Rearrangement and Elimination Reactions in 1,2,4-Triazole Derivatives

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Four possible nucleophilic sites are available when 3-amino-1,2,4-triazole (4) reacts with isocyanates or alkylating agents. In the reaction with ethoxycarbonyl isothiocyanate at 22°, addition to a ring nitrogen took place yielding 5-amino-1-[ethoxycarbonylamino(thiocarbonyl)]-1,2,4-triazole (1). The rearrangement of compound (1) to the amino-substituted isomer (2) in dimethylformamide was followed by n.m.r. spectroscopy and found to be complete in 34 min under ambient conditions. In pyridine solution compound (1) reacted differently, with HNCS elimination, to give 5-amino-1-ethoxycarbonyl-1,2,4-triazole (3). Two additional isomers of (3) were prepared, by the rearrangement of (3) and by the low temperature reaction of (4) with ethyl chloroformate. The carbonyl analogues of (1) and (2) were prepared by use of the analogous isocyanate. The ring-substituted carbonyl compound rearranged more slowly to the amino-substituted isomer than did compound (1), and elimination of HNCO was not observed. Both carbonyl analogues were cyclised to [1,2,4]triazolo[1,5-*a*][1,3,5]triazine-5,7-dione (5-azaxanthine). Two methylaminocarbonyl derivatives of (4) were also prepared, isolated, and characterized.

DURING the preparation of 1,2,4-triazole derivatives,[1] the formation of 5-amino-1-[ethoxycarbonylamino(thiocarbonyl)]-1,2,4-triazole (1) and its isomer (2) was found to depend on the reaction temperature. Isomer (1) was obtained only at low temperature, and underwent rearrangement to isomer (2) at elevated temperature. In a recent report [2] of the preparation of (2), the isolation of unstable isomer (1) was not mentioned. The ready rearrangement reaction may be responsible for this omission, as well as for a misassignment [3] of structure of

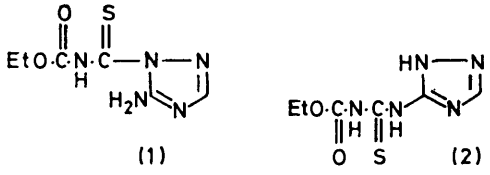
[1] T. Hirata, L. M. Twanmoh, H. B. Wood, jun., A. Goldin, and J. S. Driscoll, *J. Heterocyclic Chem.*, 1972, **9**, 99.

[2] L. Capuana and H. J. Schrepfer, *Chem. Ber.*, 1971, **104**, 3039.

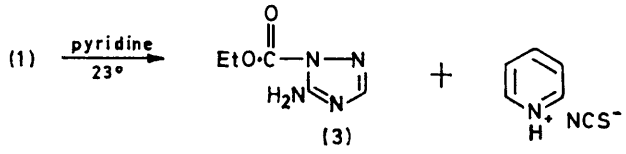
[3] G. Cipens, R. Bokaldares, and V. Grensteins, U.S.S.R. P., 213,887/1968; (*Chem. Abs.*, 1968, **69**, P67,388a).

the isomer (2). The present study was conducted to elucidate the interconversions among isomers in this series of compounds.

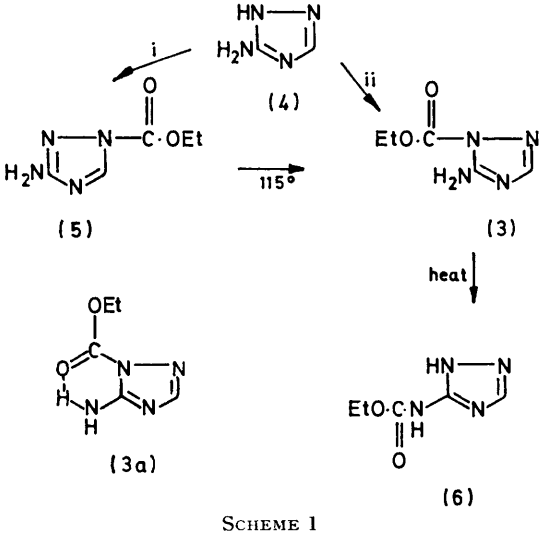
The rearrangement (1) ⟶ (2) was found to be complete in 34 min under ambient conditions or in 238



min at 10° in dry [$^2H_7$]dimethylformamide. The reaction was followed by observing the intensity of n.m.r. signal due to the C-3 proton of (1). An unexpected reaction was observed when (1) was treated with pyridine at room temperature. The product was 5-amino-1-ethoxycarbonyl-1,2,4-triazole (3) instead of the expected compound (2). The HNCS eliminated was isolated as the pyridine salt by sublimation of the



evaporated reaction mixture. A similar HNCS elimination has recently been reported in the tetrazole and benzimidazole systems.[2] Compound (3) was also prepared by the reaction of 3-amino-*s*-triazole (4) with



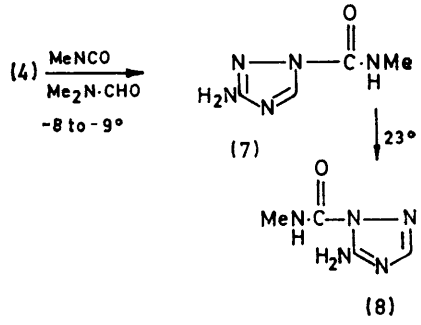
Scheme 1

Reagents: i, $ClCO_2Et$, Et_3N–Me_2N·CHO (−8°); ii, $ClCO_2Et$–C_5H_5N (ambient)

ethyl chloroformate in pyridine at room temperature (Scheme 1).

Two further isomers were prepared by the reactions shown in Scheme 1. The reaction of (4) with ethyl chloroformate in the presence of triethylamine in dimethylformamide at −8° furnished a mixture of two isomers (3) and (5). The latter was isolated and purified by fractional recrystallization. Heating the former (3) gave the isomer (6), which was easily distinguished from the other two by the characteristically [1] deshielded ring NH proton, and the relatively low frequency of i.r. carbonyl absorption. The fourth possible isomer, 3-amino-4-ethoxycarbonyl-1,2,4-triazole, which would be expected to have both the C-5 and NH_2 proton signals at low field, was not observed.

The differences in i.r. carbonyl absorption frequencies, as well as the relative stabilities of isomers (3) and (5) might be explained by intramolecular hydrogen bonding (3a). When (5) was heated in [$^2H_5$]pyridine at 115°, it rearranged first to (3) and then to (6), the reactions being followed by n.m.r. spectroscopy. The mass spectra of these three isomers gave additional confirmation of their structures. The McLafferty rearrangement [4] (loss of CH_2=CH_2 and CO_2) and the loss of CO_2 and CH_3· give odd-electron (*m/e* 84) and even-electron (*m/e* 97) common fragments, respectively, but isomer (6) has another unique fragment (*m/e* 110) due to loss of EtOH. The lower-mass fragments (*m/e* 57, 43, 42, and 27), which originate from the common ion *m/e* 84, show good agreement with previous reports.[5]



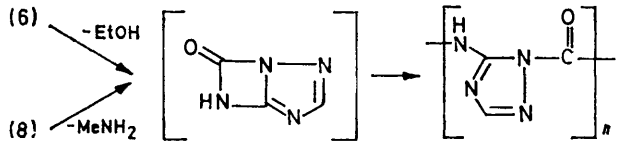
Compound (7), the methylamino-analogue of (5), rearranged even more readily than (5). Compound (7) was prepared from (4) and methyl isocyanate in dimethylformamide at −8°. The ring proton of (7) was, as expected, deshielded relative to that of (8).[1] The n.m.r. spectrum was determined at −10° in [$^2H_7$]dimethylformamide in order to reduce the rearrangement rate. The problems of low solution concentration and fast scan times were overcome by the use of the Fourier transform technique. Owing to the extreme ease of the conversion (7) ⟶ (8), an n.m.r. spectrum of (7) run under ambient conditions is essentially that of isomer (8). A small peak due to methyl isocyanate was observed. This suggests an intermolecular rearrangement mechanism. The conversion (7) ⟶ (8) also occurred in the solid state. Whereas complete conversion took several months under ambient conditions, the rearrangement was quantitative in 240 min at 85°.

[4] J. B. Thomson, P. Brown, and C. Djerassi, *J. Amer. Chem. Soc.*, 1966, **88**, 4049.

[5] (*a*) P. R. Briggs, W. L. Parker, and T. W. Shannon, *Chem. Comm.*, 1968, 727; (*b*) K. T. Potts, R. Armbruster, and E. Houghton, *J. Heterocyclic Chem.*, 1972, **8**, 773.

The formation of a urea isomer analogous to (6) was never observed.

Compounds (6) and (8) both gave similar intractable polymer-like solids when heated in pyridine at 134°. The formation of a common unstable intermediate such as (9), followed by polymerization, is conceivable. An

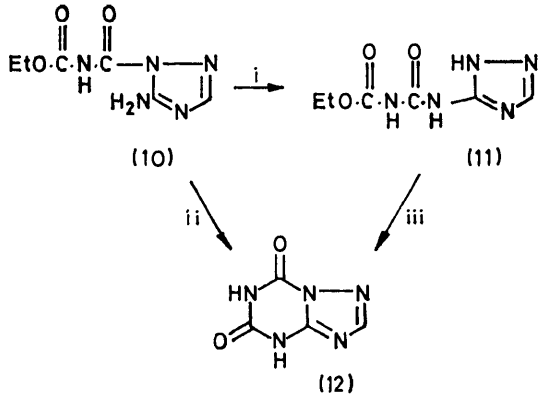


(9)

increasing n.m.r. peak intensity of EtOH methylene protons was observed as (6) decomposed.

Compound (10), the carbonyl analogue of the thiocarbonyl compound (1), was prepared in order to compare its reactivity with that of (1). Compound (10) rearranged to the known [2] isomer (11) at a slightly lower rate in dimethylacetamide (43 min at ambient temp.; 255 min at 10°) than the thio-analogue (1). In contrast with (1), the elimination of HNCO from (10) in pyridine to form (3) was not observed. This was also true even in a more basic medium (triethylamine).

Mass spectra of the 3-amino-substituted isomers (2) and (11) show several significant fragments, *e.g.* those corresponding to loss of CO_2 (*m/e* 171 and 155), loss of EtOH (*m/e* 169 and 153), and the McLafferty rearrangement (*m/e* 143 and 127), as well as a common fragment (*m/e* 84). The mass spectra of the *N*-1 substituted isomers (1) and (10) consist mainly of 3-aminotriazole radical ion (*m/e* 84), reflecting the instability of these isomers. A loss of ethyl carbamate gives a fragment (*m/e* 126 or 110) characteristic of 3-amino-substituted



SCHEME 2

Reagents: i, $AcNMe_2$ or C_5H_5N; ii, NaOEt–EtOH (23°); iii, Na_2CO_3–H_2O (100°).

isomers. The small amounts of these fragments which appear in the spectra of (1) and (10) are probably due to thermal rearrangements in the spectrometer.

Both compounds (10) and (11) were converted into 5-azaxanthine (12) by the reactions shown in Scheme 2.

EXPERIMENTAL

M.p.s were measured with a Thomas–Hoover capillary apparatus. I.r. spectra were measured with Perkin-Elmer 621 and 137 spectrometers for Nujol mulls. U.v. spectra were determined on a Cary 15 spectrometer for solutions in 95% ethanol. ^1H N.m.r. spectra were recorded on a Varian HA100D spectrometer, with tetramethylsilane as internal standard, for *ca.* 5% solutions in [$^2H_6$]dimethyl sulphoxide unless otherwise stated. Elemental analyses were carried out by P. M. Parisius and A. L. Wong (N.I.A.M.D., N.I.H.). Mass spectra were determined at *ca.* 200° and 80 eV by W. R. Landis (N.I.A.M.D., N.I.H.), on a Hitachi–Perkin-Elmer RMU-7 instrument. Pyridine and dimethylacetamide were dried over potassium hydroxide and 4A molecular sieves, respectively. Dry dimethylformamide was prepared by two distillations from phosphorus pentoxide followed by two from potassium carbonate.

5-Amino-1-ethoxycarbonyl-1,2,4-triazole (3).—To a solution of 3-amino-1,2,4-triazole (4) (4·2 g) in dry pyridine (150 ml) was added ethyl chloroformate (5·4 g) while the temperature was kept below 25°. The mixture was stirred for 20 h at room temperature and evaporated to dryness. The residual solid was dissolved in chloroform; the solution was washed thoroughly with water, dried ($CaCl_2$), and evaporated. The resulting crude solid (5 g) was dissolved in a small amount of methanol and ether was added until the solution became slightly turbid. Refrigeration gave *needles* (2·3 g, 30%), m.p. 100—105°, $\nu_{max.}$ 1745 cm^{-1} (CO), $\lambda_{max.}$ 243 nm (ε 5300), δ 7·52 (1H, s, 3-H), 7·31 (2H, s, NH_2), 4·4 (2H, q, CH_2), and 1·32 (3H, t, Me), *m/e* 156 (M^+) (Found: C, 38·8; H, 5·2; N, 35·7. $C_5H_8N_4O_2$ requires C, 38·5; H, 5·1; N, 35·9%).

3-Amino-1-ethoxycarbonyl-1,2,4-triazole (5).—To a cold solution (−8 to −5°) of 3-amino-1,2,4-triazole (4) (4·2 g) in dry dimethylformamide (50 ml) containing triethylamine (5·1 g), was added ethyl chloroformate (5·4 g). After 30 min stirring at −8°, triethylamine hydrochloride was filtered off. The filtrate was evaporated to dryness *in vacuo* below 23° to give the crude *product* (5·1 g), which was recrystallized from anhydrous ethanol; yield 0·9 g, m.p. 131—133°. The mother liquor was evaporated and the residue was recrystallized to give a second crop (0·3 g; total 1·2 g, 16%), $\nu_{max.}$ 1770 cm^{-1} (CO), $\lambda_{max.}$ 263 nm (ε 5700), δ 8·69 (1H, s, 5-H), 6·00 (2H, s, NH_2), 4·38 (2H, q, CH_2), and 1·33 (3H, t, CH_3), *m/e* 156 (M^+) (Found: C, 38·5; H, 5·3; N, 36·5%). Evaporation of the mother liquor gave an almost homogeneous sample of the more stable isomer (3), which was recrystallized (MeOH–Et_2O) to give pure (3) (1·7 g, 22·6%).

3-Ethoxycarbonylamino-1,2,4-triazole (6).—A solution of the ethoxycarbonyl derivative (3) (200 mg) in dry pyridine (4 ml) was heated in a sealed Carius tube at 134° for 3 h. The precipitate was filtered off and the filtrate was evaporated. The residue (110 mg) was recrystallized from 95% ethanol to give the *product* (6) (95 mg, 48%), m.p. 221—224° (decomp.), $\nu_{max.}$ 1711 cm^{-1} (CO), $\lambda_{max.}$ 210 nm (ε 11,200), δ 12·65br (1H, 2-H), 11·06 (1H, s, CO·NH), 7·82 (1H, s, 5-H), 4·16 (2H, q, CH_2), and 1·23 (3H, t, CH_3), *m/e* 156 (M^+) (Found: C, 38·5; H, 5·2; N, 35·7%).

3-Amino-1-methylaminocarbonyl-1,2,4-triazole (7).—To a solution of 3-amino-1,2,4-triazole (4) (2·1 g) in dry dimethylformamide (10 ml) was added methyl isocyanate (1·4 ml) while the temperature was kept at −8 to −9° with an ice–methanol bath. The precipitate was filtered off and washed with cold ether to give a white solid (2·45 g, 70%),

which appeared to be homogeneous [its solid state i.r. spectrum (Nujol) showed only one carbonyl absorption, at 1740 cm^{-1}]. Analytical techniques which required the dissolution of (7), *e.g.* n.m.r. spectroscopy, or heating (m.p. 150—183°) caused partial conversion into (8), m.p. 190°, $\nu_{max.}$ 1710 cm^{-1}, which has a significantly different n.m.r. spectrum.[1] The spectrum of the mixture (−10° in [$^2H_7$]dimethylformamide; δ from acetone methyl peak as internal reference) showed [for (7)] 6·52br (1H, NH), 6·41 (1H, s, 5-H), and 4·63 (2H, s, NH_2) and [for (8)] 6·09br (1H, NH), 5·43 (1H, s, 3-H), and 5·26 (2H, s, NH_2) (Found: C, 33·8; H, 5·0; N, 50·0. $C_4H_7N_5O$ requires C, 34·0; H, 5·0; N, 49·7%). Recrystallization from ethanol gave homogeneous white crystals, m.p. 190°, identical with a sample of (8) previously prepared.[1]

5-Amino-1-ethoxycarbonylaminocarbonyl-1,2,4-triazole (10).—To a stirred solution of 3-amino-1,2,4-triazole (4) (1·68 g) in dry dimethylformamide (20 ml) was added ethoxycarbonyl isocyanate [6] (2·32 g) below −5°. The solution was stirred for 10 min at −5 to −15°. The precipitate was filtered off and washed with cold ether to give a fine *powder* (2·48 g, 58%), m.p. 212—214° (decomp.), $\nu_{max.}$ 1793 and 1645 cm^{-1} (CO), $\lambda_{max.}$ 250 nm (ε 2650), δ ([$^2H_5$]pyridine) 11·18br (1H, NH), 8·46br (2H, NH_2), 7·81 (1H, s, 3-H), 4·22 (2H, q, CH_2), and 1·14 (3H, t, CH_3), *m/e* 199 (M^+) (Found: C, 36·1; H, 4·6; N, 35·6. $C_6H_9N_5O_3$ requires C, 36·2; H, 4·6; N, 35·2%).

3-(3-Ethoxycarbonylureido)-1,2,4-triazole (11).—A solution of the ethoxycarbonylaminocarbonyl derivative (10) (300 mg) in dry dimethylacetamide (11 ml) was heated at 50° for 12 h, then evaporated to dryness to give a white *powder* (269 mg), m.p. 219—223° (from dimethylformamide), $\nu_{max.}$ 1760 and 1621 cm^{-1} (CO), $\lambda_{max.}$ 219 nm (ε 12,000), δ 13·34vbr (1H, 2-H), 10·58br and 10·30br (2H, 2 NH), 8·20 (1H, s, 5-H), 4·21 (2H, q, CH_2), and 1·26 (3H, t, CH_3), *m/e* 199 (M^+) (Found: C, 35·9; H, 4·6; N, 35·3. $C_6H_9N_5O_3$ requires C, 36·2; H, 4·6; N, 35·2%).

[1,2,4]Triazolo[1,5-a][1,3,5]triazine-5,7-dione (12).—*Method A.* Compound (10) (500 mg) was added in portions to sodium ethoxide [sodium (200 mg) in ethanol (20 ml)]. The mixture was stirred at room temperature overnight. After addition of water, the solution was acidified with N-hydrochloric acid and evaporated to dryness. The resulting white mixture was washed with cold water and filtered to give crude *product* (200 mg), which was recrystallised from 95% ethanol (yield 120 mg, 31%); decomp. >280°, $\nu_{max.}$ 1775 and 1730 cm^{-1} (CO), $\lambda_{max.}$ 225 (ε 5750) and 257 nm (3900), δ 12·0vbr (2H, 2 NH) and 8·03 (1H, s, 2-H), *m/e* 153 (M^+) (Found: C, 31·3; H, 2·0; N, 46·0. $C_4H_3N_5O_2$ requires C, 31·4; H, 2·0; N, 45·8%).

Method B. To a hot aqueous solution (2·0 ml) of sodium carbonate (500 mg) was added compound (11) (1·0 g). The mixture was refluxed for 10 min. The clear solution was cooled to 2° and the precipitate was filtered off to give a sodium salt (700 mg). This was dissolved in warm water, acidified with N-hydrochloric acid, and cooled to 2°. The crystals were filtered off and dried to yield the product (490 mg, 35%), identical with that prepared by Method A (i.r., u.v., and n.m.r. spectra).

Method C. Compound (10) (50 mg) was pyrolysed in a test tube at 220—240° for 5 min. The resulting solid (32 mg) was recrystallized from 95% ethanol to give crystals (22 mg, 58%) identical with the samples prepared by Methods A and B.

We thank Dr. Li-Ming Twanmoh for some of the ^1H n.m.r. spectra.

[6] R. W. Lamon, *J. Heterocyclic Chem.*, 1969, **6**, 261.

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