150, 1745, 1647, 1593. ^{1}H NMR ($CDCl_3$): 1.27 and 1.33 (two t, J=7 Hz, 6H, two CH_3), 3.33 (s, 2H, CH_2CO_2Et), 4.16-4.35 (m, 4H, two OCH_2Me), 6.53 (d, J=1.2 Hz, 1H, =CH-, become singlet by irradiation on NH- signal), 6.95 (br s, 1H, NH exchangeable), 7.40-7.83 (m, 5H, arom.). ^{13}C NMR ($CDCl_3$): 14.03, 14.10, 42.94 62.08, 63.23, 63.73, 125.29, 129.15, 129.83, 134.23, 134.80, 145.39, 164.64, 168.61, 168.90, 192.27.

2H-1,3-Thiazine-2-carboxylic acid-2-propanoate-6-benzoyl-3,4-dihydro-4-oxo ethyl ester, 5d: yield 74%, mp 141-142 ^{0}C. Anal. Calcd for $C_{17}H_{17}NO_6S$: C, 56.19; H, 4.71; N, 3.85; S, 8.82. Found: C, 56.27; H, 4.60; N, 3.57; S, 8.70. IR (Nujol mull): 3160, 3080, 1745, 1650, 1590. ^{1}H NMR ($CDCl_3$): 1.31 (t, J=7 Hz, 3H, CH_3), 2.62 (s, 2H, CH_2CO_2Et), 4.23 (q, J=7 Hz, 2H, OCH_2Me), 6.42 (d, J=1.2 Hz, 1H, =CH-, become singlet by irradiation on NH- signal), 7.33-7.86 (m, 5H, arom.), 8.23 (br m,

1H, NH, exchangeable), 9.65 (br s, 1H, COOH exchangeable). ^{13}C NMR ($CDCl_3$): 14.12, 27.41, 32.15, 60.28, 63.04, 125.28, 129.30, 129.85, 134.57, 145.85, 164.76, 168.90, 177.06, 192.20.

General procedure for the preparation of diethyl acetal thiazinones **7c, d**: To a solution of diethyl acetal isothiazolone **6c, d**, 22 mmol in absolute benzene 100 ml, sodium hydride suspension in oil 55-60%, 2.3 g, was added and the mixture was allowed at room temperature, under stirring, for 24 h. The mixture was cooled in an ice-water bath and acidified with a solution of hydrochloric acid 10 %. The organic layer was separated and after the usual workup was concentrated under vacuum to a brownish resinous mass which after washing and trituration with hexane gave a solid. After recrystallization from the proper solvent the desired diethyl acetal thiazinone 7, as analytical pure compound, was received.

2H-1,3-Thiazine-2-carboxylic acid-2-acetic acid-6-[benzene-(1,1-diethoxymeth-yl)]-3,4-dihydro-4-oxo diethyl ester, 7c: yield 65%, mp 126-127 ^{0}C. Anal. Calcd for $C_{22}H_{29}NO_7S$: C, 58.52; H, 6.47; N, 3.10; S, 7.10. Found: C, 58.25; H, 6.20; N, 3.35; S, 7.31. IR (Nujol mull): 3140, 1745, 1593. ^{1}H NMR ($CDCl_3$): 1.12-1.31 (m, 12H, four CH_3), 3.06 (s, 2H, CH_2CO_2Et), 3.30-3.46 (m, 4H, two OCH_2Me), 4.02-4.14 (m, 4H, two $COOCH_2Me$), 6.54 (d, J=1.2 Hz, 1H, =CH-, become singlet by irradiation on NH- signal), 6.96 (br, 1H, NH, exchangeable), 7.27-7.73 (m, 5H, arom.). ^{13}C NMR ($CDCl_3$): 13.85, 14.05, 14.91, 14.93, 58.12, 61.75, 63.24, 63.30, 101.18, 116.81, 126.74, 128.45, 128.86, 139.37, 152.78, 165.37, 168.80, 168.90.

2H-1,3-Thiazine-2-carboxylic acid-2-propanoate-6-[benzene-(1,1-diethoxymeth-yl)]-3,4-dihydro-4-oxo ethyl ester, 7d: yield 61%, mp 153-154 ^{0}C. Anal. Calcd for $C_{21}H_{27}NO_7S$: C, 57.65; H, 6.22; N, 3.20; S, 7.33. Found: C, 57.39; H, 6.11; N, 3.40; S, 7.59. IR (Nujol mull): 3150, 3100, 1743, 1560. ^{1}H NMR ($CDCl_3$): 0.96-1.40 (m, 9H, three CH_3), 2.23-2.63 (m, 4H, $CH_2CH_2CO_2Et$), 3.06-4.27 (m, 6H, three OCH_2Me), 6.43 (d, J=1.2 Hz, 1H, =CH-, become singlet by irradiation on NH- signal), 7.13-7.60 (m, 5H, arom.), 7.96 (br s, 1H, NH, exchangeable), 9.09 (br, 1H, COOH exchangeable). ^{13}C NMR ($CDCl_3$): 14.11, 15.78, 15.90, 27.03, 32.40, 58.60, 58.81, 61.28, 64.10, 101.35, 116.57, 127.38, 127.88, 128.70, 139.67, 152.41, 165.56, 168.87, 177.06.

2H-1,3-Thiazine-2-carboxylic acid-6-[benzene-(1,1-dimethoxymethyl)]-3,4-dihy-dro-4-oxo methyl ester, 7a: To a solution of sodium methoxide in methanol (prepared from 0.30 g, 13.00 mmol, of sodium in 30 ml of absolute methanol), acetal isothiazolone **6a** 2 g, 6.20 mmol, was added and the mixture was refluxed for 30 min. The solution was cooled and acidified with a solution of 10 % hydrochloric acid. The resinous material which separated was crystallized from methanol, recrystallization from methanol gave the analytically pure thiazinone **7a**, 1.64 g, yield 61%, mp 131-134 ^{0}C. Anal. Calcd for $C_{15}H_{17}NO_5S$: C, 55.72; H, 5.30; N, 4.33; S, 9.91. Found: C, 55.81; H, 5.11; N, 4.47; S, 9.83. IR (Nujol mull): 3160, 1750, 1620, 1550. ^{1}H NMR ($CDCl_3$): 3.25 (s, 6H, two OCH_3), 3.69 (s, 3H, $COOCH_3$), 5.95 (d, J=1.2 Hz, 1H, =CH-, become singlet by irradiation on NH signal), 7.13-7.41 (m, 5H, arom.), 8.37 (br, 1H, NH, exchangeable). ^{13}C NMR ($CDCl_3$): 50.37, 50.48, 52.20, 64.25, 101.11, 116.23, 127.42, 127.90, 128.70, 139.69, 152.30, 165.60, 169.33.

General procedure for the saponification reaction of diethyl acetal thiazinone esters **7c, d**, to the corresponding diethyl acetal thiazinone acids **8c, d**: A mixture of diethyl acetal thiazinone 7, 2 g, and a solution of potassium hydroxide 5%, 40 ml, was stirred at room temperature for three days. The resulting solution was cooled in an ice-bath and acidified with a solution of hydrochloric acid 10%, the formed solid was filtered off and washed with water. After recrystallization from ethyl acetate/hexane an analytical sample of the compound 8 was obtained.

2H-1,3-Thiazine-2-carboxylic acid-2-acetic acid-6-[benzene-(1,1-diethoxymeth-yl)]-3,4-dihydro-4-oxo, 8c: yield 72%, mp 146-147 ^{0}C. Anal. Calcd for $C_{18}H_{21}NO_7S$: C, 54.67; H, 5.35; N, 3.54; S, 8.11. Found: C, 54.40; H, 5.20; N, 3.58; S, 8.29. IR (Nujol mull): 3160, 3120, 1720, 1593. ^{1}H NMR ($CDCl_3$): 1.00-1.47 (m, 6H, two CH_3), 3.00 (s, 2H, CH_2COOH), 3.13-3.70 (m, 4H, two OCH_2Me), 6.43 (s, 1H, =CH-), 7.02 (br s, 1H, NH, exchangeable), 7.15-7.67 (m, 5H, arom.), 8.33 (br, 2H, two COOH, exchangeable). ^{13}C NMR ($CDCl_3$): 14.11, 14.23, 42.80, 58.47, 58.78, 63.50, 101.45, 116.56, 127.38, 127.65, 128.70, 139.65, 152.41, 165.60, 177.05, 177.31.

2H-1,3-Thiazine-2-carboxylic acid-2-propanoic acid-6-[benzene-(1,1-diethoxy-methyl)]-3,4-dihydro-4-oxo 8d: yield 70%, mp 154-155 °C. Anal. Calcd for $C_{19}H_{23}NO_7S$: C, 55.73; H, 5.66; N, 3.42; S, 7.83. Found: C, 55.69; H, 5.45; N, 3.60; S, 7.96. IR (Nujol mull): 3150, 3100, 1717, 1590. ^{1}H

NMR ($CDCl_3$): 0.96-1.55 (m, 6H, two CH_3), 2.00-2.55 (m, 4H, $CH_2CH_2CO_2H$), 3.08-3.68 (m, 4H, two OCH_2Me), 6.48 (s, 1H, =CH-), 7.05-7.70 (m, 5H, arom.), 8.77 (br s, 1H, NH, exchangeable), 9.58 (br s, 2H, two COOH, exchangeable). ^{13}C NMR ($CDCl_3$): 14.06, 14.20, 27.21, 32.10, 58.56, 58.75, 63.80, 101.55, 116.60, 127.38, 127.90, 128.65, 139.70, 152.38, 165.45, 177.08, 177.35.

General procedure for the deacetalization reaction of acetal thiazinones **7a, c, d**, to the corresponding 6-benzoylthiazinones **5a, c, d:** A mixture of acetal thiazinone 7, 0.70 g, and concentrated sulfuric acid, (94-96%), 10 ml was stirred at room temperature for half an hour. Then the solution was added under stirring to ice, the formed solid was collected and washed well with water. Recrystallization from benzene/hexane gave analytically pure 6-benzoylthiazinone **5a, 5c** and **5d**, in yields 76, 74 and 71% respectively. The products **5c** and **5d**, on admixture with those prepared from the above referred procedure (**4**→**5**), do not depress their melting points.

2H-1,3-Thiazine-2-carboxylic acid-6-benzoyl-3,4-dihydro-4-oxo methyl ester, 5a: yield 76%, mp 129-131 ^0C. Anal. Calcd for $C_{13}H_{11}NO_4S$: C, 56.31; H, 4.00; N, 5.05; S, 11.56. Found: C, 56.11; H, 3.87; N, 5.14; S, 11.44. IR (Nujol mull): 3180, 1751, 1667, 1590. ^1H NMR ($CDCl_3$): 3.86 (s, 3H, CH_3), 5.87 (d, J=.2 Hz, 1H, C2, become singlet by irradiation on NH- signal), 6.36 (almost a d, J=1.2 Hz, 1H, =CH-, become singlet by irradiation on NH signal), 7.27-7.61 (m, 5H, arom.), 8.31 (br, 1H, NH, exchangeable), ^{13}C NMR ($CDCl_3$). 51.22, 62.67, 125.33, 129.41, 129.89, 134.55, 134.75, 145.10, 164.60, 169.33, 192.48.

General procedure for the deacetalization reaction of diethyl acetal thiazinones **8c, d**, to the corresponding 6-benzoylthiazinones **9c, d:** A mixture of diethyl acetal thiazinone **8**, 0.20 g, and a solution of sulfuric acid (50%), 10 ml, was stirred at room temperature for one day. The new solid which formed was filtered off and washed well with water. After recrystallization from ethyl acetate/hexane an analytically pure isothiazolone 9 was obtained in yields 61-64%.

2H-1,3-Thiazine-2-carboxylic acid-2-acetic acid-6-benzoyl-3,4-dihydro-4-oxo 9c: yield 64%, mp 161-162 ^0C. Anal. Calcd for $C_{14}H_{11}NO_6S$: C, 52.33; H, 3.45; N, 4.36; S, 9.98. Found: C, 52.21; H, 3.30; N, 4.43; S, 9.74. IR (Nujol mull): 3342, 3090, 1735, 1620, 1600. ^1H NMR ($CDCl_3$/DMSO-d_6): 3.32 (s, 2H, CH_2), 6.48 (s, 1H, =CH-), 7.33-7.93 (m, 5H, arom.), 8.92 (br, 1H, NH), 11.84 (br, 2H, two COOH,). ^{13}C NMR ($CDCl_3$): 42.47, 63.81, 125.31, 129.28, 129.89, 134.55, 134.87, 159.10, 168.28, 177.06, 177.31, 192.47.

2H-1,3-Thiazine-2-carboxylic acid-2-propanoic acid-6-benzoyl-3,4-dihydro-4-oxo 9d: yield 61%, mp 156-157 ^0C. Anal. Calcd for $C_{15}H_{13}NO_6S$: C, 53.73; H, 3.91; N, 4.18; S, 9.56. Found: C, 53.87; H, 4.13; N, 4.35; S, 9.37. IR (Nujol mull): 3350, 3085, 1738, 1623, 1600. ^1H NMR ($CDCl_3$/DMSO-d_6): 2.18-2.60 (m, 4H, $CH_2CH_2CO_2H$), 6.52 (s, 1H, =CH=), 7.21-7.80 (m, 5H, arom.), 8.63 (br, 1H, NH), 12.06 (br, 2H, two COOH). ^{13}C NMR ($CDCl_3$): 27.21, 31.78, 63.05, 125.31, 129.28, 129.85, 134.55, 137.81, 164.50, 168.26, 177.01, 177.27, 192.45.

5-Thia-1-azabicyclo[4.2.0]oct-3-ene-4-benzoyl-2,8-dioxo-6-carboxylic acid methylester, 10.
In a solution, under nitrogen, of the thiazine **9c**, 0.4 g, 1.24 mmol, in dry dichloromethane 3 ml, thionyl chloride 0.5 ml, 6.90 mmol, was added, and the solution was refluxed for 2h. After condensation under vacuum the received residue was refluxed for some minutes with 3 ml of dry methanol and the solution was concentrated under vacuum. After recrystallization of the solid concentrate from methanol an analytical sample of the compound **10** was obtained, 0.28 g 71% yield, mp 159-161 ^0C. Anal. Calcd for $C_{15}H_{11}NO_5S$: C, 56.78; H, 3.50; N, 4.42; S, 10.08. Found: C, 56.83; H, 3.61; N, 4.28; S, 9.87. IR (Nujol mull): 1780, 1728, 1680, 1665. ^1H NMR ($CDCl_3$): 2.56 (dd, J=14.5 Hz, 1H, C*H*H), 3.12 (dd, J=14.5 Hz, 1H, CH*H*), 3.57 (s, 3H, CH_3), 6.51 (s, 1H, =CH-), 7.45-7.83 (m, 5H, arom.). ^{13}C NMR ($CDCl_3$): 45.43, 49.65, 66.81, 125.23, 129.31, 129.78, 134.27, 134.80, 145.40, 164.42, 166.85, 168.60, 192.27.

Dihydropyrrolo[2,1-b][1,3]thiazine-4,6(7H)-dione-2-benzoyl-9-carboxylic acid methylester, 11.
Following the same procedure described above, 0.35 g of thiazine 9d yielded 0.25 g (72%) of the compound **11**, mp 174-175 ^0C. Anal. Calcd for $C_{16}H_{13}NO_5S$: C, 58.00; H, 3.96; N, 4.23; S, 9.66. Found: C, 58.11; H, 4.13; N, 4.37; S, 9.48. IR (Nujol mull): 1760, 1733, 1678, 1660. NMR ($CDCl_3$): 2.70 (m, 2H, CH_2), 3.98 (m, 2H, CH_2), 3.61 (s, 3H, CH_3), 6.54 (s, 1H, =CH-), 7.39-7.7.85 (m, 5H,

arom.). ^{13}C NMR ($CDCl_3$): 29.15, 36.24, 50.95, 66.60, 125.45, 129.13, 129.65, 134.22, 134.76, 145.44, 164.60, 171.25, 172.83, 192.34.

References

1. (a) S. G. Waley, In *The chemistry of β-Lactams;* M. I. Page, Ed., Blackie: Glasgow, 1992; pp 198-226; (b) J.-M. Frère, *Mol. Microbiol.*, **16**, 385-395 (1995).
2. D. E. Butler, J. D. Leonard, B. W. Caprathe, Y. J. L'Italien, M. R. Pavia, *J. Med. Chem.*, **30**, 498-503 (1987).
3. (a) D. H. Kim, Eur. Pat. Appl.: EP 80-300845 19800319. (b) M. G. Thomas, N. M. Allanson, Brit. UK. Pat. Apll.: GB 2001-12236 20010518.
4. A. Tsolomitis, C. Sandris, *J. Heterocycl. Chem.*, **17**, 1645-1646 (1980).
5. A. Tsolomitis, C. Sandris, *J. Heterocycl. Chem.*, **22**, 1635-1637 (1985).
6. A. Tsolomitis, C. Sandris, *Heterocycles*, **25**, 569-575 (1987).
7. (a) C. K. Wareen, B. C. L. Weedon, *J. Org. Chem.*, 3972-3986 (1958). (b) C. K. Wareen, B. C. L. Weedon, *J. Org. Chem.*, 3986-3994 (1958).

Received on January 28, 2007.