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Isothiazoles. Part IV[1]. Cycloaddition Reactions of Diaryl-Oxazolones and Münchnones to 3-Diethylamino-4-(4-methoxyphenyl)-isothiazole 1,1-dioxide: a New Synthesis of Triarylpyrroles.

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Abstract: 3-Diethylamino-4-(4-methoxyphenyl)-isothiazole 1,1-dioxide (**3**) readily reacts with oxazolones **2** and münchnones **7** affording with satisfactory yield 3-diethylamino-4,6-diaryl-3a,4-dihydro-3a-(4-methoxyphenyl)-6aH-pyrrolo[3,4-d]isothiazole 1,1-dioxides **4** and 3-diethylamino-4,6-diaryl-5-alkyl-3a-(4-methoxyphenyl)-pyrrolo[3,4-d]isothiazole 1,1-dioxides **8**, respectively. The behaviour of the cycloadducts towards elevated temperatures and/or basic conditions was investigated. Under these conditions the primary products lost SO_2 and diethylcyanamide affording 1-alkyl-2,3,5-triarylpyrroles **9** and 1H-2,3,5-triarylpyrroles **10**. These latter were found to be better obtained through thermal decomposition of N-protected cycloadducts **8** and subsequent deprotecting the final pyrroles.

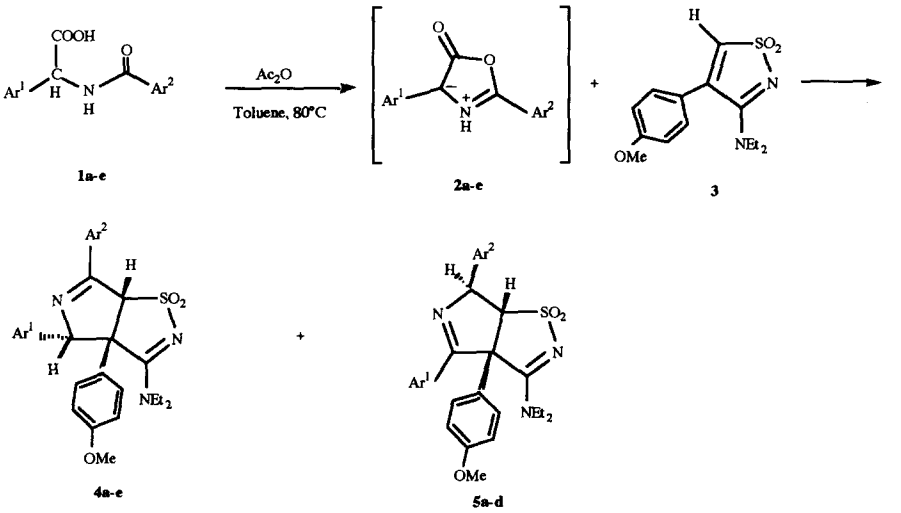
Recent work of our research group was directed to the study of the reactivity of the easily accessible 3-dialkylamino-4-arylisothiazole 1,1-dioxides.[2] It has been demonstrated that these compounds show a good reactivity as 1,3-dipolarophiles with respect to several diazoalkanes.[1] The cycloaddition products thus obtained underwent different transformations, partially due to the intrinsic lability of the condensed isothiazole-1,1-dioxide ring. For these reasons it appeared of interest to investigate the reactions with other 1,3-dipoles, both to better understand the regioselectivity of the cycloaddition reactions and to bring about the synthesis of new bicyclic heterocycles, containing the isothiazole moiety. It could be expected that new heterocyclic synthesis could be found as a consequence of transformation reactions of the cycloadducts.
This paper describes the reaction of azomethine ylide dipoles as oxazolones and münchnones both symmetrically and unsymmetrically substituted and a study of the thermal behaviour of the cycloadducts which opens a new route to the preparation of substituted pyrroles.

RESULTS

Cycloaddition reaction of isothiazole-1,1-dioxide 3 with oxazolones ***2a-e***. The cycloaddition reaction was performed by generating the oxazolone reactant **2a-e** *in situ* by heating the appropriate N-aroyl-C-aryl-glycines **1a-e** with acetic anhydride in refluxing toluene according to a well established procedure.[3] To the solution of compounds **2a-e** the isothiazole 1,1-dioxide substrate **3** was added and the reaction continued until completion (scheme 1). A mixture of the tautomeric cycloadducts **4**, as the main product, and **5**, was obtained in all cases except starting from **1e** which produced only **4e**. Compounds **4** and **5** were isolated and separated by column chromatography. The structure of cycloadducts **4** and **5** was confirmed by ^{1}H-NMR spectra showing in the case of compounds **4** two singlets at about δ 5.0 (associated with H-6*a*) and at about δ 6.3 (associated with H-4). These shift values are in good agreement with literature data of other condensed dihydroisothiazole-dioxides.[4] In the spectra of compounds **5** two doublets are present at about δ 4.4 (H-6*a*) and δ 5.4 (H-6). The

coupling constant of 5.5 Hz strongly supports the *trans* configuration. [5] The two tautomeric products are relatively stable compounds and no interconversion was observed at room temperature (above this temperature extensive degradation occurs), whereas compounds **5** were nearly completely converted into the corresponding tautomers on heating at the melting point for short times. Starting from the unsymmetric dipoles **2b-e** the problem of the unequivocal establishment of the structure of products is essential to ascertain the regiochemistry of the cycloaddition. This problem was solved by NMR utilizing COSY and NOESY or NOEDIFF. experiments. The latter evidenced a correlation between H-6a and the o,o'-hydrogens of the Ar^2 substituent in compounds **4b-e** which were correlated thermally (see above) to the corresponding **5b-d**.

Scheme 1



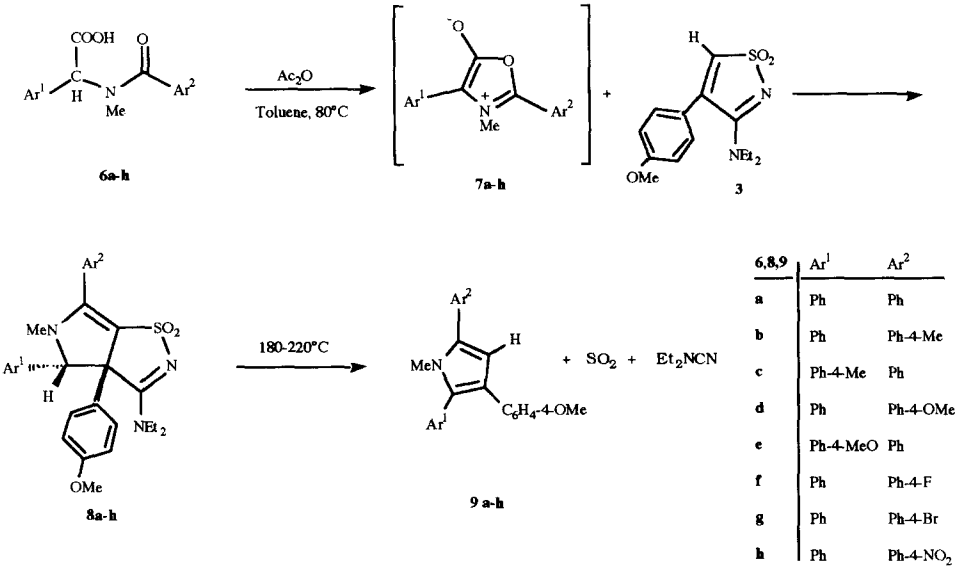
4	Ar^1	Ar^2
a	Ph	Ph
b	Ph-4-Cl	Ph
c	Ph	Ph-4-Cl
d	Ph-4-Me	Ph
e	Ph	Ph-4-Me

5	Ar^1	Ar^2
a	Ph	Ph
b	Ph-4-Cl	Ph
c	Ph	Ph-4-Cl
d	Ph-4-Me	Ph

Cycloaddition reaction of isothiazole-1,1-dioxide 3 with münchnones 7a-h. The cycloaddition reaction of **3** with münchnones **7a-h** prepared *in situ* from the corresponding N-methyl-N-aroyl-C-arylglycines **6a-h** was performed in the same way as the reaction with oxazolones. A single product was formed in the reaction mixtures and isolated in the usual manner (scheme 2). Yields were generally high and no by-products could be detected. The structure of compounds **8a-h** was established by ^{1}H-NMR spectra. A typical singlet was associated with H-4 (ca. δ 4.9) which shows an evident n.O.e. effect with the hydrogens of the 4-MeO-phenyl group linked to C-3a clearly supporting the assigned configuration. The structure of compounds **8d, e, h** was confirmed through an exact assignment of the position of Ar^1 and Ar^2 by NOESY and/or NOEDIFF. experiments showing in most cases a clear relationship between H-4 and the o,o'-hydrogens of the aryl group

linked to the same carbon. The structure to the other cycloadducts **8b**, **c**, **f**, **g** was assigned by analogy and this conclusion was confirmed by safe determination of the structure of their transformation product (see later).

Scheme 2

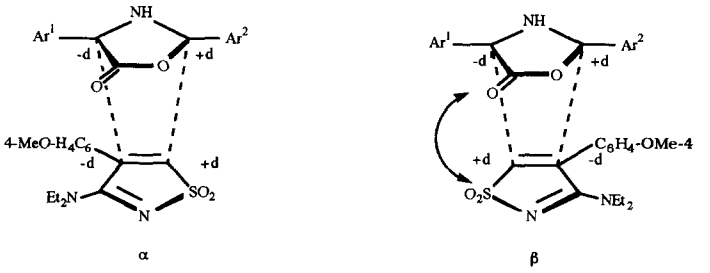


6,8,9	Ar^1	Ar^2
a	Ph	Ph
b	Ph	Ph-4-Me
c	Ph-4-Me	Ph
d	Ph	Ph-4-OMe
e	Ph-4-MeO	Ph
f	Ph	Ph-4-F
g	Ph	Ph-4-Br
h	Ph	Ph-4-NO_2

DISCUSSION

As shown above compound **3** easily underwent cycloaddition reactions both with oxazolones and with münchnones. The latter were qualitatively more reactive affording the final products in shorter times and gave better yields. In both cases the reaction was found to be completely regioselective, at least to the detection limits (^{1}H-NMR and T.L.C. on the crude reaction mixture). Many examples of cycloaddition reactions of oxazolones and münchnones to electron-deficient carbon-carbon double bonds have been reported. However a clear picture of this puzzling reaction is still lacking. Several cases are known in which the effect of the substituents on the dipole is determining for the regiochemistry together with the charge distribution in the dipolarophile,[6] but an orienting effect of the heterocycle substantially independent from substituents has been also observed.[7] In the present case the dipolarophile shows a charge distribution according to which the more electrophilic center is located on C-5.[8] Accordingly, a charge-controlled reaction would produce a regiochemistry opposite to that observed. This points out that interactions between the oxazolone or münchnone *ring system* and the substrate are overwhelming over simple charge effects. These interactions are to be seen mainly in the repulsive effect of sthe carbonyl group of the dipole and the SO_2 group of the substrate **2** (scheme 3) which unfavours the transition tate β.

Scheme 3

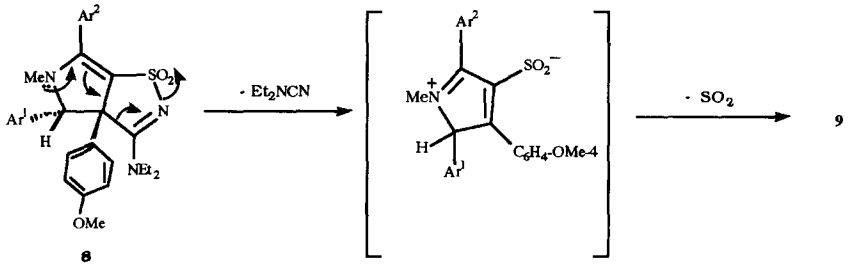


α β

Thermal behaviour. Compounds **8a-h** were stable at room temperature both in substance and in solution but quickly underwent decomposition when heated at their melting point or slightly above (180-220°C). The corresponding 1-methyl-2,3,5-triarylpyrroles **9a-h** were produced by elimination of SO_2 and N,N-diethylcyanamide (scheme 2).

The structure of compounds **9a-h** was confirmed beyond doubt by ^{1}H-NMR results. NOEDIFF. spectroscopy experiments evidenced in all cases the spatial interaction between H-4 and o,o'-hydrogens of the rings on C-3 and C-5 allowing to assign the correct structure. This reaction which did not require an added catalyst occurred rapidly. Cycloadducts **4** and **5** were practically stable at their melting point, the only reaction observed being the tautomerization of **5** into **4**. At higher temperatures extensive decomposition occurred giving untractable tars. The different behaviour of compounds **8** with respect to the cycloadducts **4** and **5** is fairly explained taking into account their stereochemistry and the mechanism of the reaction. Compounds **8** are characterized by a nearly planar ring which is strained by the presence of a trigonal bridge carbon. In **4** and **5** the heterocyclic ring forms a normal dihedral angle of about 100° and the whole system is practically unstrained. This is confirmed by molecular models. This steric difference is further enhanced by the fact that the imine structure of **4** and **5** must be regarded as associated with a stronger bond energy than the enamine group in compounds **8**. Accordingly, compounds **4** and **5** should be regarded as more stable than compounds **8**. For compounds **8** the transformation into pyrroles can be explained by the mechanism depicted in scheme 4 according to which the elimination of the cyanamide moiety is assisted by the pyrroline N-atom conjugated with the carbon-carbon double bond. A betaine intermediate is so formed which affords the final product through H-transfer and SO_2 elimination, which latter step is already known for heterocyclic sulfinic acids. [5]

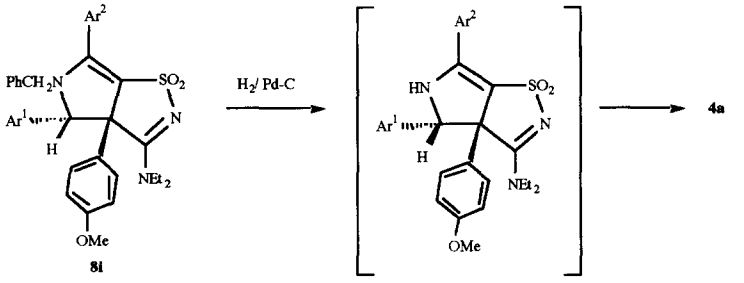
Scheme 4



8

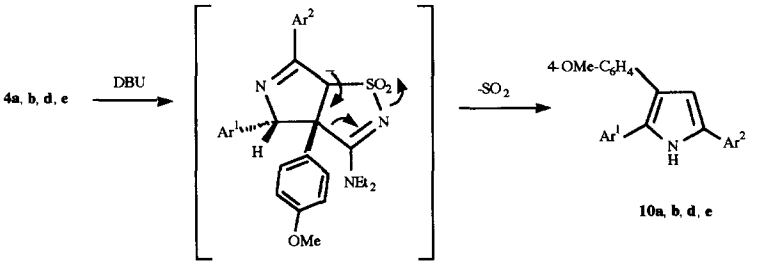
In compounds **4/5** the N-atom assistance would occur only after isomerization of the Δ^1-pyrroline structure to the Δ^2 one. Though possible in principle, this should be quite difficult due to the enhanced ring strain associated with this process, as stated above. This was experimentally confirmed by preparing the N-benzyl derivative **8i** which was reacted with H_2 and Pd/C (scheme 5). Compound **4a** was obtained through debenzylation and spontaneous tautomerization to the most stable product.

Scheme 5



Compounds **4a**, **b**, **d**, **e** were transformed into the corresponding 2,3,5-triarylpyrroles **10a**, **b**, **d**, **e** (scheme 6) in very low yield (less than 20%) by heating in the presence of a basic catalyst (DBU).

Scheme 6



10	Ar^1	Ar^2
a	Ph	Ph
b	Ph-4-Cl	Ph
d	Ph-4-Me	Ph
e	Ph	Ph-4-Me

The deprotonation of C-6a is involved because the stereochemistry of the ring does not allow a β-elimination mechanism. This occurs only by using a strong base under severe conditions, favouring detrimental side reactions. Thus, compounds of the general formula **10** may be better obtained by using N-benzylmünchnones and deprotecting the final pyrroles.

In conclusion the cycloaddition reaction of münchnones to isothiazole 1,1-dioxides followed by thermal transformation represents a useful contribution to the synthesis of 1-alkyl and 1H-2,3,5-triarylpyrroles.

Acknowledgements. This research was supported (in part) by M.U.R.S.T.

EXPERIMENTAL

Melting points were determined using a Büchi 510 (capillary) or a Electrothermal 9100 apparatus. ^{1}H-NMR spectra (ppm, tetramethylsilane as internal standard, $CDCl_3$ or DMSO-d_6 as solvent) were obtained with a Bruker AC 200, Bruker AC 300 and a Varian Gemini 200 instruments. Chemical shifts (δ) are given in ppm and the coupling constants (J) are given in Hz. TLC: ready-to-use silica gel plates. Column chromatography: silica gel [Kieselgel 60-70 230 ASTM (Merck)] with the eluant indicated. Mass spectra were obtained by an electron impact ionization technique at 70 eV from a Finningan INCOS 50 instrument using the direct exposure probe (DEP).

Materials. **3**[2], **1a**[9], **b**[10], **c**[3b], **e**[11] and **6a**[12], **b**[13], **d**[14], **e**[14], **h**[14] have already been described. **1d** and **6c**, **f**, **g** were prepared by conventional procedure from the corresponding C-arylglycines or C-aryl-N-methylglycine hydrochlorides and aroyl chloride:

N-Benzoyl-C-(4-methylphenyl)-glycine (1d): from (4-methylphenyl)-glycine hydrochloride and benzoyl chloride. M.p. 169-170°C.

N-Benzoyl-N-methyl-C-(4-methylphenyl)-glycine (6c): from N-methyl-C-(4-methylphenyl)-glycine hydrochloride and benzoyl chloride. M.p. 107°C.

N-(4-Fluorobenzoyl)-N-methyl-C-phenylglycine (6f): from N-methyl-C-phenylglycine hydrochloride and 4-fluorobenzoyl chloride. M.p. 140°C.

N-(4-Bromobenzoyl)-N-methyl-C-phenylglycine (6g): from N-methyl-C-phenylglycine hydrochloride and 4-bromobenzoyl chloride. Oil.

N-Benzoyl-N-benzyl-C-phenylglycine (6i): from N-benzyl-C-phenylglycine[15] and benzoyl chloride. Oil.

General Procedure for the Cycloaddition Reaction of Isothiazole 1,1-dioxide 3 with 1a-e. In a typical experiment the N-aroylaminoacid **1** (3 mmol) was suspended under nitrogen in anhydrous toluene (10 ml) containing acetic anhydride (0.48 ml, 5 mmol) and the mixture was stirred at room temperature for about 12-18 h. The mixture was then refluxed and when it turned yellow and clear, solid **3** was added in one portion (2 mmol). The reaction mixture was kept stirring, under nitrogen atmosphere, at 90°C until disappearance of the reactants (T.L.C. cyclohexane/ethyl acetate 3/2, 2-12 h). By adding diisopropyl ether (10 ml) to the cooled mixture, **4** precipitated as white solid and was filtered off. The filtrate was evaporated under reduced pressure and cromatographed on silica gel affording further amount of **4** and, when present, **5**. All products **4** and **5** were recrystallized from dichloromethane /diisopropyl ether.

3-Diethylamino-4,6-diphenyl-3a,4-dihydro-3a-(4-methoxyphenyl)-6aH-pyrrolo[3,4-d]isothiazole 1,1-dioxide (4a): Yield: 60%. M.p.: 213°C dec. Calcd.: C 68.97% H 5.99% N 8.52% Found: C 69.16% H 6.05% N

8.15%. ^{1}H-NMR: 0.40-0.55 (2t, 6H, CH_3); 2.30-2.45, 2.70-3.05 and 3.40-3.60 (3m, 4H, CH_2); 3.85 (s, 3H, OCH_3); 5.03 (s, 1H, H-6a); 6.30 (s, 1H, H-4); 7.00 (AB system, J=9 Hz, 2H, Aryl-H); 7.20-7.60 (m, 10H, Aryl-H); 7.98-8.10 (m, 2H, Aryl-H).

*3-Diethylamino-4,6-diphenyl-6,6a-dihydro-3a-(4-methoxyphenyl)-6aH-pyrrolo[3,4-d]isothiazole 1,1-dioxide (**5a**):* Yield: 10%. Only impure samples containing small amounts of **4a** were obtained. ^{1}H-NMR: 0.35 (t, 3H, CH_3); 1.20 (t, 3H, CH_3); 1.88-2.10, 2.50-2.70, 3.202-3.50 and 3.55-3.75 (4m, 4H, CH_2); 3.85 (s, 3H, OCH_3); 4.38 (d, J=5.5 Hz, 1H, H-6a); 5.47 (d, J=5.5 Hz, 1H, H-6); 6.90-7.70 (m, 14H, Aryl-H).

*4-(4-Chlorophenyl)-3-diethylamino-3a,4-dihydro-3a-(4-methoxyphenyl)-6-phenyl-6aH-pyrrolo[3,4-d]isothiazole 1,1-dioxide (**4b**):* Yield: 65%. M.p.: 260°C dec. ^{1}H-NMR: 0.50 (t, J=7 Hz, 3H, CH_3); 0.60 (t, J=7 Hz, 3H, CH_3); 2.30-2.45, 2.80-3.00 and 3.40-3.60 (3m, 4H, CH_2); 3.85 (s, 3H, OCH_3); 5.00 (s, 1H, H-6a); 6.25 (s, 1H, H-4); 6.90-7.00 (m, 2H, Aryl-H); 7.20-7.50 (m, 9H, Aryl-H); 7.98-8.10 (m, 2H, Aryl-H). *m/z* (M^+ 522, 100%).

*4-(4-Chlorophenyl)-3-diethylamino-6,6a-dihydro-3a-(4-methoxyphenyl)-6-phenyl-6aH-pyrrolo[3,4-d]isothiazole 1,1-dioxide (**5b**):* **5b** was obtained always in mixture with **4b** and any effort to purify it failed.

*6-(4-Chlorophenyl)-3-diethylamino-3a,4-dihydro-3a-(4-methoxyphenyl)-4-phenyl-6aH-pyrrolo[3,4-d]isothiazole 1,1-dioxide (**4c**):* Yield: 74%. M.p.: 185°C. ^{1}H-NMR: 0.40-0.60 (m, 6H, CH_3); 2.30-2.45, 2.78-3.10 and 3.40-3.60 (3m, 4H, CH_2); 3.85 (s, 3H, OCH_3); 5.00 (s, 1H, H-6a); 6.25 (s, 1H, H-4); 7.00 (AB system, J=9 Hz, 2H, Aryl-H); 7.20-7.50 (m, 9H, Aryl-H); 7.90-8.00 (m, 2H, Aryl-H). *m/z* (M^+ 522, 100%).

*6-(4-Chlorophenyl)-3-diethylamino-6,6a-dihydro-3a-(4-methoxyphenyl)-4-phenyl-6aH-pyrrolo[3,4-d]isothiazole 1,1-dioxide (**5c**):* Yield: 13%. M.p.: 228°C. Calcd.: C 64.42% H 5.41% N 8.05% Found: C 64.10% H 5.71% N 7.86%.^{1}H-NMR: 0.40 (t, J=7 Hz, 3H, CH_3); 1.10-1.30 (m, 3H, CH_3); 1.92-2.12, 2.50-2.70, 3.28-3.48 and 3.50-3.75 (4m, 4H, CH_2); 3.85 (s, 3H, OCH_3); 4.35 (d, J=5.5 Hz, 1H, H-6a); 5.40 (d, J=5.5 Hz, 1H, H-6); 6.90-7.60 (m, 13H, Aryl-H).

*3-Diethylamino-3a,4-dihydro-3a-(4-methoxyphenyl)-4-(4-methylphenyl)-6-phenyl-6aH-pyrrolo[3,4-d]isothiazole 1,1-dioxide (**4d**):* Yield: 70%. M.p.: 243.5°C dec. Calcd.: C 69.44% H 6.23% N 8.34% Found: C 69.49% H 5.87% N 7.99%.^{1}H-NMR: 0.40-0.55 (2t, 6H, CH_3); 2.33 (s, 3H, CH_3); 2.30-2.50, 2.75-3.05 and 3.40-3.60 (3m, 4H, CH_2); 3.85 (s, 3H, OCH_3); 5.00 (s, 1H, H-6a); 6.25 (s, 1H, H-4); 6.98 (AB system, J=8 Hz, 2H, Aryl-H); 7.12 (AB system, J=8 Hz, 2H, Aryl-H); 7.20-7.50 (m, 7H, Aryl-H); 8.00-8.10 (m, 2H, Aryl-H).

*3-Diethylamino-6,6a-dihydro-3a-(4-methoxyphenyl)-4-(4-methylphenyl)-6-phenyl-6aH-pyrrolo[3,4-d]isothiazole 1,1-dioxide (**5d**):* Yield: 5%. M.p.: 224°C dec. Calcd.: C 69.44% H 6.23% N 8.34% Found: C 69.09% H 6.07% N 8.25%.^{1}H-NMR: 0.40 (t, J=7 Hz, 3H, CH_3); 1.2 (t, J=7 Hz, 3H, CH_3); 1.98-2.20, 2.55-2.70, 3.25-3.45 and 3.55-3.95 (4m, 4H, CH_2); 2.38 (s, 3H, CH_3); 3.85 (s, 3H, OCH_3); 4.40 (d, J=5.5 Hz, 1H, H-

6a); 5.45 (d, J=5.5 Hz, 1H, H-6); 6.90-7.10 (m, 4H, Aryl-H); 7.20-7.45 (m, 7H, Aryl-H); 7.60 (AB system, J=7 Hz, 2H, Aryl-H).

*3-Diethylamino-3a,4-dihydro-3a-(4-methoxyphenyl)-6-(4-methylphenyl)-4-phenyl-6aH-pyrrolo[3,4-d]isothiazole 1,1-dioxide (**4e**):* Yield: 70%. M.p.: 265°C dec. Calcd.: C 69.44% H 6.23% N 8.34% Found: C 69.83% H 6.60% N 8.00%. ^{1}H-NMR: 0.40-0.60 (m, 6H, CH_3); 2.40 (s, 3H, CH_3); 2.25-2.45, 2.70-3.05 and 3.40-3.60 (3m, 4H, CH_2); 3.85 (s, 3H, OCH_3); 5.03 (s, 1H, H-6a); 6.25 (s, 1H, H-4); 7.00 (AB system, J=8 Hz, 2H, Aryl-H); 7.22 (AB system, J=8 Hz, 2H, Aryl-H); 7.20-7.60 (m, 7H, Aryl-H); 7.92 (AB system, J=8 Hz, 2H, Aryl-H).

*General Procedure for the Cycloaddition Reaction of Isothiazole 1,1-dioxide **3** with **6a-i**.* To a stirred suspension of the N-aroyl-N-methyl-C-arylglycine (3 mmol) in anhydrous toluene (10 ml), acetic anhydride (0.48 ml, 5 mmol) was added dropwise under nitrogen atmosphere. When the mixture turned yellow, solid isothiazole **3** (2 mmol) was added in one portion. The reaction mixture was then refluxed until the reactants disappeared (T.L.C. cyclohexane/ethyl acetate 3/2, 15-120 min). By adding diisopropyl ether (10 ml), **8** crystallized from the crude cooled mixture and was filtered off.

*3-Diethylamino-4,6-diphenyl-3a-(4-methoxyphenyl)-5-methyl-pyrrolo[3,4-d]isothiazole 1,1-dioxide (**8a**):* Yield: 90%. M.p.: 217°C dec. Calcd.: C 69.37% H 6.18% N 8.37% Found: C 69.00% H 6.15% N 7.99%. ^{1}H-NMR: 0.40 (t, J=7 Hz, 3H, CH_3); 0.50 (t, J=7 Hz, 3H, CH_3); 2.30-2.50, 2.70-2.80 and 3.50-3.70 (3m, 4H, CH_2); 2.90 (s, 3H, CH_3); 3.85 (s, 3H, OCH_3); 5.00 (s, 1H, H-4); 7.00 (AB system, J=9 Hz, 2H, Aryl-H); 7.30-7.50 (m, 12H, Aryl-H).

*3-Diethylamino-3a-(4-methoxyphenyl)-5-methyl-4-(4-methylphenyl)-6-phenyl-pyrrolo[3,4-d]isothiazole 1,1-dioxide (**8b**):* Yield: 91%. M.p.: 217.5°C dec. Calcd.: C 69.88% H 6.45% N 8.15% Found: C 69.82% H 6.39% N 8.42%. ^{1}H-NMR: 0.40 (t, J=7 Hz, 3H, CH_3); 0.50 (t, J=7 Hz, 3H, CH_3); 2.20-2.40, 2.70-2.90 and 3.50-3.70 (3m, 4H, CH_2); 2.35 (s, 3H, CH_3); 2.90 (s, 3H, CH_3); 3.85 (s, 3H, OCH_3); 4.90 (s, 1H, H-4); 7.00 (AB system, J=9 Hz, 2H, Aryl-H); 7.20 (AB system, J=9 Hz, 2H, Aryl-H); 7.40-7.60 (m, 9H, Aryl-H).

*3-Diethylamino-3a-(4-methoxyphenyl)-5-methyl-6-(4-methylphenyl)-4-phenyl-pyrrolo[3,4-d]isothiazole 1,1-dioxide (**8c**):* Yield: 90%. M.p.: 191°C. Calcd.: C 69.88% H 6.45% N 8.15% Found: C 69.58% H 6.30% N 8.45%. ^{1}H-NMR: 0.40-0.60 (m, 6H, CH_3); 2.30-2.50, 2.70-2.90 and 3.50-3.70 (3m, 4H, CH_2); 2.40 (s, 3H, CH_3); 2.90 (s, 3H, CH_3); 3.85 (s, 3H, OCH_3); 5.00 (s, 1H, H-4); 7.00 (AB system, J=9 Hz, 2H, Aryl-H); 7.20 (AB system, J=8 Hz, 2H, Aryl-H); 7.30-7.50 (m, 9H, Aryl-H).

*3-Diethylamino-3a,6-di-(4-methoxyphenyl)-5-methyl-4-phenyl-pyrrolo[3,4-d]isothiazole 1,1-dioxide (**8d**):* Yield: 75%. M.p.: 170°C dec. Calcd.: C 67.78% H 6.26% N 7.90% Found: C 67.58% H 5.95% N 7.60%. ^{1}H-NMR: 0.39-0.53 (m, 6H, CH_3); 2.30-2.50, 2.70-2.90 and 3.50-3.70 (3m, 4H, CH_2); 2.96 (s, 3H, CH_3); 3.82 and 3.83 (2s, 6H, OCH_3); 4.93 (s, 1H, H-4); 6.93 (AB system, J=9 Hz, 2H, Aryl-H); 6.98 (AB system, J=9 Hz, 2H, Aryl-H); 7.30-7.55 (m, 9H, Aryl-H). *m/z* 531 (M^+, 100%).

*3-Diethylamino-3a,4-di-(4-methoxyphenyl)-5-methyl-6-phenyl-pyrrolo[3,4-d]isothiazole 1,1-dioxide (**8e**):* Yield: 90%. M.p.: 178°C. Calcd.: C 67.78% H 6.26% N 7.90% Found: C 68.09% H 6.11% N 7.63%. ^{1}H-NMR: 0.45 (t, J=7.0 Hz, 3H, CH_3); 0.59 (t, J=7.1 Hz, 3H, CH_3); 2.30-2.50, 2.70-2.90 and 3.50-3.70 (3m, 4H, CH_2); 2.93 (s, 3H, CH_3); 3.80 and 3.83 (2s, 6H, OCH_3); 4.92 (s, 1H, H-4); 6.90 (AB system, J=8.8 Hz, 2H, Aryl-H); 6.98 (AB system, J=8.9 Hz, 2H, Aryl-H); 7.15-7.60 (m, 9H, Aryl-H). *m/z* 531 (M^+, 100%).

*3-Diethylamino-6-(4-fluorophenyl)-3a-(4-methoxyphenyl)-5-methyl-4-phenyl-pyrrolo[3,4-d]isothiazole 1,1-dioxide (**8f**):* Yield: 90%. M.p.: 216°C. ^{1}H-NMR: 0.33-0.55 (m, 6H, CH_3); 2.25-2.43, 2.65-2.85 and 3.45-3.65 (3m, 4H, CH_2); 2.90 (s, 3H, CH_3); 3.80 (s, 3H, OCH_3); 4.93 (s, 1H, H-4); 6.95 (AB system, J=9 Hz, 2H, Aryl-H); 7.00-7.12 (m, 2H, Aryl-H); 7.31-7.52 (m, 9H, Aryl-H). *m/z* 519 (M^+, 100%).

*6-(4-Bromophenyl)-3-diethylamino-3a-(4-methoxyphenyl)-5-methyl-4-phenyl-pyrrolo[3,4-d]isothiazole 1,1-dioxide (**8g**):* Yield: 63%. M.p.: 199-200°C. ^{1}H-NMR: 0.43 (t, J=7.0 Hz, 3H, CH_3); 0.50 (t, J=7.2 Hz, 3H, CH_3); 2.30-2.41, 2.73-2.87 and 3.55-3.75 (3m, 4H, CH_2); 2.92 (s, 3H, CH_3); 3.83 (s, 3H, OCH_3); 4.96 (s, 1H, H-4); 7.00 (AB system, J=8.4 Hz, 2H, Aryl-H); 7.34-7.60 (m, 11H, Aryl-H). *m/z* 580 (M^+, 100%).

*3-Diethylamino-3a-(4-methoxyphenyl)-5-methyl-6-(4-nitrophenyl)-4-phenyl-pyrrolo[3,4-d]isothiazole 1,1-dioxide (**8h**):* Yield: 70%. M.p.: 201°C. ^{1}H-NMR: 0.44 (t, J=7.0 Hz, 3H, CH_3); 0.53 (t, J=7.1 Hz, 3H, CH_3); 2.30-2.41, 2.73-2.87 and 3.55-3.62 (3m, 4H, CH_2); 2.95 (s, 3H, CH_3); 3.85 (s, 3H, OCH_3); 5.00 (s, 1H, H-4); 7.00 (AB system, J=9 Hz, 2H, Aryl-H); 7.30-7.50 (m, 7H, Aryl-H); 7.69 (AB system, J=9 Hz, 2H, Aryl-H); 8.27 (AB system, J=9 Hz, 2H, Aryl-H). *m/z* 481 (M^+-SO_2).

*5-Benzyl-3-diethylamino-4,6-diphenyl-3a-(4-methoxyphenyl)-pyrrolo[3,4-d]isothiazole 1,1-dioxide (**8i**):* Yield: 70%. M.p.: 263.5°C. ^{1}H-NMR: 0.23 (t, J=7 Hz, 3H, CH_3); 0.46 (t, J=7 Hz, 3H, CH_3); 2.15-2.26, 2.57-2.73 and 3.49-3.59 (3m, 4H, CH_2); 3.78 (s, 3H, OCH_3); 3.86 (AB system, J=14.6 Hz, 1H, CH_2Ph); 4.63 (AB system, J=14.6 Hz, 1H, CH_2Ph); 4.97 (s, 1H, H-4); 6.71 (AB system, J=8.8 Hz, 2H, Aryl-H); 6.97 (AB system, J=8.8 Hz, 2H, Aryl-H); 7.02-7.13, 7.30-7.52 and 7.60-7.64 (3m, 15H, Aryl-H). *m/z* 577 (M^+, 100%).

*General Procedure for Pyrolysis of the Cycloadducts **8a-h**.* The cycloadducts **8** (500 mg) were heated at their melting points and, when completely transformed, the residue was chromatographed on silica gel (petroleum ether/diethyl ether 1:0 to 0:1) affording **9a-h** which were then crystallized from dichloromethane /diisopropyl ether.

*2,5-Diphenyl-3-(4-methoxyphenyl)-1-methyl-pyrrole (**9a**):* Yield: 45%. M.p.: 107°C. ^{1}H-NMR: 3.50 (s, 3H, CH_3); 3.83 (s, 3H, OCH_3); 6.45 (s, 1H, H-4); 6.80 (AB system, J=9 Hz, 2H, Aryl-H); 7.15 (AB system, J=9 Hz, 2H, Aryl-H); 7.30-7.55 (m, 10H, Aryl-H). *m/z* 339 (M^+, 100%).

*3-(4-Methoxyphenyl)-1-methyl-2-(4-methylphenyl)-5-phenyl-pyrrole (**9b**):* Yield: 68%. M.p.: 111°C. Calcd.:

C 84.96% H 6.56% N 3.96% Found:C 84.66% H 6.90% N 4.16%. ^{1}H-NMR: 2.45 (s, 3H, CH_3); 3.50 (s, 3H, CH_3); 3.78 (s, 3H, OCH_3); 6.42 (s, 1H, H-4); 6.78 (AB system, J=9 Hz, 2H, Aryl-H); 7.12 (AB system, J=9 Hz, 2H, Aryl-H); 7.28 (AB system, J=8 Hz, 2H, Aryl-H); 7.30-7.40 (m, 5H, Aryl-H); 7.45 (AB system, J=8 Hz, 2H, Aryl-H). *m/z* 353 (M^+, 100%).

*3-(4-Methoxyphenyl)-1-methyl-5-(4-methylphenyl)-2-phenyl-pyrrole (**9c**):* Yield: 84%. M.p.: 117°C. ^{1}H-NMR: 2.40 (s, 3H, CH_3); 3.50 (s, 3H, CH_3); 3.80 (s, 3H, OCH_3); 6.50 (s, 1H, H-4); 6.80 (AB system, J=9 Hz, 2H, Aryl-H); 7.20 (AB system, J=9 Hz, 2H, Aryl-H); 7.20-7.60 (m, 9H, Aryl-H). *m/z* 353 (M^+, 100%).

*3,5-Di-(4-methoxyphenyl)-1-methyl-2-phenyl-pyrrole (**9d**):* Yield: 70%. M.p.: 116°C. ^{1}H-NMR: 3.45 (s, 3H, CH_3); 3.76 and 3.86 (2s, 6H, OCH_3); 6.39 (s, 1H, H-4); 6.75 (AB system, J=8.8 Hz, 2H, Aryl-H); 7.00 (AB system, J=8.8 Hz, 2H, Aryl-H); 7.15 (AB system, J=8.8 Hz, 2H, Aryl-H); 7.45 (AB system, J=8.8 Hz, 2H, Aryl-H); 7.40-7.45 (m, 5H, Aryl-H). *m/z* 369 (M^+, 100%).

*2,3-Di-(4-methoxyphenyl)-1-methyl-5-phenyl-pyrrole (**9e**):* Yield: 64%. M.p.: 123.5°C. ^{1}H-NMR: 3.46 (s, 3H, CH_3); 3.77 and 3.85 (2s, 6H, OCH_3); 6.44 (s, 1H, H-4); 6.75 (AB system, J=8.7 Hz, 2H, Aryl-H); 6.94 (AB system, J=8.7 Hz, 2H, Aryl-H); 7.15 (AB system, J=8.7 Hz, 2H, Aryl-H); 7.30 (AB system, J=8.7 Hz, 2H, Aryl-H); 7.30-7.53 (m, 5H, Aryl-H). *m/z* 369 (M^+, 100%).

*5-(4-Fluorophenyl)-3-(4-methoxyphenyl)-1-methyl-2-phenyl-pyrrole (**9f**):* Yield: 25%. M.p.: in spite of the many attempts to crystallize it, it was not possible to obtain a sample pure enough to have a correct melting point. ^{1}H-NMR: 3.45 (s, 3H, CH_3); 3.78 (s, 3H, OCH_3); 6.40 (s, 1H, H-4); 6.75 (AB system, J=8.5 Hz, 2H, Aryl-H); 7.12 (AB system, J=9 Hz, 2H, Aryl-H); 7.10-7.20 (m, 4H, Aryl-H); 7.30-7.40 (m, 5H, Aryl-H); 7.40-7.50 (m, 2H, Aryl-H). *m/z* 357 (M^+, 100%).

*5-(4-Bromophenyl)-3-(4-methoxyphenyl)-1-methyl-2-phenyl-pyrrole (**9g**):* Yield: 73%. M.p.: 107°C. ^{1}H-NMR: 3.50 (s, 3H, CH_3); 3.80 (s, 3H, OCH_3); 6.45 (s, 1H, H-4); 6.75 (AB system, J=8 Hz, 2H, Aryl-H); 7.15 (AB system, J=8 Hz, 2H, Aryl-H); 7.30-7.45 (m, 7H, Aryl-H); 7.60 (AB system, J=8 Hz, 2H, Aryl-H). *m/z* 418 (M^+, 100%).

*3-(4-Methoxyphenyl)-1-methyl--5-(4-nitrophenyl)-2-phenyl-pyrrole (**9h**):* Yield: 75%. M.p.: 195°C. ^{1}H-NMR: 3.54 (s, 3H, CH_3); 3.77 (s, 3H, OCH_3); 6.62 (s, 1H, H-4); 6.77 (AB system, J=8.9 Hz, 2H, Aryl-H); 7.13 (AB system, J=8.9 Hz, 2H, Aryl-H); 7.34-7.44 (m, 5H, Aryl-H); 7.66 (AB system, J=8.9 Hz, 2H, Aryl-H); 8.30 (AB system, J=8.9 Hz, 2H, Aryl-H). *m/z* 384 (M^+, 100%).

*General Procedure for Pyrolysis of the Cycloadducts **4a, b, d, e**:* Cyloadducts **4a**, **b**, **d**, **e**, were heated with a catalytic amount of DBU at their melting points and the reaction checked by T.L.C. (cyclohexane/ethyl acetate 2/3). Pyrroles **10a**, **b**, **d**, **e** were obtained in low yield (less than 20 % on the crude mixture) together with decomposition products. Only **10a** was crystallized; **10b**, **d**, **e** were obtained not pure enough to have a correct melting point and were identified by ^{1}H-NMR.

*2,5-Diphenyl-3-(4-methoxyphenyl)-pyrrole (**10a**):* M.p.: 116°C (lit. 116-117°C)[16]. ^{1}H-NMR: 3.80 (s, 3H, OCH_3); 6.68 (d, J=2.8 Hz, 1H, H-4); 6.86 (AB system, J=8.7 Hz, 2H, Aryl-H); 7.20-7.60 (m, 12H, Aryl-H); 8.4 (bs, exch.D_2O, 1H, NH).

*2-(4-Chlorophenyl)-3-(4-methoxyphenyl)-5-phenyl-pyrrole (**10b**):* ^{1}H-NMR: 3.70 (s, 3H, OCH_3); 6.65 (d, J=2.9 Hz, 1H, H-4); 6.85 (AB system, J=8.5 Hz, 2H, Aryl-H); 6.95-7.42 (m, 9H, Aryl-H); 7.47 (AB system, J=8.5 Hz, 2H, Aryl-H); 8.45 (bs, exch.D_2O, 1H, NH).

*3-(4-Methoxyphenyl)-2-(4-methylphenyl)-5-phenyl-pyrrole (**10d**):* ^{1}H-NMR: 2.40 (s, 3H, CH_3); 3.80 (s, 3H, OCH_3); 6.06 (d, J=2.2 Hz, 1H, H-4); 6.85 (AB system, J=9 Hz, 2H, Aryl-H); 7.20-7.50 (m, 11H, Aryl-H); 8.8 (bs, exch.D_2O, 1H, NH).

*3-(4-Methoxyphenyl)-5-(4-methylphenyl)-2-phenyl-pyrrole (**10e**):* ^{1}H-NMR: 2.35 (s, 3H, CH_3); 3.85 (s, 3H, OCH_3); 6.68 (d, J=2 Hz, 1H, H-4); 6.88 (AB system, J=7 Hz, 2H, Aryl-H); 7.15 (AB system, J=7 Hz, 2H, Aryl-H); 7.25-7.40 (m, 7H, Aryl-H); 7.42 (AB system, J=7 Hz, 2H, Aryl-H); 7.55 (AB system, J=7 Hz, 2H, Aryl-H); 8.4 (bs, exch.D_2O, 1H, NH).

*Hydrogenolysis of **8i**:* A mixture of **8i** (160 mg, 0.3 mmol) and 10% Pd/C (150 mg) in dioxane (20cc), was hydrogenated at atmospheric pressure. The reaction was monitored by TLC (cyclohexane/ethyl acetate 2/3). The mixture was filtered and the clear solution evaporated at reduced pressure affording a white solid which was then crystallized with dichloromethane/diisopropyl ether yelding as the main product **4a** as the main product.

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