Tricyclic Heteroaromatic Systems. 5*H*-1,2,4-Triazolo[5,1-*c*][1,4]benzodiazepine

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The synthesis of the new tricyclic heteroaromatic system 5*H*-1,2,4-triazolo[5,1-*c*][1,4]benzodiazepine, diaza-analogue of 5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine, which is the common feature of some antitumor antibiotics, is reported. The structure of the new tricyclic system and of some of its key intermediates is assigned by means of nuclear magnetic resonance studies.

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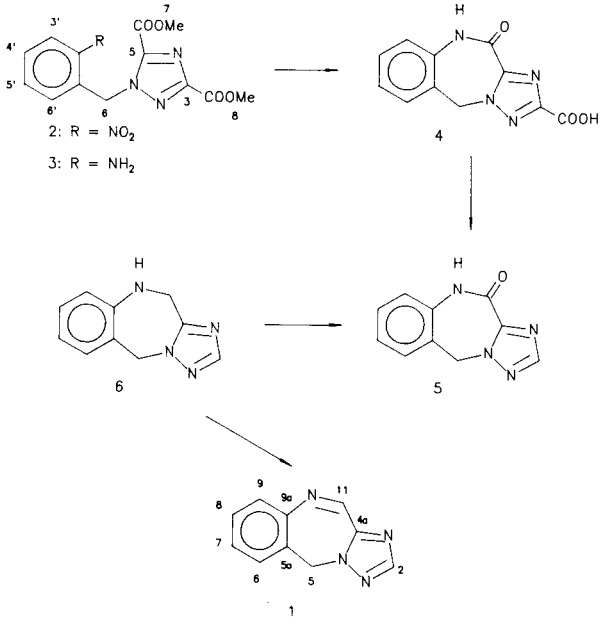
Our continuing interest in six-seven-five tricyclic heteroaromatic systems [1-6] derives from the discovery of the antitumor activity of the antibiotics anthramycin, tomaymycin and sibiromycin [7] which have the pyrrolo[2,1-*c*][1,4]benzodiazepine system as a common feature.

Following up these studies we hereby report the synthesis of the new tricyclic ring system 5*H*-1,2,4-triazolo-[5,1-*c*][1,4]benzodiazepine **1**, which may be considered a diaza-analogue of the 5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine.

The synthetic pathway used to obtain the new tricyclic ring system **1** is shown in Scheme 1. As can be seen, the synthetic strategy is straightforward and involves the reduction of the dimethyl 1-(2-nitrobenzyl)-1,2,4-triazole-3,5-dicarboxylate **2** to the 1-(2-aminobenzyl) derivative **3** and the cyclization of the latter to the 10,11-dihydro-11-oxo-5*H*-1,2,4-triazolo[5,1-*c*][1,4]benzodiazepine-2-carboxylic acid **4**. Compound **4** is decarboxylated to give **5**. The latter is reduced to **6** which by dehydrogenation yields the parent compound **1**.

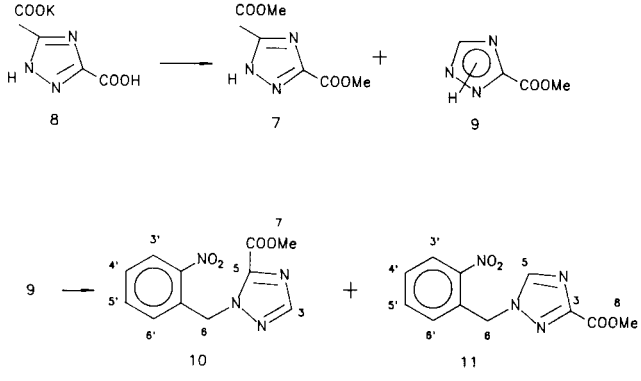
Scheme 1



The crucial step of the sequences shown in Scheme 1 is the synthesis of compound **2**, which we thought could be easily obtained by treating the silver salt of the known dimethyl 1,2,4-triazole-3,5-dicarboxylate [8] **7** with nitrobenzyl bromide.

However, following the reported procedure [8] for the preparation of **7** from the monopotassium salt of the 1,2,4-triazole-3,5-dicarboxylic acid **8**, a mixture of **7** (17%) and of methyl 1,2,4-triazole-3(5)-carboxylate [9] **9** (15%) was obtained (see Scheme 2).

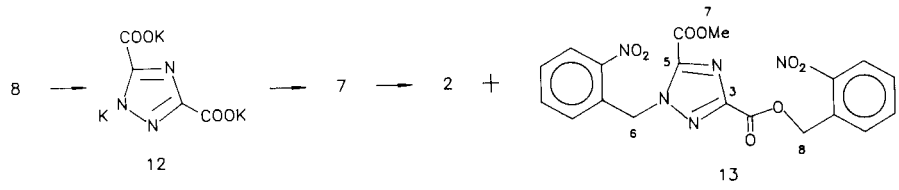
Scheme 2



At first we thought that compound **9** could be useful for preparing **1** with a reaction involving fewer steps. Thus compounds **7** and **9** were separated and compound **9** was allowed to react, *via*, its silver salt, with 2-nitrobenzyl bromide. As expected, the benzylation of the monoester **9** gave two isomeric 1-(2-nitrobenzyl) derivatives **10** and **11**, whose structures were assigned by means of nmr spectroscopy (see below). Unfortunately, the main isomer of the reaction was the 1,3-isomer **11** (24% yield) while the desired methyl 1-(2-nitrobenzyl)-1,2,4-triazole-5-carboxylate **10** was recovered with only a 3% yield.

The uselessness of compound **9** and the small amount of **7** prompted us to leave the synthetic pathway shown in Scheme 2 and try a more profitable one. This was achieved by transforming the monopotassium salt **8** into the tripotassium salt **12** which, in turn, gave the diester **7**

Scheme 3



alone in an acceptable yield (40%) (see Scheme 3). Benzylation of the silver salt of **7** gave a mixture of **2** and of the mixed diester **13** in the ratio 2:1. The structures of **2** and **13** were attributed by nmr spectroscopy (see below).

Nuclear Magnetic Resonance

The structures of the newly synthesized compounds **1-6**, **10-11** and **13** were assigned by means of a nuclear magnetic resonance study.

The ^1H and ^{13}C nmr spectra are reported in the Experimental.

Moreover, for compounds **2**, **10-11** and **13** ^1H nmr interproton nOe measurements were performed. These experiments allowed us to unambiguously assign the structure to the investigated compounds and in the case of compound **13**, it is the only method for establishing in which position the transesterification took place.

The ^1H nmr spectrum of **2** shows two singlets at 3.93 and 3.89 ppm which are attributed to the two methyl ester protons. The different chemical shift values of the two methyl protons indicate that they are not equivalent and that the molecule is asymmetrical. It follows that the 2-nitrobenzylation reaction takes place at position-1 and not at position-4 and that the structure of dimethyl 1-(2-nitrobenzyl)-1,2,4-triazole-3,5-dicarboxylate is to be assigned to compound **2**.

However with the ^1H nmr spectrum alone we cannot say which signal is due to the methyl ester protons at position-3 and which is due to the one at position-5. To resolve this ambiguity a nOe experiment was carried out. Preirradiation of the 2-nitrobenzyl methylene protons of compound **2** caused clear enhancement (0.4%) of the signal of the more shielded methyl ester protons, while no nOe effect is observed for the more deshielded one. It follows that the signal at 3.93 ppm must be nearer to the methylene protons and thus at position-5. The other signal at 3.98 ppm, for which no nOe effect is observed, is thus due to the methyl ester protons farther away at position-3.

The structures of **10** and **11** can be deduced from the unsubstituted C-3 and C-5 chemical shift values. In the ^{13}C nmr decoupled spectrum of **10**, the unsubstituted triazole carbon atom is at 151.95 ppm, while that of compound **11** is at 146.25 ppm. These two signals appear in the coupled spectra as doublets with CH coupling constants of 200 and 202 Hz, respectively. It is reported [10-11] that in the 1-substituted 1,2,4-triazole, the C-3 and the C-5 give signals between 150-155 and 143-146 ppm, respectively. Thus it follows that the structure of methyl 1-(2-nitrobenzyl)-1,2,4-triazole-5-carboxylate is to be attributed to compound **10** and that of methyl 1-(2-nitrobenzyl)-1,2,4-triazole-3-carboxylate to compound **11**. NOe experiments were nevertheless performed on these two compounds. Preirradiation of the methylene protons of the 2-nitrobenzyl substituent of **10** and **11** gave in the case of **10** a small enhancement of both the methyl ester protons (0.1%) and the triazole proton (0.3%) while in the case of **11** there was a strong enhancement of the triazole proton (9.5%) and no enhancement for the methyl protons. Such differences in the signal enhancements of compounds **10** and **11** are in agreement with the attributed structures.

The structure of the bis-(2-nitrobenzyl) derivative **13** cannot be attributed by either ^1H or ^{13}C nmr spectroscopy. In the attribution of this mixed ester structure only the nOe measurement is useful. In fact, the ^1H nmr spectrum showed two methylene proton signals at 5.59 and 5.69 ppm and the methyl proton signals at 3.86 ppm. The ^{13}C coupled spectrum showed two triplets at 47.89 and 44.25 ppm and a quartet at 53.80 ppm. It is evident that the point where transesterification took place cannot be deduced from either ^1H or the ^{13}C chemical shifts. In the nOe experiment, presaturation of the methylene protons at 5.69 ppm gave a small enhancement of the methyl ester protons (0.2%), while the preirradiation of the more shielded methylene protons at 5.59 ppm left the methyl ester protons unchanged. These data suggest that the carboxylmethyl group is at position-5, since this position is nearer to the methylene protons at 5.69 ppm. Thus the other 2-nitrobenzyl group is at the carboxylate group at position-3. It follows that the reported structure of 3-(2-nitrobenzyl), 5-methyl dicarboxylate is to be attributed to compound **13**.

EXPERIMENTAL

Silica gel plates (Merck F_{254}) and silica gel 60 (Merck, 70-230 mesh) were used for analytical and column chromatography, respectively. All melting points were determined on a Gallenkamp capillary melting point apparatus. Microanalyses were performed with a Perkin-Elmer 260 elemental analyzer. The ir spectra were recorded with a Perkin Elmer 1420 spectrometer in nujol mulls. The ^1H nmr spectra were obtained with a Varian Gemini 200 instrument in the Fourier transform mode at 200 MHz using an acquisition time of 1.5 seconds, a flip angle of 42° and a spectral width of 3000 Hz. Chemical shifts are reported in δ

(ppm) downfield from internal tetramethyl silane (TMS). The natural abundance ^{13}C nmr spectra were run on the same instrument at 50 MHz in the Fourier transform mode. All samples were recorded in 5 mm o.d. tubes at probe temperature (23°), with a concentration of approximately 10% (w/v) in deuteriochloroform or dimethyl sulfoxide-d_6, which provided the deuterium signal for the field frequency lock. Chemical shifts were measured relative to the central peak of the solvent (deuteriochloroform = 76.9 ppm, dimethyl sulfoxide-d_6 = 39.6 ppm) and corrected to internal TMS. Typical acquisition parameters of the decoupled spectra included: a spectral width of 15000 Hz, a flip angle of 41° and an acquisition time of 1 second. In order to see some quaternary carbon atoms better it was necessary to insert in the sequence a pulse delay of 4 seconds between the pulse. The coupled spectra with nuclear Overhauser effect (nOe) were obtained by putting the decoupler on during a pulse delay and off during acquisition time. For the coupled spectra an acquisition time of 1 second, a flip angle of 74° and a pulse delay of 2 seconds were used.

The ^1H homonuclear nOe experiments were run automatically by using the NOE-DIFF program (version 6.3A, Software Varian). This works by repetition of the basic sequence irradiation (4 seconds) and acquisition of one transient. During the preirradiation time the irradiation frequency was cycled through all the required positions. An off-resonance irradiation frequency (-10000 Hz) was included to provide the control spectrum. Alternate FIDs were substracted, beginning with the second pulse for which the decoupler was set to the off-resonance position and the result was collected. The numbers of repetitions of the pulse sequences were large enough to build up good signal-to-noise. In the nOe experiments the samples were not degassed.

The following abbreviations are used: s = singlet, d = doublet, dd = double doublet, t = triplet, m = multiplet, br = broad.

An arbitrary numbering, reported in the schemes, is used to identify the most significant carbon atoms of the intermediates **2-3**, **10-11**, **13**.

Dimethyl 1,2,4-Triazole-3,5-dicarboxylate (**7**) [8].

Method A.

Gaseous hydrogen chloride is bubbled for 2 hours into a stirred suspension of the monopotassium salt of 1,2,4-triazole-3,5-dicarboxylic acid **8** [8] (31 mmoles) in methanol (200 ml) at 0°. The mixture is set aside at room temperature for 48 hours. The solid is filtered off and the clear solution concentrated to half volume and then neutralized with anhydrous potassium carbonate. Elimination of the solid and evaporation of the solvent at the rotavapor gives a residue which is treated with chloroform/methanol, 7:3. The solvents of the organic layer are evaporated at the rotavapor to give a residue which is chromatographed on a silica gel column (eluting system chloroform/ethyl acetate, 7:3).

Evaporation of the first eluates gave the methyl 1,2,4-triazole-3(5)-carboxylate **9** [9] which is recrystallized from ethyl acetate, mp 200-201°, 15% yield, (lit [9] mp 198° dec); ir: 1725 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): 3.93 (s, 3H, CH_3), 8.32 (s, 1H, CH triazole).

Anal. Calcd. for $C_4H_5N_3O_2$ (127.12): C, 37.79; H, 3.97; N, 33.06. Found: C, 37.58; H, 3.89; N, 33.27.

Evaporation of the second eluates yielded dimethyl 1,2,4-triazole-3,5-dicarboxylate **7** [8] which may be recrystallized either from a little water, mp 149-151° or from diethyl ether, mp 146-147°, 17% yield (lit [8] mp 149-150° from water); ir: 3200, 1760, 1735 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): 3.96.

Anal. Calcd. for $C_6H_7N_3O_4$ (185.16): C, 38.92; H, 3.82; N, 22.70. Found: C, 38.75; H, 3.72; N, 22.98.

Following the same synthetic procedure but using concentrated sulfuric acid instead of gaseous hydrogen chloride, compounds **7** and **9** are obtained in very low yields (8%).

Method B.

Compound **7** alone is recovered in 40% yield from the tripotassium salt of the 1,2,4-triazole-3,5-dicarboxylc acid **12** with the same procedure as that described in Method A.

Methyl 1-(2-Nitrobenzyl)-1,2,4-triazole-5-carboxylate (**10**) and Methyl 1-(2-Nitrobenzyl)-1,2,4-triazole-3-carboxylate (**11**).

A solution of silver nitrate (15.3 mmoles in 7 ml of water) is added dropwise to a stirred warm (50°) solution of **9** (7.1 mmoles) in water (10 ml). The stirred mixture is allowed to cool at room temperature. The silver salt is filtered, washed with water and dried overnight at 80° under vacuum, 96% yield.

Equimolar amounts (4.3 mmoles) of powdered silver salt and 2-nitrobenzyl bromide, under stirring and nitrogen flow, are slowly heated from 75° to 130° (1 degree per minute). The residue is treated three times with hot methanol (50 ml each time). Filtration of the solid and concentration at the rotavapor of the clear solution affords a residue which is chromatographed on a silica gel column (eluting system chloroform/ethyl acetate, 1:1).

The first and second eluates are discarded. Evaporation of the third eluate gives compound **10** which is recrystallized from cyclohexane/ethyl acetate, mp 111-113°, 3% yield; ir: 1740 cm^{-1}; ^1H nmr (deuteriochloroform): 3.96 (s, 3H, CH_3), 6.22 (s, 2H, CH_2), 6.85 (dd, 1H, benzene proton in 6'), 7.46-7.61 (m, 2H, benzene protons in 4' + 5'), 8.08 (s, 1H, triazole proton in 3), 8.16 (dd, 1H, benzene proton in 3'); ^{13}C nmr (deuteriochloroform): 151.95 (d, C-3), 145.20 (s, C-5), 52.26 (t, C-6), 53.78 (q, C-7).

Anal. Calcd. for $C_{11}H_{10}N_4O_4$ (262.25): C, 50.38; H, 3.84; N, 21.37. Found: C, 49.98; H, 4.01; N, 21.30.

Evaporation of the fourth eluate gives compound **11** which is recrystallized from cyclohexane/ethyl acetate, mp 150-151°, 24% yield; ir: 1738 cm^{-1}; ^1H nmr (deuteriochloroform): 3.99 (s, 3H, CH_3), 5.83 (s, 2H, CH_2), 7.27 (dd, 1H, benzene proton in 6'), 7.53-7.70 (m, 2H, benzene protons in 4' + 5'), 8.17 (dd, 1H, benzene proton in 3'), 8.38 (s, 1H, triazole proton in 5); ^{13}C nmr (deuteriochloroform): 155.73 (s, C-3), 146.25 (d, C-5), 51.71 (t, C-6), 53.33 (q, C-8).

Anal. Calcd. for $C_{11}H_{10}N_4O_4$ (262.25): C, 50.38; H, 3.84; N, 21.37. Found: C, 50.01; H, 3.91; N, 21.45.

Dimethyl 1-(2-Nitrobenzyl)-1,2,4-triazole-3,5-dicarboxylate (**2**) and 2-Nitrobenzyl Methyl 1-(2-Nitrobenzyl)-1,2,4-triazole-3,5-dicarboxylate (**13**).

The silver salt of **7** is obtained with 80% yield from **7** (12 mmoles) and a solution of silver nitrate (23.5 mmoles in 10 ml of water), following the procedure described above to prepare the silver salt of **9**.

The powdered silver salt (6.16 mmoles) and nitrobenzyl bromide (8.3 mmoles) are reacted together using the same conditions as described to obtain **10** and **11**.

The first eluates are discarded. Evaporation of the second eluates gives compound **13** which is recrystallized from ethyl acetate, mp 197-198°, 25% yield; ir 1760, 1735 cm^{-1}; ^1H nmr (deuteriochloroform): 3.86 (s, 3H, CH_3), 5.59 (s, 2H, CH_2 ester), 5.69 (s, 2H, CH_2 at 1-N), 7.12-7.23 (m, 2H, benzene protons), 7.48-7.69 (m, 4H, benzene protons), 8.11-8.17 (m, 2H, benzene protons); ^{13}C nmr (deuteriochloroform): 47.89 (t, C-6 or C-8), 53.80 (q, C-7), 44.25 (t, C-8 or C-6).

Anal. Calcd. for $C_{19}H_{15}N_5O_8$ (441.39): C, 51.71; H, 3.43; N, 15.87. Found: C, 51.67; H, 3.45; N, 15.94.

Evaporation of the third eluate affords compound **2** which is recrystallized from methanol, mp 123-125°, 55% yield; ir: 1745, 1740 cm^{-1}; ^1H nmr (deuteriochloroform): 3.93 (s, 3H, CH_3 ester in 5), 3.98 (s, 3H, CH_3 ester in 3), 6.24 (s, 2H, CH_2), 6.83 (dd, 1H, benzene proton in 6'), 7.48-7.55 (m, 2H, benzene protons in 4' + 5'), 8.14 (dd, 1H, benzene proton in 3'); ^{13}C nmr (deuteriochloroform): 154.20 (s, C-3), 146.43 (s, C-5), 53.02 (t, C-6), 54.02 (q, C-7), 53.54 (q, C-8).

Anal. Calcd. for $C_{13}H_{12}N_4O_6$ (320.29): C, 48.76; H, 3.78; N, 17.49. Found: C, 48.55; H, 3.81; N, 17.53.

Dimethyl 1-(2-Aminobenzyl)-1,2,4-triazole-3,5-dicarboxylate (**3**).

To a solution of **2** (2.2 mmoles) in ethyl acetate (150 ml) 10% Pd/C (0.2 g) is added. The mixture is hydrogenated overnight in a Parr apparatus at 1.8 atmospheres. Removal of the catalyst and evaporation at the rotavapor of the solvent afford a residue which is recrystallized from ethanol, mp 119-120°, 90% yield; ir: 3460, 3380, 1750, 1735 cm^{-1}; ^1H nmr (deuteriochloroform): 3.0 (br s, 2H, NH_2), 3.95 (s, 3H, CH_3 ester in 5), 4.00 (s, 3H, CH_3 ester in 3), 5.79 (s, 2H, CH_2), 6.65-6.78 (m, 2H, benzene protons), 7.08-7.18 (m, 1H, benzene proton), 7.38-7.41 (m, 1H, benzene proton); ^{13}C nmr (deuteriochloroform): 153.38 (s, C-3), 145.30 (s, C-5), 52.85 (t, C-6), 53.93 (q, C-7), 53.40 (q, C-8).

Anal. Calcd. for $C_{13}H_{14}N_4O_4$ (290.31): C, 53.79; H, 4.86; N, 19.30. Found: C, 53.48; H, 5.01; N, 19.22.

10,11-Dihydro-11-oxo-5H-1,2,4-triazolo[5,1-*c*][1,4]benzodiazepin-2-carboxylic Acid (**4**).

A mixture of **3** (2.07 mmoles), anhydrous *N,N*-dimethylformamide (10 ml) and sodium hydride (80%, 0.2 g) is stirred at room temperature overnight. Ice is added with caution to the mixture, which is cooled at 0°. After 1 hour the solvent is distilled off at the rotavapor. The residue is dissolved in water (8 ml) and the solution acidified at *p*H 1 with 12 *N* hydrochloric acid. The resulting solid is collected, dried and recrystallized from methanol, mp 210° dec, 71% yield; ir: 3260, 1740, 1675 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): 5.67 (s, 2H, CH_2), 7.21-7.62 (m, 4H, benzene protons), 11.23 (s, 1H, COOH); ^{13}C nmr (dimethyl sulfoxide-d_6): 153.98 (s, C-2), 51.55 (t, C-5), 127.10 (s, C-5a), 129.64 (d, C-6), 130.17 (d, C-7), 125.69 (d, C-8), 122.39 (d, C-9), 136.62 (s, C-9a), 156.69 (s, C-11), 148.05 (s, C-11a), 160.50 (s, COOH).

Anal. Calcd. for $C_{11}H_8N_4O_3$ (244.23): C, 54.10; H, 3.30; N, 22.94. Found: C, 53.98; H, 3.36; N, 23.00.

10,11-Dihydro-5*H*-1,2,4-triazolo[5,1-*c*][1,4]benzodiazepin-11-one (**5**).

The acid **4** (2.46 mmoles) is heated at reduced pressure (0.2 mm Hg) to 210° for 10 minutes. The crude mass is purified by silica gel column chromatography (eluting system chloroform/-methanol, 9:1) and recrystallyzed from ethyl acetate, mp 254-255°, 43% yield; ir: 1690 cm^{-1}; ^1H nmr (deuteriochloroform): 5.46 (s, 2H, CH_2), 7.22-7.47 (m, 4H, benzene protons), 8.00 (s, 1H, triazole proton), 9.6 (br s, 1H, NH); ^{13}C nmr (deuteriochloroform): 151.90 (d, C-2), 52.59 (t, C-5), 126.73 (s, C-5a), 129.72 (d, C-6), 131.00 (d, C-7), 126.90 (d, C-8), 122.84 (d, C-9), 136.33 (s, C-9a), 158.97 (s, C-11), 146.80 (s, C-11a).

Anal. Calcd. for $C_{10}H_8N_4O$ (200.22): C, 60.00; H, 4.03; N, 27.99. Found: C, 60.30; H, 3.98; N, 27.89.

10,11-Dihydro-5*H*-1,2,4-triazolo[5,1-*c*][1,4]benzodiazepine (**6**).

A suspension of **5** (4.24 mmoles), lithium aluminium hydride (21 mmoles) in freshly distilled tetrahydrofuran (200 ml) is stirred at -10° for 24 hours and then at 0° for 24 hours. After removal of excess lithium aluminium hydride by adding ice, ethyl acetate (200 ml) is added. Removal of the solid and evaporation at the rotavapor of the solvent affords a residue which is chromatographed on a silica gel column (eluting system chloroform/ethanol, 9.5:0.5). Evaporation of the second eluates gives compound **6** which is recrystallized from cyclohexane/ethyl acetate, mp 170-173°, 30% yield; ir: 3300 cm^{-1}; ^1H nmr (deuteriochloroform): 3.8 (br s, 1H, NH), 4.55 (s, 2H, CH_2 at position-11), 5.40 (s, 2H, CH_2 at position-5), 6.96-7.37 (m, 4H, benzene protons), 7.80 (s, 1H, triazole proton); ^{13}C nmr (deuteriochloroform): 150.29 (d, C-2), 52.93 (t, C-5), 128.20 (s, C-5a), 130.04 (d, C-6), 130.57 (d, C-7), 123.74 (d, C-8), 121.91 (d, C-9), 152.11 (s, C-9a), 47.31 (t, C-11), 148.26 (s, C-11a).

Anal. Calcd. for $C_{10}H_{10}N_4$ (186.24): C, 64.50; H, 5.41; N, 30.09. Found: C, 64.47; H, 5.45; N, 29.99.

5*H*-1,2,4-triazolo[5,1-*c*][1,4]benzodiazepine (**1**).

A powdered mixture of **6** (0.86 mmoles) and Pd/C (10%, 1 g) is heated at reduced pressure (0.2 mm Hg) at 180° for 1 hour. The crude mass is taken up with chloroform/methanol (1:1, 75 ml). The solid is filtered off and the solvent evaporated at the rotavapor. The residue is chromatographed on a silica gel column (eluting system chloroform/absolute ethanol, 9.5:0.5) and recrystallyzed from diethyl ether, mp 149-151°, 31% yield; ^1H nmr (deuteriochloroform): 5.29 (s, 2H, CH_2), 7.28-7.59 (m, 4H, benzene protons), 7.95 (s, 1H, triazole proton), 8.73 (s, 1H, 11-proton); ^{13}C nmr (deuteriochloroform): 152.11 (d, C-2), 52.53 (t, C-5), 126.66 (s, C-5a), 129.82 (d, C-6), 130.36 (d, C-7), 129.59 (d, C-8), 129.37 (d, C-9), 146.55 (s, C-9a or C-11a), 147.39 (d, C-11), 147.81 (s, C-11a or C-9a).

Anal. Calcd. for $C_{10}H_8N_4$ (184.22): C, 65.19; H, 4.39; N, 30.42. Found: C, 65.23; H, 4.35; N, 30.48.

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