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Received June 22, 1989

The 2-methyl-2*H*-1,2-benzothiazin-4-(3*H*)-one 1,1 dioxide (**2**), obtained according to a new, one-pot method, is transformed into the pyrrolidino enamine **3**. Reaction of *p*-toluenesulphonyl azide with **3** gives, *via* an unstable triazoline adduct which loses nitrogen, the two isomeric tosylamino derivatives **4** and **5**. The structures have been assigned by exhaustive nmr analysis and some aspects on their formation and chemical behaviour are discussed.

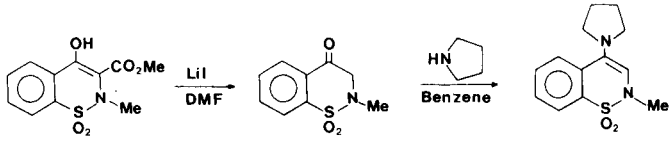
J. Heterocyclic Chem., **27**, 427 (1990).

The 1,2-benzothiazine 1,1-dioxide ring system has been scarcely studied for a long time [1] and only recently, in connection with the discovery that a number of 3-carboxamides of 2-alkyl-4-hydroxy-2*H*-1,2-benzothiazine 1,1-dioxides are antiinflammatory agents [2], has received more attention [3-5]. Our present interest [6,7] in the synthesis of polynuclear heterocyclic systems, containing the skeleton of 1,2-benzothiazine 1,1-dioxide, prompted us to investigate a possible synthetic approach based on a cycloaddition reaction between 2-methyl-4-(1-pyrrolidinyl)-2*H*-1,2-benzothiazine 1,1-dioxide and 1,3 dipoles (azides, nitrile imines, nitrile oxides) in order to obtain triazole, pyrazole and isoxazole derivatives condensed with the 1,2-benzothiazine residue.

Results.

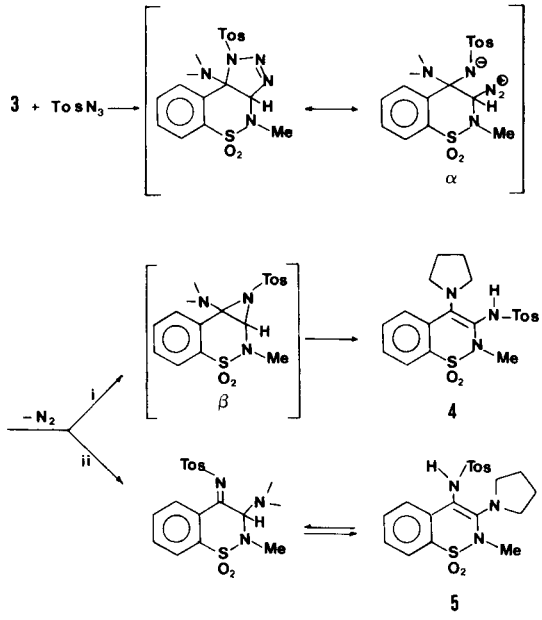
The synthesis of enamine **3** is described [8] starting from pyrrolidine and 2-methyl-2*H*-1,2-benzothiazin-4-(3*H*)-one 1,1-dioxide **2** whose preparation is possible by the following methods. In the first one [3] treatment of 3-acetyl-2*H*-1,2-benzothiazin-4-(3*H*)-one 1,1-dioxide with ethylene glycol in refluxing benzene for 120 hours and in the presence of *p*-toluenesulphonic acid, results in the formation of the corresponding ethylene ketal with simultaneous deacetylation. Hydrolysis and later *N*-methylation supplies ketone **2** with a total yield of 55%. The second method [4] includes the bromination of 3-methyl-1,2-benzoisothiazole 1,1-dioxide followed by the base-catalysed ring expansion to 1,2-benzothiazine system and by *N*-methylation (yield 66%). Both methods require three steps which are long and troublesome. We developed a new, simple and one-pot entry to **2** converting 4-hydroxy-3-methoxycarbonyl-2-methyl-1,2-benzothiazine 1,1-dioxide **1** [9,10] into the ketone **2** by reaction with lithium iodide in DMF (1 hour at 125°) in 86% yield.

In the enamines the value of the chemical shift for the β-carbon, in ^{13}C nmr spectrum, is a proof of the p-π interaction and, accordingly of the degree of delocalisation. The value measured for C-3 in **3** (113.9 ppm), compared with the C-2 value (104.0 ppm) obtained in the case of 1-pyrrolidino-3,4-dihydronaphthalene [11], taken as a model with reference to the steric effects, denotes a poor localisation of the negative charge on β-carbon owing to the presence in **3** of a group (Ph-SO_2) with an electron-withdrawing inductive effect. This point was confirmed experimentally by the poor reactivity of **3** towards both electrophiles [8] and 1,3-dipoles [12]. The reaction with phenyl azide, 4-nitrophenyl azide and diphenyl phosphorazidate does not occur and only with tosyl azide, at 80° for 7 hours it supplied two compounds **4** and **5** respectively in 42% and 8.4% of yield. On the basis of analytical and ms data the two products are isomers and result from the addition of tosyl azide to enamine with nitrogen elimination.

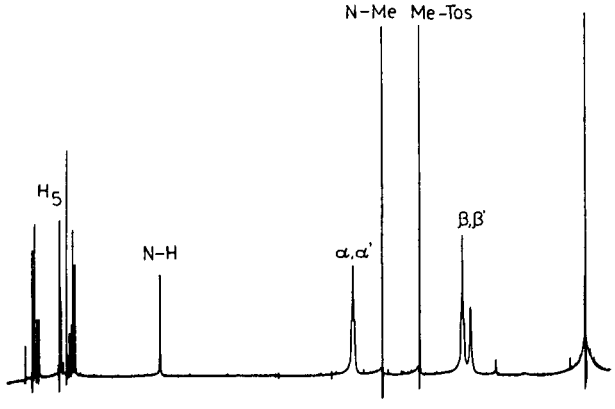


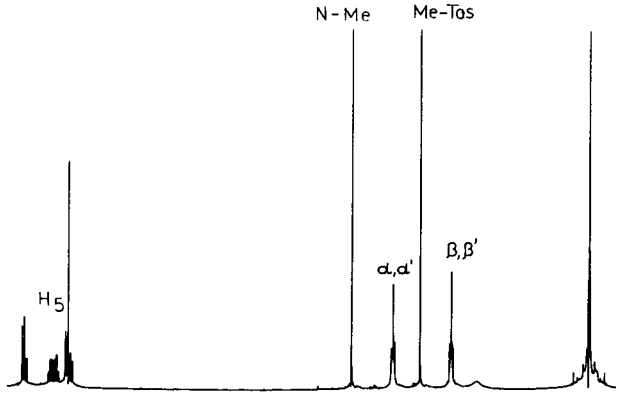
1 2 3

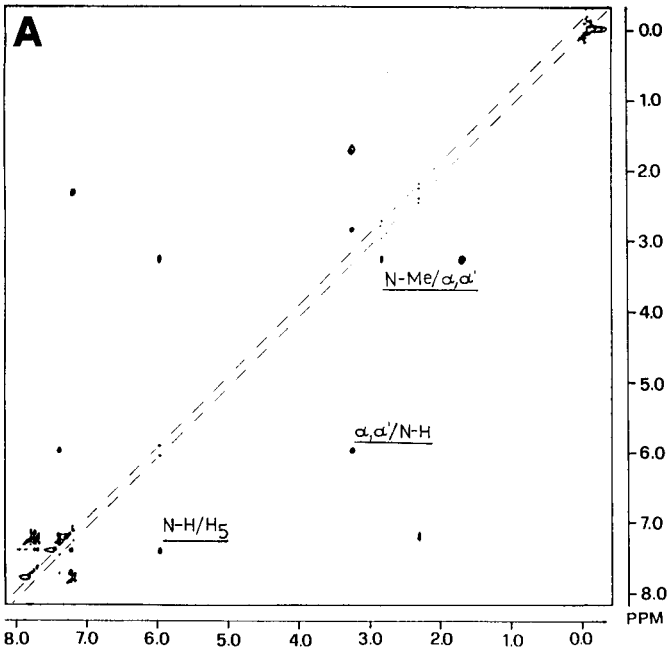
The monodimensional ^1H nmr spectra of compounds **4** and **5** do not give enough information in order to assign the right structures. The use of two dimensional experiments, such as NOESY, allow us to obtain more information and resolution: in this case we get dipolar correlations between protons lying nearby in the space, and this will let us assign the structures of the two compounds. However, the NOESY spectrum of compounds **4** and **5** is quite critical, as the methyl resonances are extremely intense when compared to the other signals, and T_1 noise is so severe as to prevent the detection of any significant cross peak in a wide spectral region. The 2D NOESY experiments are obtained with the procedure proposed by Denk *et al.* [13] based on the difference method first suggested by Boden-

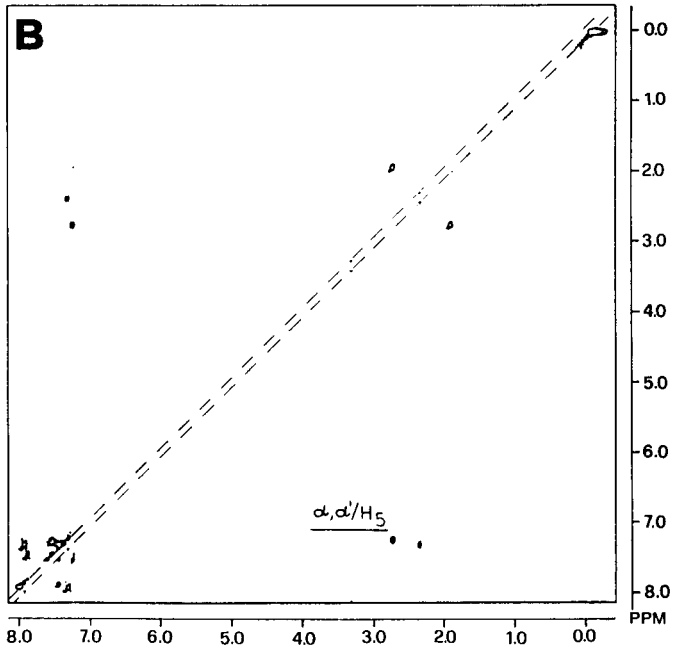


hausen and Ernst [14] in which two scans corresponding to the conventional NOESY are co-added, followed by subtraction of two transients which contain only the contribution from the diagonal peaks. In this way is eliminated most of the contribution of the main diagonal to the spectrum and the T_1 noise is reduced from the intense peaks. The remainders of the main diagonal are however of opposite sign when compared with the positive NOE's observed, and, as can be seen in Figures A and B in the "positive levels" representation only small wings are left, indicated by the dotted lines, representing the out-of-phase components of the spinning side bands. Some of the NOE's in Figures A and B are of structural origin, like those between $\alpha\alpha'$ and $\beta\beta'$ protons of the pyrrolidine ring and between the methyl and "*ortho*" aromatic protons of the tosylamino group. The results summarized in Figure A, where the NOE effects between *N*-methyl and $\alpha\alpha'$ protons, $\alpha\alpha'$ protons and the N-H proton of the tosylamino group, the N-H and aromatic H-5 are in evidence, allowing



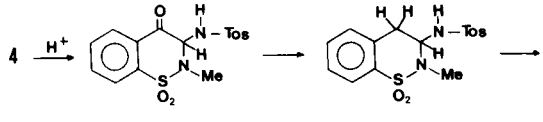




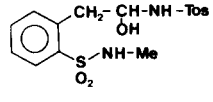


us to assign the structure reported to compound **5**. In Figure B the observation of a NOE effect between the $\alpha\alpha'$ protons and aromatic H-5 let us assign to compound **4** the structure indicated.

The structures assigned to **4** and **5** by nmr spectroscopy were also confirmed by their chemical behaviour. Acid treatment of both **4** and **5**, under controlled conditions, (see Experimental) promotes the elimination of the pyrrolidine residue with the formation of **6** and **7** respectively. The ^{1}H nmr spectra of these compounds are characterized by the presence of an AB system for the hydrogen of the NH group and respectively the one in C-3 and C-4 (this system simplifies to a singlet by deuterium exchange). It is worthwhile that the N-Me group in **6** resonates at higher field (2.60 ppm) than in **4**, (3.30 ppm), due to less steric hindrance, after pyrrolidine elimination, which offsets the interaction between SO_2-Ph and N-Me groups. An opposite effect is observed concerning the variation of chemical shift of the N-Me group passing from **5** (2.80 ppm) to **7** (3.17 ppm). In this case the shift towards lower field is due to the deshielding effect of the carbonyl group in position 3.



6 **8**



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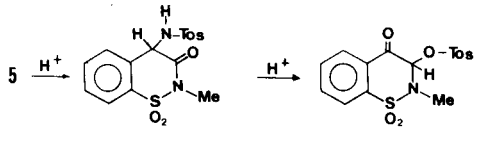

7 **10**

Compounds **6** and **7** show some remarkable transformations. Reduction of **6** with sodium borohydride in ethanol solution gives **8** which, owing to its NN-acetal structure, is transformed into the open chain product **9** by heating in protic solvents. Treatment of **7** with 10% hydrochloric acid in dioxane solution promotes the migration of the tosyl residue from nitrogen to the oxygen atom affording **10** *via* elimination of ammonia from the intermediate imine. Such behaviour is reported for the acid catalysed rearrangement of α-benzoylaminocinnamyl alcohols [15] with migration of the benzoyl group from nitrogen to oxygen and results analogous to the one observed in the chemistry of ephedrine [16,17].

Discussion.

Sulphonyl azides react with enamines giving intermediate triazolines which are unstable and rearrange or undergo a cycloreversion according to various schemes mainly as a function of the type of enamine [18]. Generally, enamines derived from cyclohexanone give a ring contraction [19], but this course did not occur in our case. The formation of products **4** and **5** can be explained through a zwitterionic intermediate (α) which evolves by two competitive paths: (i) formation of an unstable aziridine (β) which leads to **4**, *via* ring opening and prototropy (main product); (ii) migration of the pyrrolidine residue from C-4 to C-3 with achievement of **5** (minor product).

That the two mechanisms are simultaneously operative is not exceptional, but it is well documented [20-22] in other cases of reaction between tosyl azide and enamines.

EXPERIMENTAL

Both 1D and 2D spectra of Figure A and B were acquired on Bruker AM-270 MHz equipped with an Aspect 3000 computer. For the 2D NOESY spectra 256 t_1 increments were implemented over 1024 data points in the t_2 dimension; mixing time was 1 second and the spectra were collected in the phase-sensitive mode using TPPI sequence. Fourier transformation was performed after applying a shifted (π/2) sine bell function in both dimension and zero filled to 512 in F_1. All the other nuclear magnetic resonance spectra were recorded by using a Varian XL-200 and a Bruker WP-80-SY spectrometers. In all cases, the solvent for nmr measurements was deuteriochloroform. Chemical shifts were recorded in parts per million relative to that solvent. Positive ion FAB spectra were recorded with a VG Analytical 7070EQ mass spectrometer with attached VG Analytical 11/250 data system. FAB measurements were performed in glycerol and sulfolane matrix using xenon as a bombarding gas at 6-8 Kev energy. Infrared spectra were recorded on a Perkin-Elmer 298 spectrometer; only the most significant absorptions are listed. Melting points were determined with a Buchi apparatus and are uncorrected.

2-Methyl-2*H*-1,2-benzothiazin-4-(3*H*)-one 1,1-Dioxide **2**.

A mixture of **1** (41.7 g, 155 mmoles) and lithium iodide dihydrate [23] (52.7 g, 310 mmoles) in 250 ml of DMF was stirred and heated at 125° for 1 hour under a nitrogen atmosphere until carbon dioxide evolution had ceased. The solvent was evaporated off *in vacuo* giving a brown syrup which was treated with 100 ml of water with stirring. The orange precipitate was collected and washed with cold water affording 28.0 g (86%) of **2**, mp 106-107° (from ethanol) (lit [3] 107-108°).

2-Methyl-4-(1-pyrrolidinyl)-3-tosylamino-2*H*-1,2-benzothiazine 1,1-Dioxide **4** and 2-Methyl-3-(1-pyrrolidinyl)-4-tosylamino-2*H*-1,2-benzothiazine 1,1-Dioxide **5**.

A solution of the enamine **3** (2.9 g, 11 mmoles) and 4-toluenesulphonyl azide (2.3 g, 11.5 mmoles) in 100 ml of benzene was stirred and heated at 80° for 7 hours under a nitrogen atmosphere. The reaction mixture was concentrated *in vacuo* giving an oily residue which was subjected to column chromatography

on silica gel (ethyl acetate/hexane, 30:70) giving 2.0 g (42%) of **4**, 0.4 g (8.4%) of **5** and 0.45 g (20%) of 4-toluenesulphonyl azide.

Compound **4**.

This compound had mp 163-164° (from ethanol); ir (chloroform): 3240 cm^{-1}; ^1H nmr 200 MHz, 1.9 (4H, m, CH_2-CH_2), 2.35 (3H, s, Me), 2.71 (4H, m, CH_2-N-CH_2), 3.3 (3H, s, N-Me), 7.21 (1H, d, J = 8.0 Hz, 5-H), 7.26 (2H, d, J = 8.0 Hz, Tosyl), 7.36-7.55 (2H, m, 6-H, 7-H), 7.83 (1H, dd, J = 8.0, 2.0 Hz, 8-H), 7.88 (2H, d, J = 8.0 Hz, Tosyl); ms: Fab m/z 433.

Anal. Calcd. for $C_{20}H_{23}N_3O_4S_2$: C, 55.42; H, 5.34; N, 9.70. Found: C, 55.41; H, 5.42; N, 9.68.

Compound **5**.

This compound had mp 198-200° (from ethanol); ir (nujol): 3340 cm^{-1}; ^1H nmr: 200 MHz, 1.68 (4H, m, CH_2-CH_2), 2.3 (3H, s, Me), 2.8 (3H, s, N-Me), 3.25 (4H, m, CH_2-N-CH_2), 6.3 (1H, s, NH, exch with deuterium oxide), 7.14 (2H, d, J = 8.0 Hz, Tosyl), 7.18 (1H, dd, J = 8.0, 1.7 Hz, 5-H), 7.26-7.42 (2H, m, 6-H, 7-H), 7.64 (1H, dd, J = 7.5, 1.3 Hz, 8-H), 7.72 (2H, d, J = 8.0 Hz, Tosyl); ms: Fab m/z 433.

Anal. Calcd. for $C_{20}H_{23}N_2O_4S_2$: C, 55.42; H, 5.34; N, 9.70. Found: C, 55.18; H, 5.46; N, 9.61.

2-Methyl-3-tosylamino-2*H*-1,2-benzothiazin-4-(3*H*)-one 1,1-Dioxide **6**.

A mixture of compound **4** (1.0 g, 2.3 mmoles), 15% sulphuric acid (30 ml) and ethanol (15 ml) was stirred at room temperature for 12 hours. The suspension was concentrated *in vacuo* to eliminate ethanol, then extracted with dichloromethane (2 × 25 ml). The combined organic phase was dried (sodium sulphate) and evaporated to give **6** (0.7 g, 80%), mp 162-163° (from ethanol); ir (nujol): 3260, 1720 cm^{-1}; ^1H nmr: 80 MHz, 2.4 (3H, s, Me), 2.6 (3H, s, N-Me), 6.0 (1H, d, J = 4.6 Hz, NH, exch with deuterium oxide), 6.17 (1H, d, J = 4.6 Hz, 3-H), 7.28 (2H, d, J = 8.0 Hz, Tosyl), 7.6-7.9 (5H, m, Tosyl and 6-H, 7-H, 8-H), 8.05 (1H, m, 5-H), (+ deuterium oxide); 6.17 (1H, s, 3-H); ms: Fab m/z 381.

Anal. Calcd. for $C_{16}H_{16}N_2O_5S_2$: C, 50.53; H, 4.24; N, 7.37. Found: C, 50.33; H, 4.24; N, 7.25.

2-Methyl-4-tosylamino-2*H*-1,2-benzothiazin-3-(4*H*)-one 1,1-Dioxide **7**.

A mixture of **5** (0.4 g, 0.9 mmole), 10% hydrochloric acid (4 ml) and dioxane (5 ml) was stirred and heated at 85° for 25 minutes until the solid was dissolved. The cold solution was diluted with water (100 ml) and extracted with dichloromethane (2 × 15 ml). The organic extracts were dried (sodium sulfate) and concentrated *in vacuo* giving an oil which was chromatographed on silica gel eluting with dichloromethane/ether (95:5) to afford compound **7** (0.11 g, 32%), mp 157-158° (from ethanol); ir (nujol): 3240, 1710 cm^{-1}; ^1H nmr: 80 MHz, 2.40 (3H, s, Me), 3.17 (3H, s, N-Me), 5.5 (1H, d, J = 4.6 Hz, 4-H), 5.90 (1H, d, J = 4.6 Hz, NH, exch with deuterium oxide), 7.22-8.10 (8H, m, aromatic), (+ deuterium oxide); 5.5 (1H, s, 4-H); ms: Fab m/z 381.

Anal. Calcd. for $C_{16}H_{16}N_2O_5S_2$: C, 50.53; H, 4.24; N, 7.37. Found: C, 50.36; H, 4.31; N, 7.24.

2-Methyl-3-tosylamino 3,4-dihydro-2*H*-1,2-benzothiazine 1,1-Dioxide **8**.

To a suspension of **6** (0.450 g, 1.2 mmoles) in ethanol (20 ml) was added portionwise sodium borohydride (0.133 g, 3.6 mmoles) and the mixture was stirred at room temperature for 2 hours. The residue, after evaporation of the solvent, was diluted with water (10 ml) and extracted with dichloromethane (2 × 15 ml). The organic phase was dried (sodium sulfate) and evaporated giving 0.4 g (86%) of **8**, which was purified by washing with diisopropylether and finally air dried, mp 51°; ir (nujol): 3470 cm^{-1}; ^1H nmr: 80 MHz, 2.30 (3H, s, Me), 2.50 (3H, s, N-Me), 3.05 (1H, dd, A of ABX, J = 12.0, 9.0 Hz, 4-H), 3.25 (1H, dd, B of ABX, J = 12.0, 3.0 Hz, 4-H), 4.9 (3H, sb, NH, H_2O, exch with deuterium oxide), 5.70 (1H, dd, X of ABX, J = 9.0, 3.0 Hz, 3-H), 7.2-8.05 (8H, m, aromatic); ms: Fab m/z 385, 367.

Anal. Calcd. for $C_{16}H_{18}N_2O_4S_2 \cdot H_2O$: C, 50.00; H, 5.25; N, 7.29. Found: C, 49.83; H, 5.34; N, 7.19.

1-Hydroxy-2-[2-[(Methylamino)sulphonyl]phenyl]-1-tosylaminoethane **9**.

Compound **8** in 1-butanol was heated under reflux until the solid was dissolved. The mixture was cooled to room temperature, and the precipitate was recovered by filtration to give compound **9**, mp 93-94°; ir (nujol): 3200, 3310, 3390 cm^{-1}; ^1H nmr: 80 MHz, 2.37 (3H, s, Me), 2.57 (3H, d, J = 4.5 Hz, N-Me), 2.80-3.50 (2H, mb), 4.0 (1H, sb, OH), 5.48-6.05 (3H, mb), (+ deuterium oxide); 2.37 (3H, s, Me), 2.54 (3H, s, N-Me), 3.06 (1H, dd, A of ABX, J = 13.7, 9.1 Hz, CH_2-CH), 3.2 (1H, dd, B of ABX, J = 13.7, 2.3 Hz, CH_2-CH), 5.68 (1H, dd, X of ABX, J = 9.1, 2.3 Hz, CH_2-CH), 7.17-8.03 (8H, m, aromatic); ms: Fab m/z 385, 367.

Anal. Calcd. for $C_{16}H_{20}N_2O_5S_2$: C, 50.00; H, 5.25; N, 7.29. Found: C, 49.85; H, 5.14; N, 7.15.

2-Methyl-3-toluenesulphonyloxy-2*H*-1,2-benzothiazin-4-(3*H*)-one 1,1-Dioxide **10**.

A mixture of **5** (0.2 g, 0.46 mmole), 10% hydrochloric acid (2 ml), ethanol (3 ml) was stirred and heated at 90° for 1 hour. The solvent was evaporated off and the residue taken up with dichloromethane (2 × 10 ml). The organic phase was dried (sodium sulfate) and evaporated *in vacuo* giving a residue which was subjected to column chromatography on silica gel (hexane/ethyl acetate 70:30) to afford **10** (0.060 g, 34%), mp 169-170° (from ethanol); ^1H nmr: 80 MHz, 2.3 (3H, s, Me), 3.2 (3H, s, N-Me), 5.3 (1H, s, 3-H), 7.0-8.14 (8H, m, aromatic); ms: Fab m/z 381.

Anal. Calcd. for $C_{16}H_{15}NO_6S_2$: C, 50.40; H, 3.97; N, 3.67. Found: C, 50.70; H, 4.16; N, 3.77.

Acknowledgements.

We thank M. P. I. and C. N. R. for financial support.

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