

## Reductive Heterocyclization Leading to Some 9,9-Dioxy-4*H*-pyrazolo[1,5-*b*]-1,2,4-benzothiadiazine Derivatives

*Salvatore Plescia, Enrico Aiello, Giuseppe Daidone and Vincenzo Sprio*

Istituto di Chimica Farmaceutica-Facoltà di Farmacia  
Via Archirafi, 32, 90123 Palermo, Italy

Received July 14, 1975

*J. Heterocyclic Chem.*, **13**, 395 (1976).

During the course of research work on the synthesis of novel heterocyclic systems, it became necessary to prepare 1-(2-nitrobenzenesulfonyl)-3,4-*R,R'*-5-aminopyrazoles. The general method followed for the preparation of compounds Va,b,c,d, involves the reaction of 3(5)aminopyrazoles with 2-nitrobenzenesulfonyl chloride (III). The identity of the materials was confirmed by elemental analysis and spectral data.

An examination of the ir spectra shows bands at 3300 and 3480  $\text{cm}^{-1}$  attributable to an  $\text{NH}_2$  group. The fact that the products contain an amino group was confirmed by the nmr spectra which revealed a singlet (2H) at 4.60-4.86  $\delta$  exchangeable with deuterium oxide. Moreover, compounds Va,b,c,d were also conveniently obtained from the reaction of  $\beta$ -ketonitriles IIa,b,c,d and 2-nitrobenzenesulfonyl hydrazide (I).

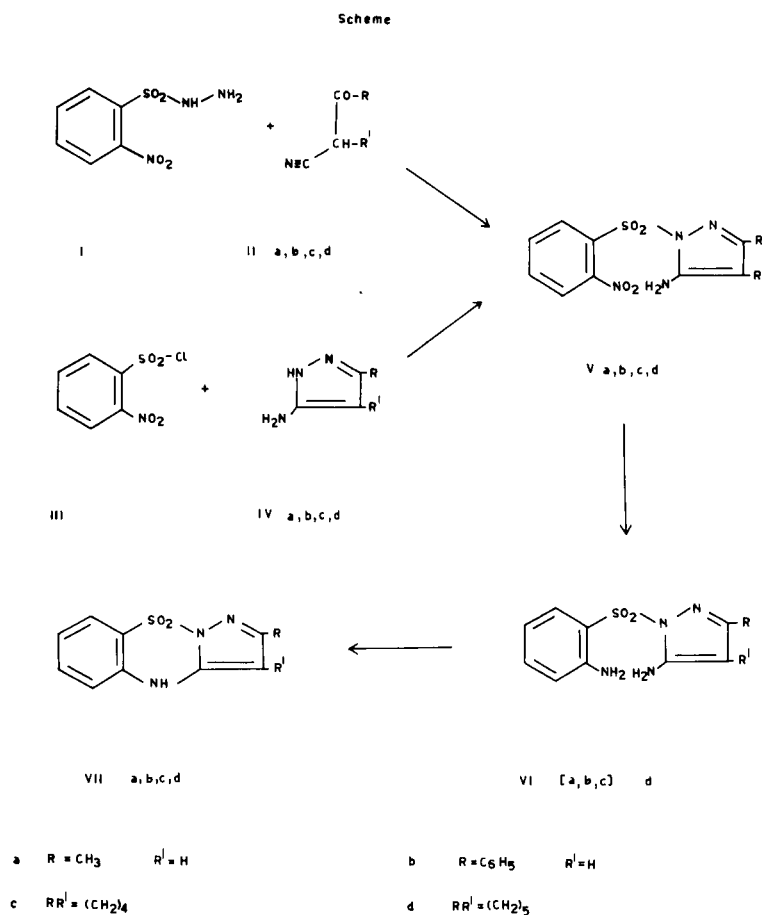
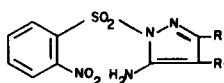


Table I

## 1-(2-Nitrobenzenesulfonyl)-3,4-R,R'-5-aminopyrazoles

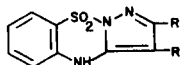


	R	R'	M.p., °C	Formula	C	Analysis			Found	
						Calcd.	H	N	C	H
Va	CH <sub>3</sub>	H	140-142°	C <sub>10</sub> H <sub>10</sub> N <sub>4</sub> O <sub>4</sub> S (a)	42.56	3.57	19.85	42.46	3.46	19.75
Vb	C <sub>6</sub> H <sub>5</sub>	H	123-125°	C <sub>15</sub> H <sub>12</sub> N <sub>4</sub> O <sub>4</sub> S (b)	52.33	3.51	16.28	52.36	3.51	16.42
Vc	(CH <sub>2</sub> ) <sub>4</sub>		115-118°	C <sub>13</sub> H <sub>14</sub> N <sub>4</sub> O <sub>4</sub> S (c)	48.45	4.38	17.39	48.51	4.34	17.42
Vd	(CH <sub>2</sub> ) <sub>5</sub>		140-143°	C <sub>14</sub> H <sub>16</sub> N <sub>4</sub> O <sub>4</sub> S (d)	50.00	4.80	16.66	49.91	4.91	16.61

(a) Ir: 3380 and 3480 cm<sup>-1</sup> (NH<sub>2</sub>); nmr (deuteriochloroform): 2.08 δ (3H, s, CH<sub>3</sub>), 4.86 δ (2H, s, NH<sub>2</sub>), 5.28 δ (1H, s, pyrazole CH), 7.80-8.30 δ (4H, m, C<sub>6</sub>H<sub>4</sub>). (b) Ir: 3300 and 3480 cm<sup>-1</sup> (NH<sub>2</sub>); nmr (deuteriochloroform): 4.80 δ (2H, s, NH<sub>2</sub>), 5.70 δ (1H, s, pyrazole CH), 7.20-8.30 δ (9H, m, C<sub>6</sub>H<sub>5</sub> and C<sub>6</sub>H<sub>4</sub>). (c) Ir: 3380 and 3480 cm<sup>-1</sup> (NH<sub>2</sub>); nmr (deuteriochloroform): 1.30-2.80 δ (8H, m, (CH<sub>2</sub>)<sub>4</sub>), 4.60 δ (2H, s, NH<sub>2</sub>), 7.50-8.00 δ (4H, m, C<sub>6</sub>H<sub>4</sub>). (d) Ir: 3370 and 3490 cm<sup>-1</sup> (NH<sub>2</sub>); nmr (deuteriochloroform): 1.20-2.70 δ (10H, m, (CH<sub>2</sub>)<sub>5</sub>), 4.50 δ (2H, s, NH<sub>2</sub>); 7.60-8.00 δ (4H, m, C<sub>6</sub>H<sub>4</sub>).

Table II

## 9,9-Dioxo-4H-Pyrazolo[1,5-b][1,2,4]benzothiadiazine



	R	R'	M.p., °C	Formula	Calcd.			Found		
					C	H	N	C	H	N
VIIa	CH <sub>3</sub>	H	278-280°	C <sub>10</sub> H <sub>9</sub> N <sub>3</sub> O <sub>2</sub> S (a)	51.06	3.86	17.87	50.99	3.95	17.78
VIIb	C <sub>6</sub> H <sub>5</sub>	H	274-275°	C <sub>15</sub> H <sub>11</sub> N <sub>3</sub> O <sub>2</sub> S (b)	60.60	3.73	14.14	60.48	3.75	14.10
VIIc	(CH <sub>2</sub> ) <sub>4</sub>		302-304°	C <sub>13</sub> H <sub>13</sub> N <sub>3</sub> O <sub>2</sub> S (c)	56.72	4.76	15.27	56.83	4.74	15.35
VIIId	(CH <sub>2</sub> ) <sub>5</sub>		293-295°	C <sub>14</sub> H <sub>15</sub> N <sub>3</sub> O <sub>2</sub> S (d)	58.12	5.23	14.53	58.16	5.36	14.59

(a) Ir (hexachlorobutadiene): 3280 cm<sup>-1</sup> (NH); nmr (DMSO-d<sub>6</sub>): 2.28 δ (3H, s, CH<sub>3</sub>), 5.30 δ (1H, s, pyrazole CH), 7.00-8.20 δ (4H, m, C<sub>6</sub>H<sub>4</sub>), 12.00 δ (broad, NH); Mass: M<sup>+</sup> 235. (b) Ir (hexachlorobutadiene): 3320 cm<sup>-1</sup> (NH); nmr (DMSO-d<sub>6</sub>): 6.40 δ (1H, s, pyrazole CH), 7.00-8.20 δ (9H, m, C<sub>6</sub>H<sub>5</sub> and C<sub>6</sub>H<sub>4</sub>), 12.00 δ (broad NH); Mass: M<sup>+</sup> 297. (c) Ir (hexachlorobutadiene): 3280 cm<sup>-1</sup> (NH); nmr (DMSO-d<sub>6</sub>): 1.50-3.00 δ (8H, m, (CH<sub>2</sub>)<sub>4</sub>), 8.00-8.10 δ (4H, m, C<sub>6</sub>H<sub>4</sub>), 11.00 δ (broad NH); Mass: M<sup>+</sup> 275. (d) Ir (hexachlorobutadiene): 3300 cm<sup>-1</sup> (NH); nmr (DMSO-d<sub>6</sub>): 1.20-2.90 δ (10H, m, (CH<sub>2</sub>)<sub>5</sub>), 7.00-8.10 δ (4H, m, C<sub>6</sub>H<sub>4</sub>), 10.90 δ (1H, s, NH); Mass: M<sup>+</sup> 289.

This second synthetic approach employed to form Va,b,c,d support the proposed structure (see Scheme). Compounds Va,b,c were found to undergo facile reductive intramolecular cyclisation at 70° in high yield to products formulated as 4H-Pyrazolo[1,5-b]-1,2,4-benzothiadiazines. By reduction at 70° of Vd the corresponding diamino derivative VIId was isolated and identified, which on heating in acetic acid at 110-120° yielded the desired pyrazolobenzothiadiazine derivative. By reduction at 110-120° of Vd the compound VIIId was directly obtained (see Scheme).

Clearly, these title compounds must be considered as arising directly from intermediates VIa,b,c,d resulting from reduction of the nitro group, which readily cyclized by loss of ammonia. The assigned structure of the obtained products was supported by elemental analyses, molecular weight determined by mass spectroscopy and were in agreement with nmr and ir spectra. In fact nmr spectra, besides other signals for remaining protons, exhibit a broad signal at 11-12 δ attributable to the thiadiazine NH group and the ir spectra determined in hexachlorobutadiene show a NH stretching at 3280-3320 cm<sup>-1</sup>.

Refluxing VIIb, taken as an example, with acetic anhydride for 20 minutes yielded a monoacetyl derivative as confirmed by analytical data and nmr spectrum, which shows a singlet (3H) at 2.50  $\delta$  (COCH<sub>3</sub>).

Furthermore, compounds VIIa and VIIb were found to be identical (m.p. and mixed m.p., ir, nmr), with samples synthesized by a patent independent route (1).

#### EXPERIMENTAL

All melting points were taken on a Buchi-Tottoli capillary melting point apparatus and are uncorrected. Ir spectra were determined in nujol mulls (unless otherwise specified) with a Perkin Elmer infracord 137 spectrophotometer. The nmr spectra were obtained with a Jeol C-60H spectrometer (TMS as internal reference). A 270 Perkin Elmer mass spectrometer was employed for determination of low resolution 70 ev mass spectra.

General Procedure for 1-(2-Nitrobenzenesulfonyl)-3,4-R,R'-5-aminopyrazoles.

##### Method A.

Compounds IVa (2) b (3), c (4), d (5), (10 mmoles) were dissolved in 200 ml. of dry chloroform and 10 mmoles of 2-nitrobenzenesulfonyl chloride (III) were added. Triethylamine (10 mmoles) was added in one portion and the mixture was then refluxed for 2 hours. The solution was evaporated under vacuum and the residue was mixed with water (200 ml.). The water-insoluble material was extracted with ether (3 x 200 ml.) and extracts were dried (sodium sulfate) and evaporated; the residue was recrystallized from ethanol to yield 80-90% of the desired products V, which are listed in Table I.

##### Method B.

Equimolar amounts of IIa,b (6), c (7), d (7), (10 mmoles) and I (8) (10 mmoles) in ethanol (40 ml.) were stirring at r.t. for 48 hours. The solid which precipitated was collected and recrystallized, yield 80-90%. The products were identical with Va,b,c,d, respectively, obtained by method A (m.p. and mixed m.p., ir, nmr).

General Procedure for the Pyrazolobenzothiadiazines.

A solution of Va,b,c (10 mmoles) in glacial acetic acid (20 ml.) was heated at 70°, when iron powder (1.5 g.) was added over a period of 1 hour. After adding, the mixture was kept at 70° for 2 hours then poured into crushed ice and extracted with ethyl

acetate (2 x 150 ml.). The extracts were dried (sodium sulfate) and evaporated under vacuum to give 70-75% of VIIa,b,c. In the case of Vd the temperature of bath was maintained at 110-120° to give VIId. The products were recrystallized from ethanol and are listed in Table II.

1-(2-Aminobenzenesulfonyl)-3,4-cyclohepta-5-aminopyrazole (VIId).

The title compound was obtained by general procedure for the pyrazolobenzothiadiazine maintaining the bath temperature at 70°, m.p. 163-165° (ethanol); ir: multiple bands in the 3  $\mu$  region; nmr (DMSO-d<sub>6</sub>): 1.20-2.60  $\delta$  (10H, m, (CH<sub>2</sub>)<sub>5</sub>) 5.68  $\delta$  (2H, s, NH<sub>2</sub>) 6.26  $\delta$  (2H, s, NH<sub>2</sub>) 6.50-7.80  $\delta$  (4H, m, C<sub>6</sub>H<sub>4</sub>).

Anal. Calcd. for C<sub>14</sub>H<sub>18</sub>N<sub>4</sub>O<sub>2</sub>S: C, 55.25; H, 5.30; N, 18.41. Found: C, 54.93; H, 5.61; N, 18.41.

VIId.

By heating VIId (10 mmoles) in acetic acid (20 ml.) at 110-120° for 2 hours and by evaporation the solution under vacuum a residue was obtained which was triturated with ethanol and recrystallized from ethanol. The product was identical with VIId obtained by procedure described above (m.p. and mixed m.p., ir, nmr).

2-Phenyl-4-acetyl-9,9-dioxy-pyrazolo[1,5-b]-1,2,4-benzothiadiazine.

A mixture of VIIb (1 g.) and acetic anhydride (30 ml.) was refluxed for 20 minutes, then poured on crushed ice and treated with solid sodium bicarbonate. The product which precipitated was filtered off and recrystallized, m.p. 175-178° (ethanol); ir: 1710 cm<sup>-1</sup> (CO); nmr (deuteriochloroform): 2.50  $\delta$  (3H, s, CH<sub>3</sub>) 6.84  $\delta$  (1H, s, pyrazole CH) 7.30-8.30  $\delta$  (9H, m, C<sub>6</sub>H<sub>5</sub> and C<sub>6</sub>H<sub>4</sub>).

Anal. Calcd. for C<sub>16</sub>H<sub>12</sub>N<sub>3</sub>O<sub>3</sub>S: C, 60.17; H, 3.86; N, 12.39. Found: C, 60.34; H, 4.01; N, 12.39.

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