New Synthesis of some 1,2,5-Benzothiadiazepine 1,1-Dioxide Derivatives. I.

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2-Nitrobenzenesulfonyl chloride reacts with ω-aminoacetophenone and 4-amino-3,5-dimethylisoxazole to give **3** and **7**, respectively. Reduction of **3** with zinc powder and acetic acid afforded the 2,5-dihydro- and 2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine 1,1-dioxide derivatives (**4** and **5**). Catalytic hydrogenolysis of **7** and successive cyclization of the intermediate **8** gave the 3-acethyl-2,5-dihydro-4-methyl-1,2,5-benzothiadiazepine 1,1-dioxide (**9**). The structures were assigned on the basis of correct elemental data and spectroscopic evidences.

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Although the 2,3-dihydro-1,2,5-benzothiadiazepin-4(5*H*)one 1,1-dioxide derivatives demonstrated interesting sedative, hypnotic, tranquillizer and diuretic activities, only a few routes leading to this ring system have been explored.

All the reported syntheses of this ring system are reported in the patent literature (1,2,3) and one work referred to 2,5-dihydro-1,2,5-benzothiadiazepine 1,1-dioxide which was obtained by ring expansion of chloromethylbenzothiadiazine (4). Moreover, some tetrahydroderivatives of 1,2,5-benzothiadiazepine 1,1-dioxide were also described (4,5).

Thus, we believe it to be of special interest to provide a new facile synthetic route to 1,2,5-benzothiadiazepine 1,1-dioxide derivatives substituted at C-4 and bearing also an acetyl group at C-3 of potential biological importance. We have found that the action of 2-nitrobenzenesulfonyl chloride (**1**) on ω-aminoacetophenone hydrochloride (**2**) in dry chloroform in the presence of triethylamine under mild conditions gave compound **3**, which, by reduction with zinc-powder and acetic acid, was directly cyclized into a mixture of the desired ring system, (**4** and **5**) which were separated by fractional crystallization from ethanol.

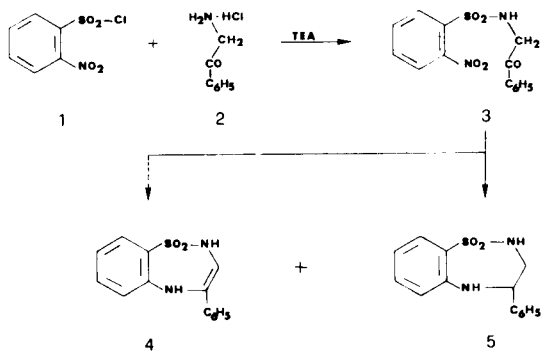
The structures of these compounds were assigned as 4-phenyl-2,3-dihydro-1,2,5-benzothiadiazepine 1,1-dioxide (**4**) and 4-phenyl-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine 1,1-dioxide (**5**), on the basis of elemental analysis and spectroscopic data (ir and nmr).

The nmr spectrum of **4** was in agreement with two tautomeric structures **4** and **4a** in equilibrium in DMSO-d_6 solution, since it showed two singlets at δ 4.40 and δ 5.90 attributable to the C_3-H_2 and C_3-H protons. Moreover, a set of signals for aromatic protons and two NH groups, exchangeable with deuterium oxide, were observed.

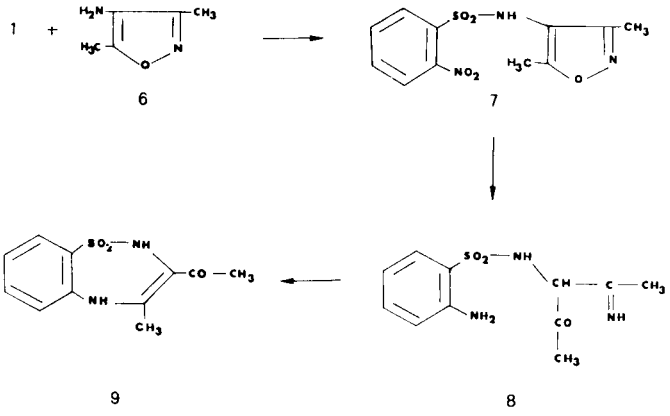
4 4a

The nmr spectrum of **5** was a more complex one due to the presence of a system -NH-CH_2-CH-NH-. It showed a multiplet at δ 3.30-3.90 (2H) for a CH_2 and a multiplet at δ 4.20-4.50 attributable to CH and NH groups. Moreover, it exhibited a multiplet at δ 5.70 (1H) attributable to an amide NH group. In fact, upon exchange with deuterium oxide a set of signals for an ABX system appeared, attributable to -CH_2-CH-group, which was not analyzed.

SCHEME I



SCHEME II



The synthetic approach to the acetyl-substituted derivative **9** was established by a route starting from the 4-amino-3,5-dimethylisoxazole (**6**) which was reacted with **1** in pyridine, to yield 2-nitro-*N*-(3′,5′-dimethyl-4′-isoxazolyl)benzenesulfonamide (**7**). Catalytic hydrogenation with W-2 Raney Nickel caused ring opening to afford the intermediate **8**, which readily cyclized into 3-acetyl-4-methyl-2,5-dihydro-1,2,5-benzothiadiazepine 1,1-dioxide (**9**) (Scheme II). The spectroscopic data, elemental analysis and molecular weight (ms) were consistent with the assigned structure. The nmr spectrum exhibited, besides other signals for the remaining protons, two broad absorptions at δ 8.90 (1H) and δ 9.10 (1H), exchangeable with deuterium dioxide, attributable to two NH groups. The ir spectrum showed NH absorptions in the 3μ region and a strong band at 1660 cm^{-1} due to the carbonyl of the acetyl group. Further investigation of the scope and limitations of the reactions is in progress.

EXPERIMENTAL

All melting points were taken on Buchi-Tottoli capillary melting point apparatus and are uncorrected. Ultraviolet absorption spectra were determined in ethanol solution with a Beckmann DB recording spectrophotometer and infrared absorption spectra with a Perkin-Elmer Infracord 137 using nujol mulls. Nmr spectra (DMSO-d_6) (unless otherwise specified) were measured using TMS as the internal standard, with a Jeol C-60H spectrometer. The mass spectra were measured with a Jeol JMS-01SG-2 double focusing spectrometer at 75 eV (100 μA). Exact masses were measured on Ilford Q-2 photoplates; perfluorokerosene was used as a reference at a resolving power better than 15,000.

2-Nitro-ω-phenacylbenzenesulfonamide (**3**).

To a suspension containing equimolar amounts of ω-aminoacetophenone hydrochloride (**2**) (6) (10 mmoles) and 2-nitrobenzenesulfonyl chloride (**1**) (10 mmoles) in dry chloroform (200 ml.), triethylamine (10 mmoles) was added in one portion. After stirring at room temperature for 60 hours the solution was filtered and evaporated under vacuum. The obtained residue was triturated with water (100 ml.) and the solid which separated was collected and recrystallized from ethanol, m.p. 145° (yield 80%); ir cm^{-1}: 3320 (NH), 1710 (CO), 1150 (SO_2); nmr (deuteriochloroform): 4.75 (2H, m, CH_2, upon exchangeament with deuterium oxide, 2H, s), δ 6.55 (1H, broad, amide NH, exchangeable with deuterium oxide), 7.40-8.30 (9H, m, C_6H_5 and C_6H_4).

Anal. Calcd. for $C_{14}H_{12}N_2O_5S$: C, 52.50; H, 3.78; N, 8.75. Found: C, 52.41; H, 3.81; N, 8.65.

4-Phenyl-2,5-dihydro-1,2,5-benzothiadiazepine 1,1-Dioxide (**4**) and 4-Phenyl-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine 1,1-Dioxide (**5**).

To a solution of **3** (1 g.) in acetic acid (20 ml.), zinc powder (2 g.) was added over a period of one hour. After the addition was complete, the mixture was refluxed for three additional hours. After standing overnight, the solution was filtered and the residue was washed with hot ethanol. The acetic and ethanolic liquors were evaporated under reduced pressure to give a residue which was triturated with water and filtered off. The examination of the crude product revealed (tlc) the presence of two products **4** and **5**, which were separated by fractional crystallization from ethanol.

Compound **4**.

This compound had 270° (ethanol) (yield 25%); ir cm^{-1}: 3350 and 3180 (NH), 1160 (SO_2); uv λ max nm log ε: 254 (3.65), 300 (3.13); nmr δ: 4.40 (s, CH_2), 5.90 (s, CH), 6.70-7.80 (m, aromatic protons and 2 x NH); exact mass measurement: Calcd. for $C_{14}H_{12}N_2O_2S$: 272.0619. Found: 272.0641 (± 0.0027).

Anal. Calcd. for $C_{14}H_{12}N_2O_2S$: C, 61.76; H, 4.44; N, 10.29. Found: C, 61.69; H, 4.58; N, 10.24.

Compound **5**.

This compound had m.p. 198° (ethanol) (yield 25%); ir cm^{-1}: 3370 and 3250 (NH), 1150 (SO_2): uv λ max nm log ε: 253 (3.70), 3.02 (3.15); nmr (deuteriochloroform): δ 3.30-3.90 (2H, m, CH_2), 4.20-4.50 (2H, m, -CH-, -NH-) 5.70 (1H, m, -NH- amidic), 6.70-7.50 (9H, m, C_6H_5, C_6H_4); exact mass measurement: Calcd. for $C_{14}H_{14}N_2O_2S$: 274.0775. Found: 274.0764 (± 0.003).

Anal. Calcd. for $C_{14}H_{14}N_2O_2S$: C, 61.31; H, 5.15; N, 10.21. Found: C, 61.26; H, 5.31; N, 10.24.

2-Nitro-*N*-(3′,5′-dimethyl-4′-isoxazolyl)benzenesulfonamide (**7**).

A solution of 10 mmoles of **6** (7) in dry pyridine (10 ml.) was treated with 10 mmoles of 2-nitrobenzenesulfonyl chloride (**1**). After stirring at room temperature for 24 hours, the solution was evaporated under vacuum and the residue was mixed with water (60 ml.). The solid precipitate was collected and crystallized from ethanol, m.p. 201-206° (yield 85%); ir cm^{-1}: 3320-3010 (broad, NH), 1150 (SO_2).

Anal. Calcd. for $C_{11}H_{11}N_3O_5S$: C, 44.45; H, 3.73; N, 14.14. Found: C, 44.61; H, 3.87; N, 13.93.

2-Amino-*N*-(2′-acetimidoylacetamyl)benzenesulfonamide (**8**).

A mixture of 10 mmoles of **7**, 100 ml. of ethanol and *ca.* 2 g. of W2-Raney Nickel (8) was hydrogenated in a Parr apparatus at 45-50 psi for 6 hours in room temperature. After removal of the catalyst, the solution was evaporated under vacuum to dryness to leave a crystalline product, m.p. 195° (ethanol) (yield 75%); ir cm^{-1}: 3428, 3322 and 3270 (NH and NH_2), 1650 (CO), 1150 (SO_2).

Anal. Calcd. for $C_{11}H_{15}N_3O_3S$: C, 49.07; H, 5.62; N, 15.61. Found: C, 49.05; H, 5.68; N, 15.53.

3-Acetyl-4-methyl-2,5-dihydro-1,2,5-benzothiadiazepine 1,1-Dioxide (**9**).

To a solution of 10 mmoles of **8** in ethanol (20 ml.), 2 ml. of 18% aqueous hydrochloric acid was added. After refluxing for one hour, the solution was concentrated to a small volume and the crystalline product separated was recrystallized, m.p. 240° (ethanol); uv λ max nm log ε: 340 (4.15), 298 (3.95) 234 (4.01); ir cm^{-1}: 3300 and 3180 (NH), 1660 (CO), 1160 (SO_2); nmr δ: 2.20 (3H, s, CH_3), 2.45 (3H, s, CH_3-CO), 6.90-7.80 (4H, m, C_6H_4), 8.90 (1H, broad, NH, exchangeable with deuterium oxide), 9.10 ∂ (1H, broad, NH, exchangeable with deuterium oxide); mass: 252 (M^+).

Anal. Calcd. for $C_{11}H_{12}N_2O_3S$: C, 52.38; H, 4.80; N, 11.11. Found: C, 52.38; H, 4.93; N, 11.04.

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