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BENZOXADIAZOCINES, BENZOTHIADIAZOCINES AND BENZOTRIAZOCINES—II

THE SYNTHESIS OF 3,4,5,6-TETRAHYDRO- AND 1,2,3,4,5,6-HEXA-HYDRO-1,3,6-BENZOTRIAZOCINES

FERENC BERTHA, GYULA HORNYÁK* and KÁROLY ZAUER
Research Group for Alkaloid Chemistry of the Hungarian Academy of Sciences, Budapest, Hungary

and

KÁROLY LEMPERT*
Department of Organic Chemistry, Technical University, H-1521, Budapest, Hungary

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Abstract—The general method devised by two of the authors for the synthesis of derivatives of the novel 3,1,6-benzoxadiazocine, 3,1,6-benzothiadiazocine and 1,3,6-benzotriazocine ring systems has been applied to the preparation of a series of 3,4,5,6-tetrahydro- and 1,2,3,4,5,6-hexahydro-1,3,6-benzotriazocines for pharmacological screening.

In Part I† of the present series a general method was described for the synthesis of derivatives of the novel 3,1,6-benzoxadiazocine, 3,1,6-benzothiadiazocine and 1,3,6-benzotriazocine ring systems. We how report on the application of this method to the synthesis of a series of 3,4,5,6-tetrahydro- (**6**) and 1,2,3,4,5,6-hexahydro-1,3,6-benzotriazocines (**7**), all having, for the reasons explained in Part I, a tosyl group attached to N(6). The key-intermediates of the syntheses were the type **5** diamines most of which, because of their sensitivity to air, were not isolated but immediately condensed with suitable C_1-components to obtain the desired compounds **6** and **7**, respectively. Ortho esters, cyanogen bromide, carbonyl diimidazole, thiocarbonyl diimidazole and diethyl carbonate were used as C_1 components. In one case, as clearly shown by the IR and ^{1}H NMR spectra of the product, the non-heterocyclic product **8** was obtained rather than its expected heterocyclic isomer **7** (R = Me, V and W = Me and OEt, Y = MeO). The method of synthesis of the benzotriazocine derivatives is outlined in Chart 1 (Experimental).

The compounds **6** and **7** have been screened for pharmacological activities by Dr. L. Petőcz. All benzotriazocine derivatives described are of low toxicity. Especially the compounds **6** with Z = H and Me proved to be potent Tremorine antagonists and Hexobarbital potentiating agents on mice. A detailed description of the screening results will be published elsewhere.

EXPERIMENTAL

IR spectra were obtained in KBr pellets using Perkin-Elmer Model 421 and Spectromom Model 2000 (Hungarian Optical Works, Budapest) spectrometers. ^{1}H NMR spectra were obtained at 60 MHz using a Perkin–Elmer Model R-12 Spectrometer. For the ^{13}C and 100 MHz ^{1}H NMR spectra of compounds **6** (Y = MeO, R = H, Z = MeS) and **7** (Y = MeO, R = H, V + W = S), see Part III, accompanying paper.

N-(2-Bromoethyl)-4'-methoxy-2'-nitrotosylanilide (**2**, Y = MeO). Na (4.6 g; 0.2 mol) and **1**[1] (Y = MeO; 67.2 g; 0.2 mol) were successively dissolved in dry MeOH (400 ml). The soln was refluxed for 0.5 hr and concentrated to about 1/3 its original volume *in vacuo* to obtain, on cooling, the crystalline Na salt (60 g; 84%) of the starting compound which was washed with ether.

A mixture of the Na salt (60 g; 0.18 mol), 1,2-dibromoethane (16 ml; 0.2 mol) and DMF (200 ml) was stirred for 12 hr at 120° and, after being allowed to cool, poured into an aqueous (500 ml) soln of NaOH (4 g). The aqueous layer was decanted the next morning; the residue was triturated with two portions of water (200 ml, each) and the semicrystalline product was crystallized from EtOH to obtain 52.3 g (70%) of the title compound, light yellow crystals, m.p. 114–115° from EtOH. (Found: Br, 18.22; N, 7.05; S, 7.77. $C_{16}H_{17}BrN_2O_5S$ (429.3) requires: Br, 18.61; N, 6.52; S, 7.47%.)

N-(2-Bromoethyl)-2'-nitrotosylanilide (**2**, Y = H), m.p.: 90° from MeOH, was similarly obtained in 41% yield starting from **1**[2] (Y = H). (Found: C, 45.34; H, 4.00; N, 6.75. $C_{15}H_{15}BrN_2O_4S$ (399.3) requires: C, 45.12; H, 3.79; N, 7.02%.)

N-(2-Bromoethyl)-4'-methyl-2'-nitrotosylanilide (**2**, Y = Me). A mixture of **1**[3] (Y = Me; 76.6 g; 0.25 mol), K_2CO_3 (41.5 g; 0.3 mol), 1,2-dibromoethane (52 ml; 0.6 mol) and DMF (120 ml) was stirred for 24 hr on a steam bath and evaporated to dryness *in vacuo*. The residue was triturated with three portions of water (150 ml, each) and crystallized from EtOH to obtain 101.6 g (82%) of the title compound, m.p. 110–111° from EtOH. (Found: Br, 18.99; N, 6.92; S, 8.19. $C_{16}H_{17}BrN_2O_4S$ (413.3) requires; Br, 19.33; N, 6.77; S, 7.76%.)

N-(2-Aminoethyl)-4'-methoxy-2'-nitrotosylanilide (**3**, R = H, Y = MeO) and *N,N'-(aminodiethylene)bis(4'-methoxy-2'-nitrotosylanilide)* (**4**, R = H, Y = MeO). A mixture of **2** (Y = MeO) (17.2 g; 40 mmol) and EtOH (160 ml) which had been previously saturated with ammonia at 0° was heated in a sealed vessel for 5 hr at 130°. The resulting red soln was evaporated to dryness *in vacuo*. The residue was boiled for a few min with EtOAc (60 ml) and the insoluble inorganic material was filtered off from the hot soln. The filtrate was concentrated to about half its orignal volume and allowed to cool to obtain **3** (R = H, Y = MeO) (9.1 g; 62%) in form of a red crystalline powder, m.p.: 122–123° from EtOAc. (Found: C, 52.63; H, 5.50; N, 11.67; S, 8.29. $C_{16}H_{19}N_3O_5S$ (365.4) requires: C, 52.59; H, 5.24; N, 11.50; S 8.77%.)

The mother liquor of crude **3** (R = H, Y = MeO) was evaporated to dryness. The oily residue was kept for 2 days at room temp to obtain 1.9 g (13.3%) of **4** (R = H, Y = MeO), yellowish needles, m.p.: 120–121° from benzene. (Found: C, 53.85;

† *Tetrahedron* **39**, 479 (1983).

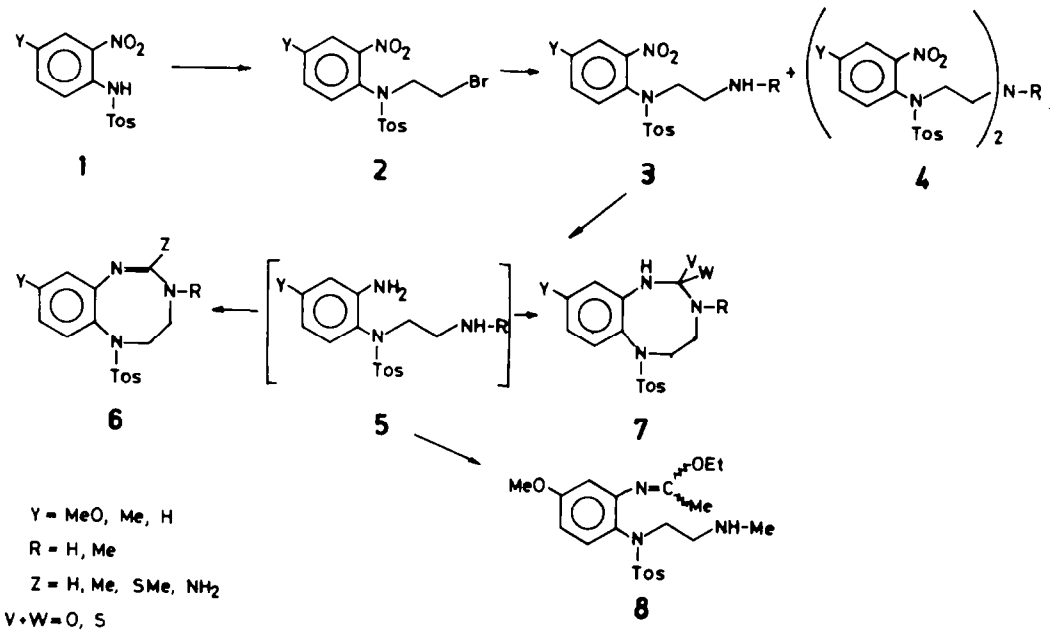

Chart 1.

H, 4.82; S, 9.16. $C_{32}H_{35}N_5O_{10}S_2$ (713.8) requires: C, 53.84; H, 4.94; S, 8.98%.)

The following compounds were similarly obtained.

(a) *N-(2-Aminoethyl)-4'-methyl-2'-nitrotosylanilide*, (3, R = H, Y = Me), 71%, red crystalline powder, m.p.: 130–131° from MeOH. (Found: C, 55.20; H, 5.56; N, 12.19; S, 9.54; $C_{16}H_{19}N_3O_4S$ (349.4) requires: C, 54.99; H, 5.47; N, 12.02; S, 9.17%), and (b) *N-(2-aminoethyl)-2'-nitrotosylanilide* (3, R = Y = H), 52%, orange crystalline powder, m.p. 152–153° from EtOAc; (Found: C, 53.99; H, 5.33; N, 12.10; $C_{15}H_{17}N_3O_4S$ (335.4) requires: C, 53.72; H, 5.11; N, 12.53%.)

4'-Methoxy-N-(2-methylaminoethyl)-2'-nitrotosylanilide (3, Y = MeO, R = Me). A mixture of 2 (Y = MeO) (32 g; 75 mmol) and ethanolic (200 ml) $MeNH_2$ (0.7 mol) was heated in a sealed vessel for 14 hr at 105° and evaporated to dryness. The residue was extracted with hot EtOAc and the hot soln was filtered and evaporated to dryness. The residue was crystallized from EtOH to obtain 11 g (39%) of the title compound, m.p. 78°. (Found: C, 53.93; H, 6.03; N, 11.01. $C_{17}H_{21}N_3O_5S$ (379.4) requires: C, 53.82; H, 5.58; N, 11.08%.)

2'-Amino-4'-methoxy-N-(2-methylaminoethyl)tosylanilide (5, R = Me, Y = MeO). Compound 3 (R = Me, Y = MeO) (15.2 g; 40 mmol) was reduced in dioxane soln (150 ml) at room temp and normal pressure in the presence of an 8% Pd–C catalyst (5 g). After uptake of the calculated amount of H_2 the catalyst was filtered off. The filtrate was evaporated to dryness and the oily residue was crystallized from a small amount of EtOH to obtain the colourless crystals (10.7 g; 76%) of the title compound, m.p. 105–107° from EtOH. (Found: C, 58.47; H, 6.76; N, 12.34; S, 8.98. $C_{17}H_{23}N_3O_3S$ (349.4) requires: C, 58.43; H, 6.63; N, 12.02; S, 9.18%.)

9-Methoxy-6-tosyl-3,4,5,6-tetrahydro-1,3,6-benzotriazocine (6, Y = MeO, R = Z = H). Compound 3 (Y = MeO, R = H) (3.6 g; 10 mmol) was reduced in anhyd dioxane soln (100 ml) at room temp and normal pressure in the presence of an 8% Pd–C catalyst (1 g). After uptake of the calculated amount of H_2 the mixture was filtered into a mixture of triethyl orthoformate (3 ml) and AcOH (30 ml). The mixture was refluxed for 4 hr and evaporated to dryness. The residue was triturated with a small amount of MeOH to obtain 2.6 g (75%) of the title compound, colourless plates, m.p. 186–187° from nitromethane. (Found: C, 59.51; H, 5.62; N, 11.87; S, 9.74. $C_{17}H_{19}N_3O_3S$ (345.4) requires: C, 59.10; H, 5.54; N, 12.16; S, 9.28%.) IR (KBr): 1620w, 1330, 1150 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.37s (3H), 3.20t + 4.27t (2H, each; J = 6 Hz); 3.79s (3H); 6.7–7.8m (8H); 8.05 bs (1H).

9-Methyl-6-tosyl-3,4,5,6-tetrahydro-1,3,6-benzotriazocine (6, Y = Me, R = Z = H) and *6-tosyl-3,4,5,6-tetrahydro-1,3,6-benzotriazocine* (6, Y = R = Z = H) were similarly obtained in 70 and 57% yields, respectively.

9-Methyl compound. Colourless plates, m.p. 194–195° from nitromethane. (Found: C, 61.73; H, 5.43; N, 12.47; S, 9.65. $C_{17}H_{19}N_3O_2S$ (329.4) requires: C, 61.98; H, 5.81; N, 12.75; S, 9.74%.) IR (KBr): 1580w, 1310, 1130 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.28s (3H); 2.33s (3H); 3.05t + 4.20t (2H, each; J = 6 Hz); 7.21 + 7.50 (4H, AB, J = 8.5 Hz), 6.85–7.75m (4H); 7.95s (1H).

9-Unsubstituted compound. Colourless crystals, m.p. 179° from EtOH or nitromethane. (Found: C, 60.88; H, 5.23; N, 13.42. $C_{16}H_{17}N_3O_2S$ (315.4) requires: C, 60.93; H, 5.43; N, 13.32%). IR (KBr): 1610w, 1320, 1130 cm^{-1}.

9-Methoxy-2-methyl-6-tosyl-3,4,5,6-tetrahydro-1,3,6-benzotriazocine (6, Y = MeO, R = H, Z = Me), colourless crystals, m.p. 226–7° from $MeNO_2$ was obtained in 86% yield as described for its 2-unsubstituted analogue (see above), replacing triethyl orthoformate in the second step by the orthoacetate. (Found: C, 60.38; H, 5.54; N, 11.74; S, 8.50. $C_{18}H_{21}N_3O_3S$ (359.4) requires: C, 60.14; H, 5.88; N, 11.69; S, 8.92%.) IR (KBr): 1620w, 1315, 1140 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.35s (3H); ~2.50s (merged with the signal of DMSO-d_5); 3.08t + 4.15t (2H, each; J = 6 Hz); 3.83s (3H); 6.55–7.8m (4H); 7.28 + 7.57 (AA'BB'; J = 8.5 Hz).

2-Methyl-6-tosyl-3,4,5,6-tetrahydro-1,3,6-benzotriazocine (6, Y = R = H, Z = Me) was obtained similarly in 67% yield, colourless crystals, m.p. 215° from nitromethane. (Found: C, 62.04; H, 5.65; N, 13.05. $C_{17}H_{19}N_3O_2S$ (329.4) requires: C, 61.98; H, 5.81; N 12.76. IR (KBr): 1620w, 1320, 1140 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.35s (3H); 2.50s (3H); 2.80–3.25m (2H); 4.20t (2H; J = 6 Hz); 7.35 + 7.62 (4H; AA'BB', J = 8.5 Hz); 7.05–7.90m.

9-Methoxy-2-methylthio-6-tosyl-3,4,5,6-tetrahydro-1,3,6-benzotriazocine (6, Y = MeO, R = H, Z = MeS). Na (76 mg; 3.3 mmol) and 7 (Y = MeO, R = H, V + W = S; see below) (1.25 g; 3.3 mmol) were successively dissolved in MeOH (25 ml). MeI (0.2 ml; 3.3 mmol) was added, and the mixture was refluxed for 3 hr and evaporated to dryness *in vacuo*. The residue was dissolved in acetone. Crystallization of the title compound (0.9 g; 70%), m.p.

159–160° from MeOH started upon addition of water. (Found: C, 55.38; H, 5.52; N, 10.70; S, 16.91. $C_{19}H_{21}N_3O_3S_2$ (391.5) requires: C, 55.22; H, 5.40; N 10.73; S, 16.38%.) IR (KBr): 1610w, 1340, 1160 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.33 s (3H); 2.66s (3H); 2.99t + 4.11t (2H, each; J = 6.5 Hz); 3.76s (3H), 6.66–7.91 m (8H).

The *hydrochloride* was obtained by refluxing the base (0.39 g) for 6 hr with a mixture of conc HCl (2 ml), water (3 ml) and dioxane (5 ml). (No evolution of methanethiol took place.) The soln was evaporated to dryness and the crystalline residue was triturated with ether to obtain 0.35 g (82%) of the hydrochloride, m.p. 204–205° dec; from nitromethane. (Found: C, 50.51; H, 5.18; Cl, 8.29; N, 9.81; S 14.48. $C_{18}H_{22}ClN_3O_3S_2$ (428.0) requires: C, 50.62; H, 5.19; Cl, 8.33; N, 9.84; S, 15.01%.) IR (KBr): 1640m, 1340, 1160 cm^{-1}.

2-*Amino*-9-*methyl*-6-*tosyl*-3,4,5,6-*tetrahydro*-1,3,6-*benzotriazocine* (6, Y = MeO, R = H, Z = NH_2), HBr *salt*. Compound 3 (Y = MeO, R = H) (3.6 g; 10 mmol) was reduced as described for the preparation of 6 (Y = MeO, R = Z = H), and the resulting mixture was filtered into a soln of cyanogen bromide (1.1 g; 10 mmol) in dioxane (20 ml). The mixture was refluxed for 3 hr and allowed to cool to obtain the long colourless thin needles (3.5 g; 79%) of the title compound, m.p. 210–211° from nitromethane. (Found: C, 46.35; H, 5.09; Br, 18.16. $C_{17}H_{21}BrN_4O_3S$ (441.4) requires: C, 46.26; H, 4.80; Br, 18.10). IR (KBr): 3400–2800 vs, 1660 vs, 1325, 1155 cm^{-1} ^1H NMR (DMSO-d_6): δ 2.33s (3H); 3.0–3.3m + 4.1–4.35m (2H, each); 3.77s (3H); 7.24 + 7.50 (4H, AB, J = 8.5 Hz); 6.75–7.75m (4H); 8.5 bs.

2-*Amino*-9-*methyl*-6-*tosyl*-3,4,5,6-*tetrahydro*-1,3,6-*benzotriazocine* (6, Y = Me, R = H, Z = NH_2), HBr *salt* was similarly obtained in 63% yield starting from 3 (Y = Me, R = H), except that the reaction with cyanogen bromide was conducted in ethanolic rather than dioxane soln. The mixture was finally evaporated to dryness *in vacuo* and the residue was triturated with acetone to obtain the colourless crystals of the title compound, m.p. 235–6° dec; from ethanol–ether. (Found: Br, 18.73; N, 13.04; S, 7.81. $C_{17}H_{21}BrN_4O_2S$ (425.4) requires: Br, 18.79; N, 13.17; S, 7.54%.) IR (KBr): 3400–2800 vs, 1650 vs, 1315, 1150 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.35s (3H); 2.40s (3H); ~3.2m + ~4.15m (2H, each); 7.23 + 7.28 (4H, AB, J = 8.5 Hz); 6.9–7.9m (4H); 8.45 bs.

2-*Amino*-9-*methoxy*-3-*methyl*-6-*tosyl*-3,4,5,6-*tetrahydro*-1,3,6-*benzotriazocine* (6, Y = MeO, R = Me, Z = NH_2), HBr *salt*. A mixture of 5 (Y = MeO, R = Me) (3.5 g; 10 mmol), cyanogen bromide (1.2 g; 12 mmol) and anhyd dioxane (20 ml) was refluxed for 4 hr and evaporated to dryness *in vacuo*. The residue was crystallized from EtOH–ether to obtain the colourless crystals (3.1 g; 68%) of the title compound, m.p. 230–232° (dec). (Found: Br, 17.34; N, 12.25; S, 7.36. $C_{18}H_{23}BrN_4O_3S$ (455.4) requires: Br, 17.54; N, 12.30; S 7.04%.) IR (KBr): 3400–2800 vs, 1650 vs, 1320, 1140 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.31s (3H); 3.25m + 4.15m (2H, each); 3.72s (3H); 3.78s (3H); 6.9–7.8m (7H); 8.6 bs.

9-*Methoxy*-6-*tosyl*-3,4,5,6-*tetrahydro*-1,3,6-*benzotriaocin*-2(1H)-*one* (7, Y = MeO, R = H, V + W = O). Compound 3 (Y = MeO, R = H) (3.6 g; 10 mmol) was reduced as described for the preparation of 6 (Y = MeO, R = Z = H), and the resulting mixture was filtered into a soln of carbonyl(diimidazole) (2.0 g; 12.5 mmol) in dry dioxane (20 ml). The mixture was refluxed for 0.5 hr and evaporated to dryness *in vacuo*. The resulting oil was dissolved in ether (50 ml) and the soln was kept overnight in a refrigerator to obtain 2.4 g (66%) of the title compound, colourless crystalline powder, m.p. 210–211° from nitromethane. (Found: C, 56.07; H, 5.45; N, 11.46; S, 8.62). $C_{17}H_{19}N_3O_4S$ (361.4) requires: C, 56.49; H, 5.29; N, 11.62; S, 8.87%. IR (KBr): 3280, 1695, 1330, 1150 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.34s (3H); 2.99t + 3.77t (2H, each; J = 6 Hz); 3.70s (3H); 6.4–7.0m (3H); 7.30 + 7.60 (AA'BB'; J = 8.5 Hz).

9-*Metoxy*-6-*tosyl*-3,4,5,6-*tetrahydro*-1,3,6-*benzotriazocine*-2(1H)-*thione* (7, Y = MeO, R = H, V + W = S) was similarly obtained using a dioxane (100 ml) soln of thiocarbonyl-(diimidazole) (2.1 g; 12.5 mmol) as the reagent in the second step. The oily crude product was dissolved in MeOH (20 ml) and kept overnight in a refrigerator to obtain the colourless needles (2.8 g; 74%) of the title compound, m.p.: 218° from nitromethane. (Found: C, 54.28; H, 4.81; N, 11.11; S, 16.70). $C_{17}H_{19}N_3O_3S_2$ (377.5) requires: C, 54.09; H, 5.07; N, 11.13; S, 16.98%.) IR (KBr): 3150, 1320, 1150 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.32s (3H); 3.19t + 4.18t (2H, each; J = 6 Hz); 3.63s (3H); 6.66–7.76m (7H); 12.7 bs (1H).

3,9-*Dimethyl* - 6 - *tosyl* - 3,4,5,6 - *tetrahydro* - 1,3,6 - *benzotriazocin* - 2(1H) - one (7, Y = R = Me, V + W = O). Compound 2 (Y = Me) (28 g; 67.6 mmol) was heated with a methanolic (50 ml) $MeNH_2$ (400 mmol) soln in a sealed vessel for 24 hr at 120° and concentrated to about 10 ml. EtOH (10 ml) was added and the crystalline methylammonium bromide (6.4 g; 85%) filtered off. The filtrate which contained 3 (Y = R = Me) was diluted with EtOH (270 ml) and reduced at room temp and normal pressure in the presence of a 10% Pd–C catalyst (4 g). After uptake of the calculated amount of H_2 the catalyst was filtered off and diethyl carbonate (40 ml) was added to the filtrate. The mixture was refluxed for 2 hr and concentrated to about 40 ml. AcOH (5 ml) was added and refluxing was continued for an additional 2 hr. The crystalline title compound, 9 g (37%), m.p. 255° from DMF was filtered off on the next morning. (Found: C, 59.98; H, 6.21; N, 11.48; S, 9.15. $C_{18}H_{21}N_3O_3S$ (359.5) requires: C, 60.16; H, 5.89; N, 11.69; S, 8.90%.) IR (KBr): 3160, 1690, 1310, 1145 cm^{-1}.

2' - (1 - *Ethoxyethylideneimino*)-4'-*methoxy* - N - (2 - *methylaminoethyl*)*tosylanilide* (8). A mixture of 5 (Y = MeO, R = Me) (1.75 g; 5 mmol), triethyl orthoacetate (2 ml) and AcOH (1 drop) was refluxed for 3 hr and evaporated to dryness *in vacuo*. The oily residue was dissolved in nitromethane (10 ml) and kept overnight in a refrigerator to obtain 1.7 g (81%) as colourless needles of the title compound, m.p.: 100° from EtOH. (Found: C, 60.19; H, 6.67; N, 10.26; S, 7.53. $C_{21}H_{29}N_3O_4S$ (419.5) requires: C, 60.12; H, 6.96; N, 10.01; S, 7.64%.) IR (KBr): 1660, 1320, 1150 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.39t (3H) + 4.38q (2H; J = 7.2 Hz); 1.82s (3H); 2.35s (3H); 2.45s (3H); 2.6–2.95m (4H); 6.1–7.25m (4H); 7.17 + 7.63 (AA'BB'; J = 8.5 Hz).

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