On Triazoles. XXXIV [1]. The Correct Structure of the Ethoxycarboxylated 5-Amino-1*H*-1,2,4-triazole and its Product with Hydrazine

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The structure of the ethoxycarboxylated product of 5-amino-1*H*-1,2,4-triazole and its hydrazide was corrected using their ir, pmr, cmr and mass spectra.

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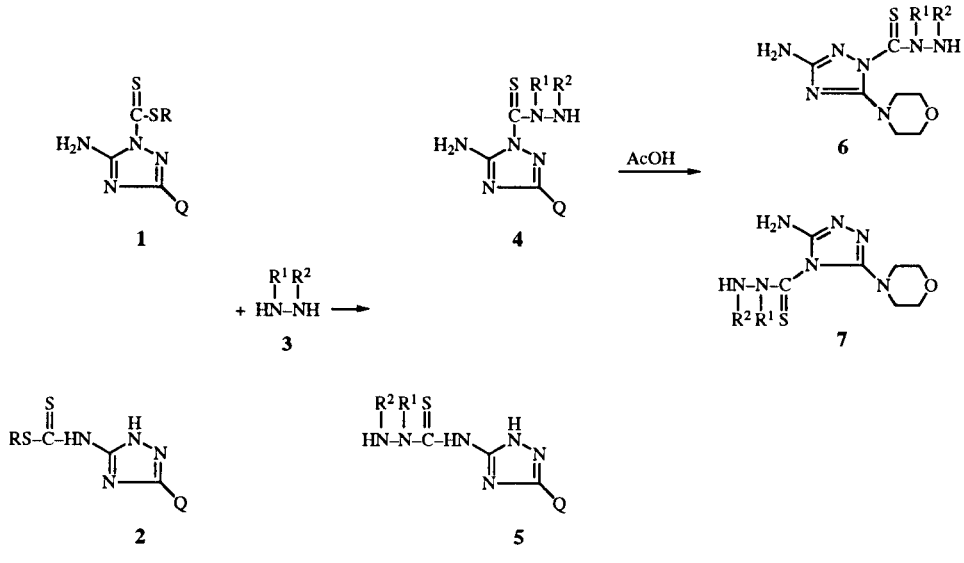
Recently we have reported on the synthesis of different 1,2,4-triazolylcarbothiohydrazides **4** and **5** by the reaction of the corresponding dithioesters **1** and **2** with hydrazines **3** as well as the thermal rearrangement of derivatives **4** under acidic conditions to yield isomers **6** and **7**, respectively (Scheme 1) [2].

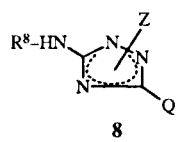
Scheme 1



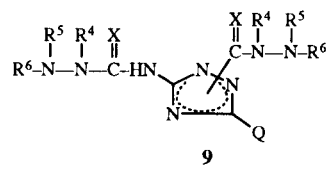
Since derivatives **4-7** possessed valuable antianginal, tranquillo-sedative, cardiovascular and antiulcerogenic activities they were patented prior to the above report [3]. In this Patent Application we wanted to claim compounds of the General Formula **8** (Scheme 2) where Z denoted a hydrogen atom or a group $C(=X)NR^4NR^5R^6$, where X denoted an oxygen or sulphur atom and R^8 denoted a hydrogen atom or a group Z with the proviso that if R^8 denoted a hydrogen atom, Z had to denote a group of formula $C(=X)NR^4NR^5R^6$ and if Z denoted a group of formula $C(=X)NR^4NR^5R^6$, Z had to denote hydrogen atom, representing all four isomeric types **4-7** prepared by routes shown on Scheme 1.

In the Office Action the US Patent Office queried the necessity of the above provisos since in their opinion during the thermal rearrangement of derivatives **4** disubstituted derivatives of type **9** (Scheme 3) could also be formed. We argued that derivatives **4** had only **one** $C(=X)NR^4NR^5R^6$ group and consequently their rearrangement had to leave preferably to **5, 6** or **7** type monosubstituted derivatives, moreover it was also known [4-6] that the diacylated triazoles were highly sensitive to water making practically impossible their biological evaluation. The Office wanted to reject our Patent Application on the basis that there was a published paper by W. Rudnicka [7] in which the author described the reaction of

Scheme 2

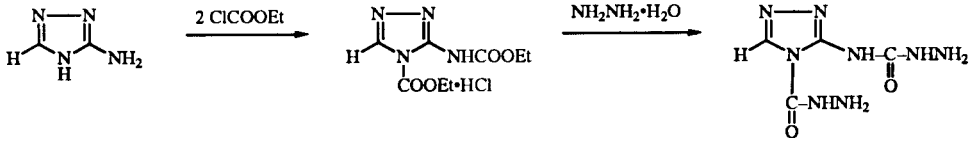


Scheme 3



reaction of 5-amino-1*H*-1,2,4-triazole (**10**) with ethyl chloroformate to yield the diester **11** which on reaction with hydrazine hydrate gave the dihydrazide **12** (Scheme 4, all derivatives are depicted with incorrect isomeric and tautomeric structures given by W. Rudnicka [7]). Product **11** was characterised by the above author with a melting point of 145-147°, while product **12** was claimed to be an oil. Both products were further characterised with correct analytical data.

Scheme 4

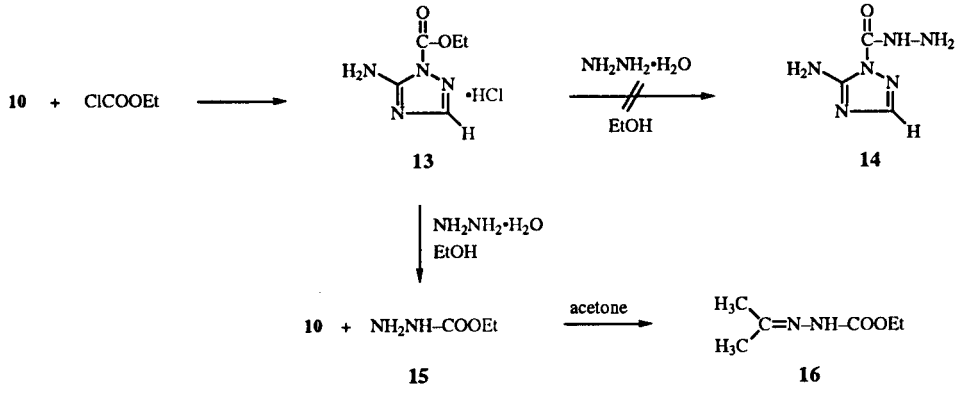


10 **11** **12**

Taking in account the previous observations [4-6], structures **11** and **12** described by W. Rudnicka seemed to be scarcely possible. Thus I have repeated the above experiments using exactly the same reaction conditions as described in [7]. The product obtained in the first reaction step (Scheme 4) showed a melting point of 150-152°, practically identical with that of given by W. Rudnicka (145-147°). However, its analytical data (See Experimental) were very different from those of given by W. Rudnicka and corresponded to the molecular formula $C_5H_8N_4O_2$•HCl, *i.e.* a monoacylated product **13** (Scheme 5). This is also in agreement with its mass spectra taken in both EI and CI modes showing molecular ions of 156 and 157, respectively. In the pmr spectra of derivative **13** the ratio of integrals of the peaks appearing at 8.14 (s, CH), 4.46 (qa, OCH_2), 1.36 (t, CH_3) and 8.5-9 (b, NH_3^+)was 1:2:3:3, respectively, also excluding the possibility of structure **11** stipulated by W. Rudnicka. The chemical shifts of the CH proton and the NH_2 groups of **13 base** liberated from the above material appeared at 7.56 and 7.35 ppm, respectively, in perfect agreement with those obtained by Winkler and Kristinson [8] for the analogues methyl (5-amino-1*H*-1,2,4-triazole-1-yl)carbonate (7.50 and 7.33 ppm, respectively), and also the chemical shifts of the triazole carbon atoms 3 and 5 followed those published earlier [8] for the methyl ester (δ C-3 = 151.5 and 151.2; δ C-5 = 157.9 and 157.5, respectively), corroborating the 1-acylated triazole structure of **13**.

Thus it was clear that in the above reaction of **10** and ethyl chloroformate not the diester **11** but the monoester **13** was formed. For patent reasons I have repeated Rudnicka's reaction of the "diester" **11** with hydrazine hydrate, too, again using the same reaction conditions. I have really obtained an oily product, however, it was neither the dihydrazide **12**, nor the hydrazide **14**, but showed two spots by tlc. After addition of acetone it crystallized to yield 5-amino-1*H*-1,2,4-triazole (**10**), mp 152-153° (Interestingly, W. Rudnicka [7] gave an mp of 150-152° for the "picrate" formed from the oily reaction product of **11** and hydrazine hydrate claimed to be **12**!). Column chromatography of the mother liquor yielded acetone carbethoxyhydrazone (**16**). Its formation could be easily explained by assuming that after nucleophilic attack of hydrazine against the carbonyl carbon atom of **13** the 5-amino-1*H*-1,2,4-triazole was split off and the resulting carbethoxyhydrazine (**15**) gave a Schiff's base during work up with acetone. It is worth mentioning that the

Scheme 5



13 **14** **15** **16**

reaction of **13** with hydrazine hydrate led even under very mild reaction conditions (0°) to the splitting of the 5-amino- 1*H*-1,2,4-triazole moiety to yield **10** and **15**. The formation of the expected hydrazide **14** was not observed in this reaction.

Experimental

Melting points were determined on a Koffler-Boëtius micro apparatus and are uncorrected. The infrared spectra were obtained as potassium bromide pellets using a Bruker IFS 113-V spectrophotometer. The ultraviolet spectra were obtained by a Pye Unicam SP 8-150 and a Perkin-Elmer 555 Instrument, The pmr and the cmr measurements were performed using Bruker WM-250 and Bruker WP-80 SY instruments All tlc determinations were carried out on Kieselgel GF_{254} (Merck) plates. The spots were detected by uv and I_2 vapors.

Ethyl (5-Amino-1*H*-1,2,4-triazol-1-yl)carboxylate Hydrochloride (**13•HCl**) (Reproduction of Rudnicka's Experiment claimed to yield **11**).

To a solution of 2.0 g (0.0238 mole) of 5-amino-1*H*-1,2,4-triazole (**10**) in 20 ml of ethanol, 5.2 g (0.05 mole) of ethyl chloroformate were added and the reaction mixture was refluxed with stirring for 3 hours. Within 10 minutes, white crystals started to separate. After cooling the crystals were filtered off and washed with a small amount of ethanol to yield 1.7 g (37%) of ethyl (5-amino-1*H*-1,2,4-triazol-1-yl)carboxylate hydrochloride (**13•HCl**), mp 146-150°. After recrystallization from ethanol the melting point rose to 150-152° (melting point given by W. Rudnicka for **11** is 145-147°); ir: ν C=O = 1769 cm^{-1}, ν C=N = 1687 and 1581 cm^{-1}; pmr (DMSO-d_6) δ ppm 1.36 (t, 3H, CH_3), 4.46 (qa, 2H, OCH_2), 8.14 (s, 1H, CH), 8.5-9.0 (b, 3H, NH_3^+); cmr (DMSO-d_6): δ ppm 13.8 (CH_3), 65.0 (OCH_2), 144.1 (C-**3**), 149.0 (C=0), 153.6 (C-**5**); ms: (EI): M^+ = 156; ms: (CI) M^+ = 157.

Anal. Calcd. for $C_5H_9ClN_4O_2$ (MW 192.61): C, 31.18; H, 4.71; N, 29.09; Cl, 18.41. Found: C, 31.50; H, 4.75; N, 28.90; Cl, 18.18.

Ethyl (5-Amino-1*H*-1,2,4-triazol-1-yl)carboxylate (**13**).

To the solution of 1 g (0.0052 mole) of ethyl (5-amino-1*H*-1,2,4-triazol-1-yl)carboxylate hydrochloride (**13•HCl**) in 50 ml of water, 50 ml of chloroform and 1 ml of triethylamine were added and the mixture was stirred at room temperature for 10 minutes. The layers were separated, the chloroform phase was washed with water, dried over anhydrous sodium sulfate and evaporated to dryness to yield 0.54 g (67%) of white crystals that after recrystallisation from 2-propanol melted at 117-120°; ir: ν NH_2 = 3468 cm^{-1}, ν C=O = 1746 cm^{-1}, ν C=N = 1631 and 1547 cm^{-1}; pmr (DMSO-d_6): δ ppm 1.34 [t (J = 7.1 Hz), 3H, CH_3], 4.41 [qa (J = 7.1 Hz), 2H, OCH_2], 7.35 (bs, 2H, NH_2), 7.56 (s, 1H, CH); cmr (DMSO-d_6): δ, ppm 14.0 (CH_3), 64.1 (OCH_2), 150.3 (C=O), 151.5 (C-3), 157.9 (C-5) (assignment checked by INEPT).

The Reaction of Ethyl (5-Amino-1*H*-1,2,4-triazol-1-yl)carboxylate Hydrochloride (**13•HCl**) with Hydrazine Hydrate in Boiling Ethanol [Reproduction of Rudnicka's Experiment claimed to yield dihydrazide of 3-Carboxyamino-4-carboxy-1,2,4-triazole (**12**)].

To the mixture of 2.0 g (0.0104 mole) of ethyl (5-amino-1*H*-1,2,4-triazol-1-yl)carboxylate hydrochloride (**13•HCl**) and 10 ml of ethanol, 10 ml of 80% hydrazine hydrate was added and the mixture was refluxed with stirring for 2 hours. The solvents were evaporated *in vacuo* to dryness. The residue (2.4 g) crystallized upon standing. This was triturated with 30 ml of benzene, the unsoluble hydrazine monohydrochloride (mp 85-89°) was filtered off and the filtrate was evaporated again *in vacuo* to dryness. Thus 1.85 g of an oily product was obtained that showed two spots by tlc (eluent a 3:1 mixture of chloroform and methanol). This was dissolved by slight heating in 30 ml of acetone and allowed to crystallize. The crystals which precipitated were filtered off and recrystallized from 2-propanol to yield 0.4 g (46%) of 5-amino-1*H*-1,2,4-triazole, mp 152-153° that was identical with that of starting material **10**. The acetone containing mother liquor was evaporated *in vacuo* to dryness and the residue was chromatographed on a silica-gel column (eluent chloroform) to yield 0.72 g (48%) of acetone carbethoxyhydrazone (**16**), mp 73-74° (ether) (Lit [9] mp 74-75°); pmr (DMSO-d_6): δ ppm 1.32 (t, 3H, CH_2CH_3), 1.88 (s, 3H, CH_3), 2.07 (s, 3H, CH_3), 4.30 (qa, 2H, CH_2), 7.85 (s, 1H, NH); ms: (El) M^+ = 144. Washing up the column with methanol afforded a further crop (0.37 g, 42%) of 5-amino-1*H*-1,2,4-triazole increasing its yield to 88%.

The Reaction of Ethyl (5-Amino-1*H*-1,2,4-triazol-1-yl)carboxylate Hydrochloride (**13•HCl**) with Hydrazine Hydrate at 0°.

A mixture of 0.32 g (0.002 mole) of ethyl (5-amino-1*H*-1,2,4-triazol-1-yl)carboxylate hydrochloride (**13•HCl**), 3 ml of ethanol and 0.19 ml (0.0184 g, 0.004 mole) of 100% hydrazine hydrate was stirred at 0° for 6 hours. The suspension was filtered to yield 0.1 g of hydrazine monohydrochloride (mp 84-89°). To the filtrate 10 ml of acetone was added, boiled for 10 minutes and evaporated *in vacuo* to dryness, The oily residue was chromatographed on a silica gel column (eluent chloroform) to yield 0.21 g (73%) of acetone carbethoxyhydrazone (**16**), mp 74-75° (ether) that was identical with that obtained in the previous experiment. Washing up the column with methanol afforded 0.13 g (77%) of 5-amino-1*H*-1,2,4-triazole, mp 151-152° that was identical with the authentic sample obtained in the previous experiment.

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