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Treatment of 5-methylmercapto-1,4-benzodiazepine (I) with hydrazine hydrate gave the 5-hydrazino derivative (II, R = H) which, in turn, was conveniently cyclized to the title compounds. Another method for the synthesis of triazolo[4,3-*d*][1,4]benzodiazepines (III) is also described.

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In recent years considerable attention has been drawn to the synthesis of tricyclic 1,4-diazepines, in particular the triazolobenzodiazepines, which show similar pharmacological profiles to the benzodiazepines from which they are derived, but which are an order of magnitude more potent. A great amount of this synthetic work, however, has been directed mainly toward the introduction of the third ring (triazole, pyrrole, pyrazole, etc.) at positions 1 and 2 of the benzodiazepine nucleus.

In the present report we wish to describe the synthesis of some of these tricyclic 1,4-diazepines in which the new ring has been fused at positions 4 and 5 of the 1,4-benzodiazepine moiety.

In this context, we have first carried out the synthesis of a series of 5*H*-s-triazolo[4,3-*d*][1,4]benzodiazepine derivatives (III, Table I) which have received scant attention up to date (2). Thus, compounds IIIa-i were prepared by the two methods given in Scheme I. Method A consisted of treating the 5-hydrazino-1,4-benzodiazepine (II, R = H) with an acid anhydride in methylene chloride at room temperature. Method B involved the condensation of I with the corresponding monoacylhydrazines followed by

cyclodehydration. 6,7-Dihydro-7-methyl-5*H*-s-triazolo[4,3-*d*][1,4]benzodiazepine (IV) was obtained in excellent yield by cyclization of the hydrazine II with ethyl orthoformate. The ir spectra of all these compounds showed the C = N absorptions at 1605-1580  $\text{cm}^{-1}$ . In the  $^1\text{H}$  nmr spectra, the signals of the methylene protons at C-2 and C-3 occurred as two doublets centered at  $\delta$  3.50 and 4.15 respectively. The signals of the *N*-methyl protons appeared at  $\delta$  3.0.

Compound II (R = H) was obtained by nucleophilic displacement of the thioalkoxy group of the 5-methylmercapto-1,4-benzodiazepine (I) with hydrazine hydrate in refluxing ethanol. Compound II (R =  $\text{C}_6\text{H}_5$ ) was better prepared by refluxing I and phenylhydrazine in absence of the solvent. II (R = H) was shown to be somewhat unstable and did not form the corresponding isopropylidene derivative (V) when recrystallized from acetone. It was obtained instead of the *bis*-type compound (VI) as evidenced by its spectral data and elemental analysis (see Experimental). On the other hand, a direct synthesis of VI by reaction of I with II (R = H) did not give satisfactory results.

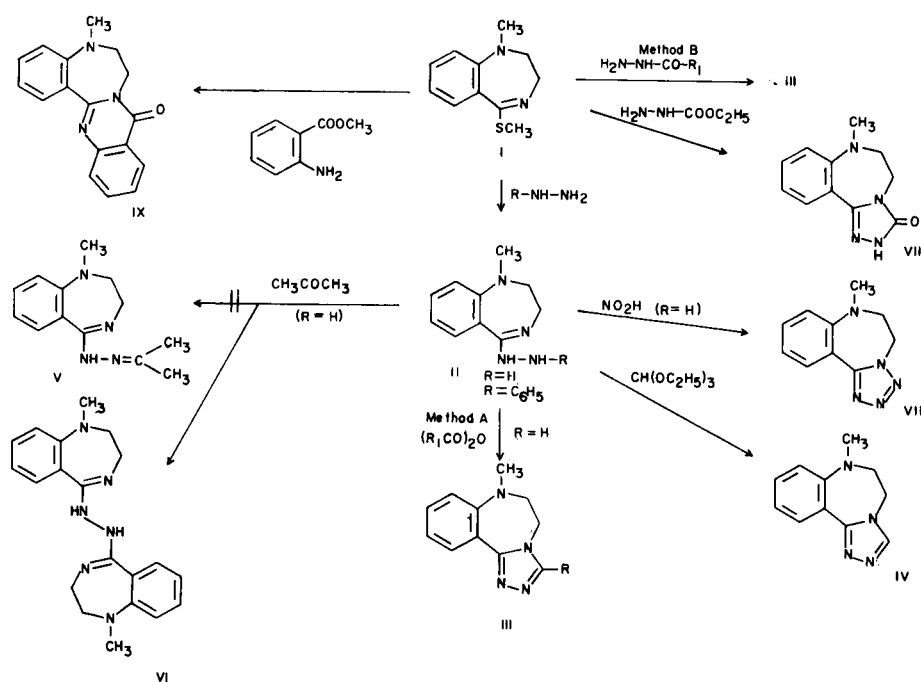
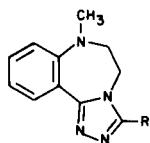


Table I

## 3-Substituted-6,7-dihydro-7-methyl-5H-s-triazolo[4,3-d][1,4]benzodiazepines (III)



Compound	R <sub>1</sub>	Method	Yield %	M.p. °C	Recrystallization Solvent	Molecular Formula	Analyses %		
							Calcd./Found		
IIIa	CH <sub>3</sub>	A	82	178-179	Benzene (charcoal)	C <sub>12</sub> H <sub>14</sub> N <sub>4</sub>	67.28	6.54	26.16
		B	84				67.17	6.67	26.10
IIIb	CH <sub>2</sub> -CH <sub>3</sub>	A	88	162-163	Benzene	C <sub>13</sub> H <sub>16</sub> N <sub>4</sub>	68.39	7.06	24.54
							68.16	7.26	24.60
IIIc	C <sub>6</sub> H <sub>5</sub>	A	81	98-99	Ethanol	C <sub>17</sub> H <sub>16</sub> N <sub>4</sub>	73.91	5.83	20.27
							74.12	6.08	19.97
III d	<i>o</i> -COOH C <sub>6</sub> H <sub>5</sub>	A	86	283	<i>N,N</i> -DMF	C <sub>18</sub> H <sub>16</sub> N <sub>4</sub> O <sub>2</sub>	67.48	5.03	17.49
							67.40	4.96	17.32
III e	CH=CH-COOH	A	85	171-172	Ethanol	C <sub>14</sub> H <sub>14</sub> N <sub>4</sub> O <sub>2</sub>	62.20	5.22	20.79
							62.40	5.38	20.68
III f	CH <sub>2</sub> -C <sub>6</sub> H <sub>5</sub>	B	99	140	Benzene/ Petroleum ether (charcoal)	C <sub>18</sub> H <sub>18</sub> N <sub>4</sub>	74.45	6.24	19.29
							74.56	6.38	19.30
III g	CH <sub>2</sub> -CN	B	92	179	Ethanol	C <sub>13</sub> H <sub>13</sub> N <sub>5</sub>	65.25	5.47	29.27
							65.43	5.49	29.24
III h		B	94	176-177	Toluene	C <sub>16</sub> H <sub>15</sub> N <sub>5</sub>	69.29	5.45	25.25
							69.18	5.69	25.18
III i	<i>p</i> -OHC <sub>6</sub> H <sub>4</sub>	B	82	313	<i>N,N</i> -DMF	C <sub>17</sub> H <sub>16</sub> N <sub>4</sub> O	69.84	5.51	19.16
							70.02	5.32	19.38

Condensation of I with ethyl carbazate gave directly the 1-methyl-3-oxo-2,5,6,7-tetrahydro-3*H*-s-triazolo[4,3-*d*][1,4]benzodiazepine (VII). Attempts to prepare VII from 1-methyl-1,2,3,4-tetrahydro-5*H*-5-thioxo-1,4-benzodiazepine (3) and ethyl carbazate *via* the corresponding intermediate carbazic acid ethyl ester was unsuccessful.

Finally, in view of the potent pharmacological activity of tetrazole and quinazolone systems it was also of our interest to incorporate these rings (4,5) in the 1,4-benzodiazepine moiety. Therefore, 5-hydrazino-1,4-benzodiazepine II (R = H) was allowed to react with sodium nitrite in acid medium to give the desired tetrazole derivative (VIII) in high yield. The oxo-quinazolino-benzodiazepine (IX) was obtained by treatment of the thioether compound (I) with methyl anthranilate at reflux temperature in the presence of a catalytic amount of acetic acid.

## EXPERIMENTAL

All melting points (uncorrected) were determined using a Gal-lenkamp capillary apparatus. The ir spectra were recorded with a Perkin-Elmer Model 257 instrument. <sup>1</sup>H nmr spectra were obtained with a Perkin-Elmer R-12 spectrophotometer using TMS

as internal reference and mass spectra on a Varian MAT-711 spectrometer.

2,3-Dihydro-5-hydrazino-1-methyl-1*H*-1,4-benzodiazepine (II, R = H).

A mixture of 2,3-dihydro-1-methyl-5-methylmercapto-1*H*-1,4-benzodiazepine (I) (6) (4.1 g., 0.02 mole), hydrazine hydrate (3 g., 0.06 mole) and ethanol (50 ml.) was heated at reflux temperature for 48 hours. Removal of the solvent afforded 2.8 g. (72%) of II (R = H), m.p. 148° (from benzene or methanol); ir (nujol): 3370 and 3350 cm<sup>-1</sup> (NH-NH<sub>2</sub>), 1625 cm<sup>-1</sup> (C=N); <sup>1</sup>H nmr (deuteriochloroform): δ 2.80 (s, 3, N-CH<sub>3</sub>), 3.25 (m, 4, -CH<sub>2</sub>-CH<sub>2</sub>-), 4.10-4.70 (m, 3, NH-NH<sub>2</sub>), 6.90-7.60 (m, 4, aromatic).

*Anal.* Calcd. for C<sub>10</sub>H<sub>14</sub>N<sub>4</sub>: C, 63.12; H, 7.41; N, 29.45. Found: C, 62.86; H, 7.19; N, 29.22.

In order to prepare the corresponding isopropylidene derivative (V) we recrystallized II (R = H) from acetone, obtaining instead the *bis*-type compound (VI) as colorless needles of m.p. 221°; ir (nujol): 3420 cm<sup>-1</sup> (NH), 1600 cm<sup>-1</sup> (C=N); <sup>1</sup>H nmr (deuteriochloroform): δ 2.85 (s, 3, N-CH<sub>3</sub>), 3.25 (m, 4, -CH<sub>2</sub>-CH<sub>2</sub>-), 6.80-7.90 (m, 4, aromatic); ms: m/e 348 (M<sup>+</sup>).

*Anal.* Calcd. for C<sub>20</sub>H<sub>24</sub>N<sub>6</sub>: C, 68.96; H, 6.89; N, 24.13. Found: C, 68.96; H, 6.63; N, 23.83.

2,3-Dihydro-5-(2-phenyl)hydrazino-1-methyl-1*H*-1,4-benzodiazepine (II, R = C<sub>6</sub>H<sub>5</sub>).

A mixture of 2,3-dihydro-1-methyl-1*H*-1,4-benzodiazepine (I) (2.1 g., 0.01 mole) and *N*-phenylhydrazine (12 ml.) was heated at reflux temperature for 36 hours. The mixture was evaporated to dryness *in vacuo* to give an oil that could not be induced to crystallize. It was dissolved in a small amount of ethanol and water was added dropwise until the solution was not clear. On scratching, a solid crystallized, which was filtered and washed with ethanol to give 3.7 g. (70%) of II (R = C<sub>6</sub>H<sub>5</sub>), m.p. 147-149° (from ethanol); ir (nujol): 3410-3260 cm<sup>-1</sup> (NH-NH), 1620-1600 (C=N); <sup>1</sup>H nmr (deuteriochloroform): δ 2.80 (s, 3, N-CH<sub>3</sub>), 3.25 (m, 4, -CH<sub>2</sub>-CH<sub>2</sub>-), 5.0-5.6 (m, 2, -NH-NH-), 6.80-7.80 (m, 9, aromatic).

*Anal.* Calcd. for C<sub>16</sub>H<sub>18</sub>N<sub>4</sub>: C, 72.14; H, 6.81; N, 21.03. Found: C, 71.97; H, 6.57; N, 20.93.

6,7-Dihydro-7-methyl-5*H*-s-triazolo[4,3-*d*][1,4]benzodiazepines (IIIa-i).

#### Method A.

To a stirred solution of 2,3-dihydro-5-hydrazino-1-methyl-1*H*-1,4-benzodiazepine (II, R = H) (1.9 g., 0.01 mole) in methylene chloride (50 ml.), was added the appropriate acid anhydride (0.02 mole) at room temperature. After 20-30 minutes the solvent was removed under reduced pressure and the residue was treated with anhydrous ether, crystallizing a solid which was filtered, washed with anhydrous ether and recrystallized. Yields, physicochemical and analytical data of IIIa-i are summarized in the Table I.

#### Method B.

A mixture of 2,3-dihydro-1-methyl-5-methylmercapto-1*H*-1,4-benzodiazepine (I) (4.1 g., 0.02 mole), the corresponding hydrazide (0.02 mole) and absolute ethanol (50 ml.) was heated at reflux temperature for 90-100 hours. The mixture was concentrated *in vacuo* to give an oil which crystallized on standing.

6,7-Dihydro-7-methyl-5*H*-s-triazolo[4,3-*d*][1,4]benzodiazepine (IV).

A mixture of 2,3-dihydro-5-hydrazino-1-methyl-1*H*-1,4-benzodiazepine (II, R = H) (1.9 g., 0.01 mole) and ethyl orthoformate (15.0 g., 16 ml., 0.1 mole) was heated at 130° for 3 hours. The excess of orthoformate was evaporated under reduced pressure and the residual oil, treated with anhydrous ether yielded 1.9 g. (95%) of a white solid which was filtered and recrystallized from benzene, m.p. 107°; ir (nujol): 1605-1580 (C=N).

*Anal.* Calcd. for C<sub>11</sub>H<sub>12</sub>N<sub>4</sub>: C, 66.00; H, 6.00; N, 28.00. Found: C, 66.20; H, 6.19; N, 27.82.

The maleate had m.p. 128° (from methanol).

*Anal.* Calcd. for C<sub>15</sub>H<sub>16</sub>N<sub>4</sub>O<sub>4</sub>: C, 56.96; H, 5.06; N, 17.72. Found: C, 57.14; H, 5.15; N, 17.84.

7-Methyl-3-oxo-2,5,6,7-tetrahydro-3*H*-s-triazolo[4,3-*d*][1,4]-benzodiazepine (VII).

A solution of I (4.1 g., 0.02 mole) and ethyl carbazate (2.1 g., 0.02 mole) in ethanol (50 ml.) was refluxed for 60 hours. On cooling, the precipitate was collected by filtration to give 2.6 g. (60%) of VII, m.p. 237° (from dioxane); ir (nujol): 3140-3120 cm<sup>-1</sup> (NH), 1710 cm<sup>-1</sup> (C=O), 1610-1585 cm<sup>-1</sup> (C=N); <sup>1</sup>H nmr (DMSO-*d*<sub>6</sub>): δ 3.02 (s, 3, N-CH<sub>3</sub>), 3.1-3.6 (m, 2, -CH<sub>2</sub>-), 3.7-3.9 (m, 2, -CH<sub>2</sub>-), 6.8-8.2 (m, 4, aromatic).

*Anal.* Calcd. for C<sub>11</sub>H<sub>12</sub>N<sub>4</sub>O: C, 61.09; H, 5.59; N, 25.91. Found: C, 61.31; H, 5.76; N, 25.87.

6,7-Dihydro-7-methyl-5*H*-tetrazolo[1,5-*a*][1,4]benzodiazepine (VIII).

To a stirred suspension of the 5-hydrazino compound II (R = H) (1.9 g., 0.01 mole) in *N* acetic acid (70 ml.), heated at 45°, was added 0.75 g. (0.11 mole) of sodium nitrite. After 2 hours, the reaction mixture was cooled and the solid obtained, 1.8 g. (86%) was collected and recrystallized from acetone-water, giving colorless needles of m.p. 138°; ir (nujol): 1610-1575 cm<sup>-1</sup> (C=N); <sup>1</sup>H nmr (deuteriochloroform): δ 3.17 (s, 3, N-CH<sub>3</sub>), 3.4-3.7 (t, 2, -CH<sub>2</sub>-), 4.6-4.8 (t, 2, -CH<sub>2</sub>-), 6.9-7.6 (m, 3, aromatic), 8.6-8.7 (d, 1, aromatic).

*Anal.* Calcd. for C<sub>10</sub>H<sub>11</sub>N<sub>5</sub>: C, 59.70; H, 5.47; N, 34.82. Found: C, 59.76; H, 5.28; N, 34.65.

6,7-Dihydro-5-methyl-8-oxo-8*H*-quinazolino[3,2-*d*][1,4]benzodiazepine (IX).

A mixture of I (2.06 g., 0.01 mole), methyl anthranilate (3.1 g., 0.02 mole) and acetic acid (2 drops) was refluxed for 120 hours. After cooling, the mixture was extracted with ether. The extracts, washed and dried (magnesium sulfate), were concentrated to dryness giving an oil which on treatment with benzene-petroleum ether yielded 1.8 g. (33%) of a white solid of m.p. 209° (from methanol); ir (nujol): 1675 cm<sup>-1</sup> (C=O); 1605-1590 cm<sup>-1</sup> (C=N); <sup>1</sup>H nmr (deuteriochloroform): δ 2.80 (s, 3, N-CH<sub>3</sub>), 3.42 (t, 2, -CH<sub>2</sub>-), 4.40 (t, 2, -CH<sub>2</sub>-), 7.0-8.5 (m, 8, aromatic).

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