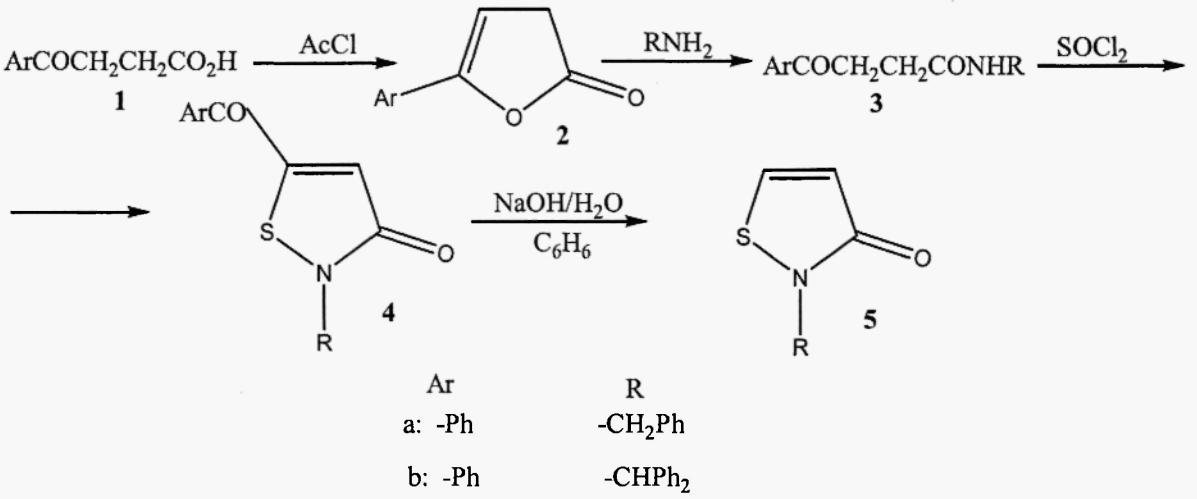
REARRANGEMENT OF 5-BENZOYL-3(2H)-ISOTHIAZOL-3-ONES TO 6-BENZOYL 2,3-DIHYDRO-1,3-THIAZIN-4(2H)-ONES

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

Abstract: 5-Benzoyl-3(2H)-isothiazol-3-ones **4** were converted to the corresponding isomeric 6-benzoyl-2-substituted-2,3-dihydro-1,3-thiazin-4(2H)-ones **13** by the following reaction sequence: the preparation of aroylpropionamides (**3**), the conversion of (**3**) to aroylisothiazolones (**4**), the protection, by ketalization, of the aroyl carbonyl group of (**4**), the transformation of isothiazolone ketals (**11**) to the corresponding thiazinone ketals (**12**) and finally the deketalization reaction to aroylthiazinones (**13**) in good overall yields.

The 1,3-thiazine nucleus is the active core of cephalosporins which are among the widely used β-lactam antibiotics. They are claimed to have utility also as pesticides and herbicides[1] and as agrochemicals fungicides.[2] The 1,3-thiazines have been extensively studied and may be classified according to the position of the extra hydrogen atoms in the parent structure. 2,3-Dihydro-1,3-thiazin-4-ones are the least studied. Only a few reactions based on the ring enlargement of the isothiazolones[3,4,5,6] are developed.

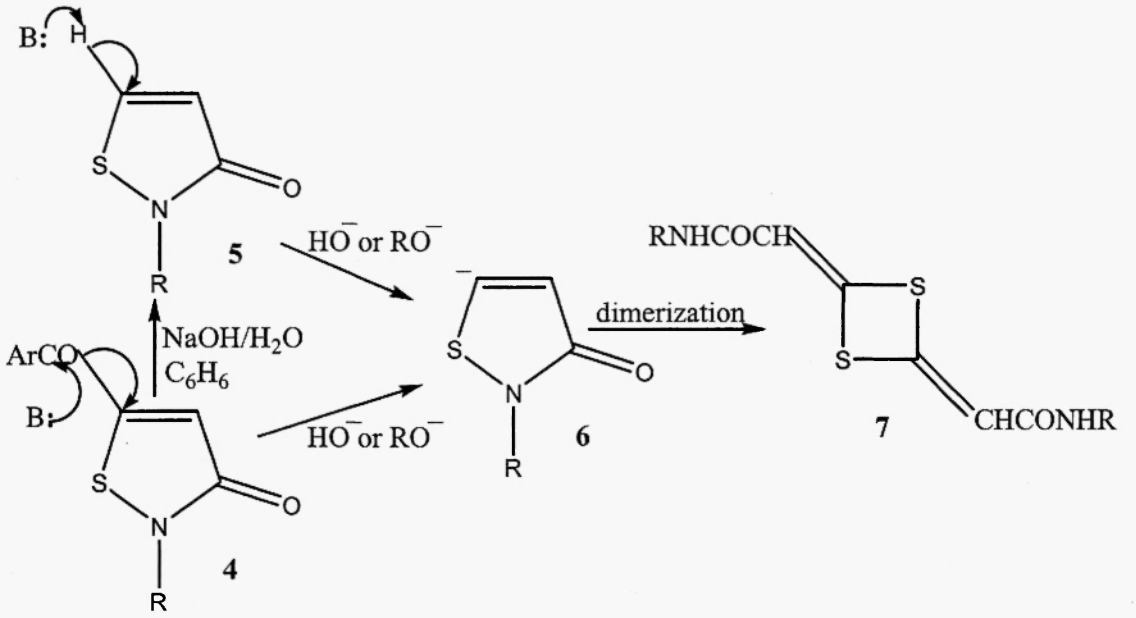
In previous works we have reported[7,8] the preparation of a series of 5-aroylisothiazol-ones **4** as well as a series of dearoylated isothiazolones[8,9] **5**, by the sequence of reactions shown in Scheme-1.



Scheme-1

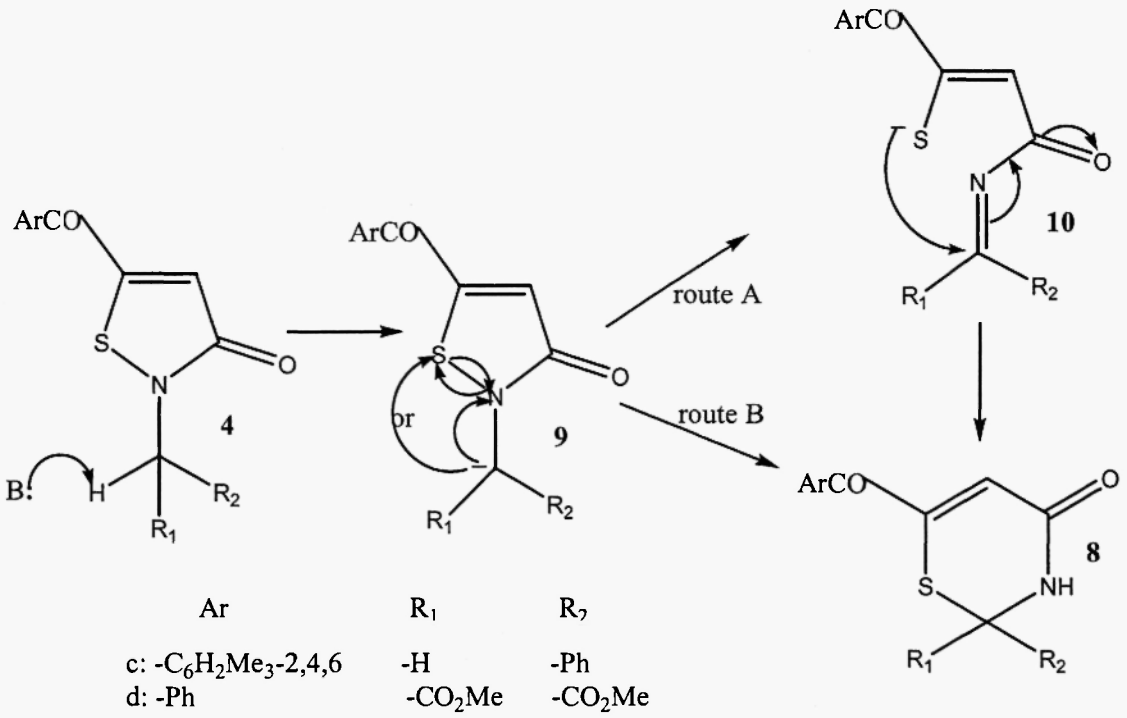
The readily available 3-aroylpropionic acids **1** were activated by lactonization on reaction with excess of acetyl chloride to the corresponding 5-arylfuran-2(3H)-ones **2** which reacted with a series of primary amines RNH_2, where R is an alkyl, an aralkyl or a substituted aryl group, to yield the N-substituted 3-aroylpropionamides **3**. A simple cyclization reaction of 3-aroylpropionamides **3** with excess of thionyl chloride gave the corresponding 5-aroyl-3(2H)-isothiazolones **4**, the later were converted[9] to N-substituted 3(2H)-isothiazolones **5** through a nucleophilic displacement of the 5-aroyl group.

N-substituted 3(2H)-isothiazolones bearing a free 5-position, of the general formula **5**, have been found[10] to be dimerized readily by bases to 2,4-bismethylene-1,3-dithietanes **7** (Scheme 2). Dithietanes of the formula **7** have been also obtained from N-substituted 5-aroylisothiazolones **4**. For instance, the reaction of the isothiazolone **4** (Ar=-C_6H_5, R=-$CH_2C_6H_5$) with bases (e.g. EtOH/EtONa, NaOH/H_2O) has been found[7] to yield the corresponding dithietane **7** (R=-$CH_2C_6H_5$). The dimerization proceeded through the attack of the formed 5-anion **6** on the labile S-N bond of a second isothiazolone molecule **5**. In the case of isothiazolone **4**, the 5-anion **6** would result from a nucleophilic displacement of the 5-aroyl group. As above-mentioned, in a previous work,[9] we have reported a simple synthesis of N-substituted 3(2H)-isothiazolones **5**, through a nucleophilic displacement on the 5-aroyl group of compounds **4**. This displacement and the subsequent isolation of the isothiazolone **5**, by protonation of the resulting 5-anion **6**, prior the dimerization process, (Scheme 2), could be observed experimentally in sodium hydroxide solution. Following this observation, the dearoylation of compounds **4** was performed in a two-phase aqueous-organic system, in order to remove the resulting isothiazolones **5** from the basic medium needed for the dimerization reaction.



Scheme-2

A different route[11] (Scheme 3) was developed on the reaction of the isothiazolone **4c** (Ar=-$C_6H_2Me_3$-2,4,6, R_1=-H, R_2=-Ph) bearing an aroyl group not accessible, as anticipated, to nucleophilic attack. Instead of dimerization, an isomeric compound, the 1,3-thiazin-4(2H)-one **8c**, was isolated in good yield. Under these conditions the 5-benzoyisothiazolone **4** (Ar=-Ph, R_1=-H, R_2=-Ph) was found to give the corresponding dithietane. On the other hand, the 5-benzoylisothiazolone **4d** (Ar=-Ph, R_1=R_2=-COOMe), a compound with a sufficiently acidic C-H bond next to the heterocyclic nitrogen, was found[12] to proceed easily on mild treatment with triethylamine, to the corresponding thiazinone **8d**, equally well.

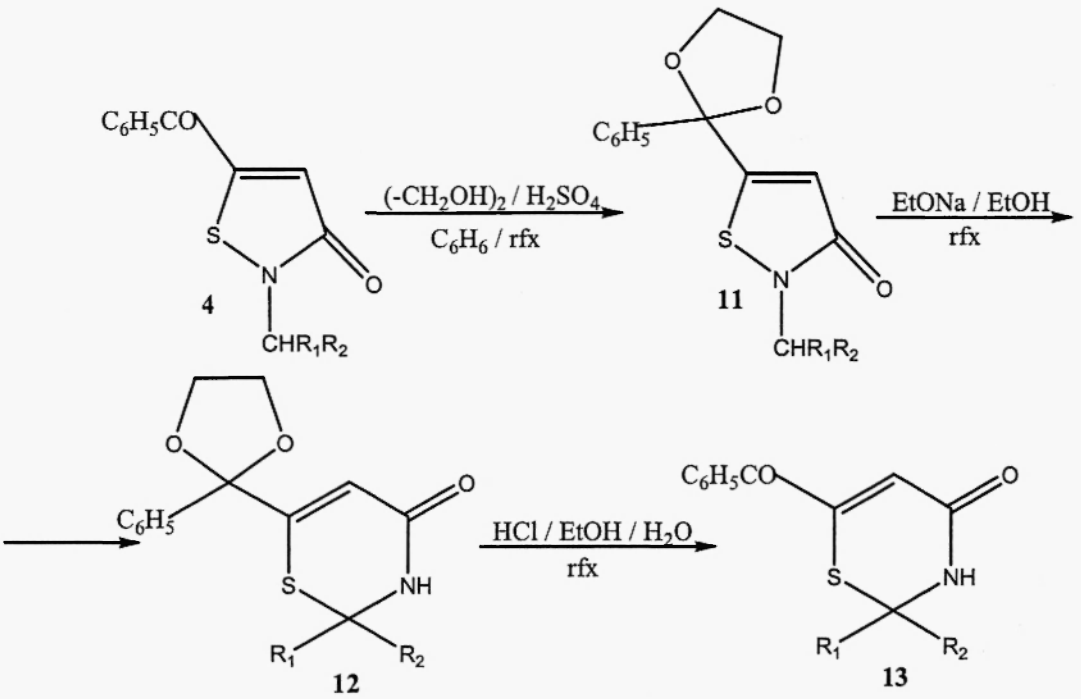


Scheme-3

The ring enlargement of **4c,d** to **8c,d** can only be explained by the abstraction of an acidic C-H proton from N-benzyl or N-dimethylmalonate group to form the anion **9**. This anion can then be assumed to give compounds **8** either through the acylimine intermediate **10**, an elimination-addition process (E1cb mechanism), route A, or through an 1,2-shift, route B, (Scheme 3).

Here we describe the transformation of the prepared 5-benzoylisothiazolones **4a** and **4b** to the dihydrothiazinones **13a** and **13b** respectively, which was accomplished through protection of the benzoyl carbonyl by ketalization with ethylene glycol (Scheme 4). The rearrangement **11**→**12** was then possible using sodium ethoxide as base and the dihydrothiazinones **13a** and **13b** were finally obtained after deketalization.

All these transformations clearly show the general character of this ring expansion reaction, provided that a stabilized anion, such as **9**, Scheme 3, can be generated under suitable conditions prior the cleavage of the isothiazolone S-N bond, a readily feasible ambiphilic bond, which can undergo a variety of nucleophilic ring cleavage reactions when subjected to the action of bases and nucleophiles[13,14] through attack on sulfur, or electophilic attack on nitrogen.



a: R_1 = -H, R_2 = -Ph; b: R_1 = R_2 = -Ph

Scheme-4

In conclusion, 5-benzoyl-3(2H)-isothiazol-3-ones which when are treated with bases are transformed, depending on the reaction conditions, to 2,4-bis(N-substituted-carboxamido)methylene-1,3-dithietanes or to N-substituted 3(2H)-isothiazol-3-ones, can also be converted into the corresponding 6-benzoy-2,3-dihydro-1,3-thiazin-4(2H)-ones. After protection, by ketalization, of the easily accessible to nucleophilic displacement benzoyl group (of the benzoylisothiazolones), the basic treatment of the isothiazolone ketals results, through the expected rearrangement, in the respective benzoylthiazinones, with the prerequisite the 2-substituent of the isothiazolone ring to consist of a relative acidic C-H bond. The expansion of the method to aroylisothiazolones bearing different active C-H substituents or other ones that could form other anions, are in our immediate plan.

Experimental

Melting points were determined in capillary tubes and are uncorrected. Microanalyses were performed by microanalytical laboratory of CNRS (France). IR spectra were obtained at a Nicolet Magna 560 spectrometer as nujol mulls and were calibrated against the polystyrene 1601 cm^{-1} band, and given in reciprocal centimeters. NMR spectra were recorded at ambient temperature using a Varian EM-360 60 MHz spectrometer. The data are reported as follows: chemical shifts are quoted in ppm on the δ scale downfield from TMS (internal standard), multiplicity (br=broad, s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet), coupling constants are given in (Hz).

5-Phenylfuran-2(3H)-one (2). This compound was prepared from β-benzoylpropionic acid and acetyl chloride at reflux conditions.[15]

3-Benzoylpropionamide-N-benzyl (3a). A mixture of 8 g (49.95 mmol) of 5-phenylfuran-2(3H)-one and 5.62 g (52.45 mmol) of benzylamine was stirred at room temperature for 30 min and then was heated on a steam bath for 10 min. The solid product after recrystallization from ethanol gave 11.50 g (86 %) of a crystalline solid mp 110-112 ^{0}C, lit[16] 110-111 ^{0}C. IR: 3257, 1681, 1634 and 1550. ^{1}H NMR ($CDCl_3$): 2.70 (t, J=6.2 Hz, 2H, >$NCOCH_2$-), 3.45 (t, J=6.2 Hz, 2H, -CH_2COPh), 6.38 (br m, 1H, -NHCO-), 7.35-8.30 (m, 10H, arom.).

3-Benzoylpropionamide-N-diphenylmethyl (3b). A mixture of 7.48 g (46.70 mmol) of 5-phenylfuran-2(3H)-one and 9 ml (52.25 mmol) of α-aminodiphenylmethan was stirred at room temperature for 30 min and then 20 min on a steam bath. The resulting solid after recrystallization from ethanol gave an analytically pure sample 13.50 g (85.12 %), mp 158-159 ^{0}C. Anal. Calcd for $C_{23}H_{21}NO_2$: C, 80.44; H, 6.16; N, 4.08. Found: C, 80.68; H, 6.22; N, 4.04. IR: 3316, 1677, 1647 and 1522. ^{1}H NMR ($CDCl_3$): 2.70 (t, J=6.2 Hz, 2H, >$NCOCH_2$-), 3.36 (t, J=6.2 Hz, 2H, -CH_2COPh), 6.2 (d, J=8 Hz, 1H, -$CHPh_2$), 6.56 (br m, 1H, -NHCO-), 7.13-8.10 (m, 15H, arom.).

5-Benzoyl-2-benzylisothiazol-3(2H)-one (4a). This compound was prepared according to the procedure described in a previous work.[7]

5-Benzoyl-2-diphenylmethylisothiazol-3(2H)-one (4b). Following the general procedure,[7] a solution of the keto amide **3b**, 5 g (14.56 mmol) in 40 ml of thionyl chloride, was stirred at room temperature for 2 h. The dark green solution was concentrated under vacuum at room temperature and the solid residue was recrystallized from ethanol to give 4.90 g (90.60 %) of a yellow crystalline analytically pure sample mp 110-111 ^{0}C. Anal. Calcd for $C_{23}H_{17}NO_2S$: C, 74.37; H, 4.61; N, 3.77; S, 8.63. Found: C, 74.35; H, 4.64; N, 3.74; S, 8.47. IR: 1663, 1632, 1595 and 1550. ^{1}H NMR ($CDCl_3$): 6.86 (s, 1H, vinylic), 7.00 (s, 1H, -$CHPh_2$), 7.20-8.18 (m, 15H, arom.).

General procedure for the preparation of isothiazolone ethylene ketals **11**. To a mixture of the 5-benzoylisothiazolone **4** (13.54 mmol) and 3 ml (53.79 mmol) ethylene glycol in benzene 50 ml, six drops of concentrated sulphuric acid were added and the mixture was refluxed on an apparatus connected with a dean-stark trap, for azeotropic water collection, for 24 h. The resultant solution was concentrated under vacuum and the yellow solid residue was recrystallized from ethanol to give 10-11.3 mmol (73.85-83.46 %) of the corresponding isothiazolone ketal **11** of analytical grade.

Isothiazolone ketal 11a: yield, 83.46 %, mp 113-114 ^{0}C. Anal. Calcd for $C_{19}H_{17}NO_3S$: C, 67.24; H, 5.05; N, 4.13; S, 9.45. Found: C, 67.17; H, 4.87; N, 3.98; S, 9.32. IR: 1624, 1550 and 1490. ^{1}H NMR ($CDCl_3$): 4.07 (s, 4H, -CH_2CH_2-), 4.87 (s, 2H, -CH_2Ph), 6.17 (s, 1H, vinylic), 7.25-7.80 (m, 10H, arom.).

Isothiazolone ketal 11b: yield, 73.85 %, mp 155-156 ^{0}C. Anal. Calcd for $C_{25}H_{21}NO_3S$: C, 72.27; H, 5.09; N, 3.37; S, 7.72. Found: C, 72.37; H, 5.11; N, 3,25; S, 7.64. IR: 1633, 1544 and 1488. ^{1}H NMR ($CDCl_3$): 4.07 (s, 4H, -CH_2CH_2-), 6.18 (s, 1H, vinylic), 6.87 (s, 1H, -$CHPh_2$), 7.03-7.80 (m, 15H, arom.).

General procedure for the preparation of 1,3-thiazin-4-one ethylene ketals **12**. To a solution of sodium ethoxide in ethanol (prepared from 0.5 g, 21.75 mmol of sodium in 25 ml of absolute ethanol), 2.95 mmol of isothiazolone ketal **11** were added and the mixture was refluxed for 2 h. The solution was cooled, poured in 50 ml of an aqueous solution of 10 % hydrochloric acid. The precipitated solid was filtered and crystallized from ethanol to give 2.1-2.3 mmol (71.20-77.97 %) of a colorless crystalline analytically pure product, the 1,3-thiazin-4-one ketal **12**.

1,3-Thiazin-4-one ketal 12a: yield, 71.20 %, mp 119-120 ^{0}C. Anal. Calcd for $C_{19}H_{17}NO_3S$: C, 67.24; H, 5.05; N, 4.13; S, 9.45. Found: C, 67.07; H, 5.19; N, 3.86; S, 9.19. IR: 3135, 1658, 1618 and 1555. ^{1}H

NMR $CDCl_3$/DMSO-d_6):[17] 4.07 (s, 4H, -CH_2CH_2-), 5.83 (d, J=3 Hz, 1H, >CHPh), 6.30 (d, J=1.2 Hz, 1H, vinylic), 7.23-7.63 (m, 10H, arom.), 8.06 (br s, 1H, >NH).

1,3-Thiazin-4-one ketal 12b: yield, 77.97 %, mp 214-215 ^{0}C. Anal. Calcd for $C_{25}H_{21}NO_3S$: C, 72.27; H, 5.09; N, 3.37; S, 7.72. Found: C, 72.34; H, 5.13; N, 3.21; S, 7.61. IR: 3144, 1647 and 1551. ^{1}H NMR ($CDCl_3$/DMSO-d_6):[17] 4.03 (s, 4H, -CH_2CH_2-), 6.26 (d, J=2Hz, 1H, vinylic), 7.10-7.53 (m, 15H, arom.), 8.81 (br m, 1H, >NH).

General procedure for the preparation of 6-benzoyl-3,4-dihydro-1,3-thiazin-4(2H)-ones **13**. A mixture of 2.95 mmol of 1,3-thiazin-4-one ketal **12** in 20 ml of ethanol and 10 ml of 10 % aqueous hydrochloric acid was refluxed for 2 h. After cooling of the resultant solution, the precipitated solid was filtered and washed with water. After recrystallization from ethanol an analytical sample was obtained in 78-82 % yield.

6-Benzoyl-2-phenyl-2,3-dihydro-1,3-thiazin-4(2H)-one (13a): yield, 78 %, mp 155-157 ^{0}C. Anal. Calcd for $C_{17}H_{13}NO_2S$: C, 69.13; H, 4.43; N, 4.74; S, 10.85. Found: C, 68.87; H, 4.37; N, 4.49; S, 10.67. IR: 3154. 1658, 1644,1592 and 1560. ^{1}H NMR ($CDCl_3$/DMSO-d_6):[17] 6.03 (d, J=1.5 Hz, 1H, >CHPh), 6.53 (d, J=1.2 Hz, 1H, vinylic), 7.26-7.93 (m, 10H, arom.), 8.13 (m, 1H, >NH).

6-Benzoyl-2,2-diphenyl-2,3-dihydro-1,3-thiazin-4(2H)-one (13b): yield, 82 %, mp 195-197 ^{0}C. Anal. Calcd for $C_{23}H_{17}NO_2S$: C,74.37; H, 4.61; N, 3.77; S, 8.63. Found: 74.09; H, 4.57; N, 3.60; S, 8.44. IR:3144, 1655, 1647, 1589 and 1572. ^{1}H NMR (DMSO-d_6): 6.26 (d, J=1.5 Hz, 1H, vinylic), 7.23-7.80 (m, 15H, arom.), 9.73 (br m, 1H, >NH).

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17. The coupling between the C5-H and the >NH proton would be a typical case of long range coupling, as encountered in unsaturated systems incorporating a planar W-path.The >NH signal disappears on addition of D_2O and the doublets become singlets. Also when irradiating the >NH signal the doublets corresponding to the coupled C-H protons become singlets too.

Received on November 23, 2005.