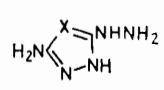
Triazines and Related Products. Part 21.[1] Cyclisation of 3-Amino-5-hydrazinopyrazole and 3-Amino-5-hydrazino-1,2,4-triazole to Azolo-[5,1-*c*][1,2,4]triazines

By **Elizabeth Jane Gray Howard N. E. Stevens,** and **Malcolm F. G. Stevens,*** Department of Pharmacy, University of Aston in Birmingham, Birmingham B4 7ET

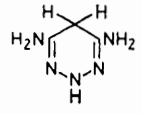
Interaction of malononitrile with two equivalents of hydrazine hydrate affords 3-amino-5-hydrazinopyrazole in high yield. The pyrazole reacts with ethyl pyruvate, diacetyl, and benzil to yield derivatives of 2-aminopyrazolo[5,1-*c*]-[1,2,4]triazine: amino-1,2,4-triazolo[5,1-*c*][1,2,4]triazines are similarly formed from 3-amino-5-hydrazino-1,2,4-triazole.

As part of our programme to explore synthetic routes to azolo[1,2,4]triazines [2-4] we required a sample of 3-amino-5-hydrazinopyrazole (1): the 1,2,4-triazole analogue (2) reacts smoothly with benzil to afford an entry to the 1,2,4-triazolo[5,1-*c*][1,2,4]triazine ring-system.[2] The pyrazole (1) was suggested by Sato [5] as being a possible product of the reaction of malononitrile with two equivalents of hydrazine hydrate. However, the compound (isolated as a dihydrochloride) failed to react with acetone and Sato concluded that the isomeric diaminodihydro-1,2,3-triazine structure (3) was more likely.

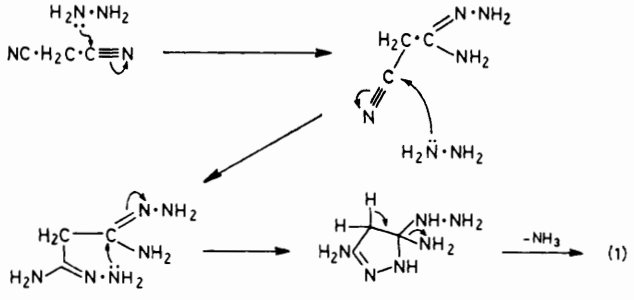
We have repeated this synthesis and find that the aminohydrazinopyrazole (1) can be isolated in good yield. Although ring-contraction of the triazine (3) is a conceivable route to the pyrazole (1) it is more likely that successive nucleophilic additions of hydrazine to the cyano-groups of malononitrile are followed by cyclo-deamination (Scheme 1). The pyrazole reacted with ethyl pyruvate to afford the pyrazolo[5,1-*c*][1,2,4]triazinone (4) with spectroscopic properties comparable to



(1) X = CH
(2) X = N

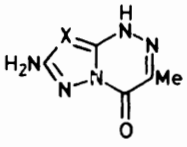


(3)

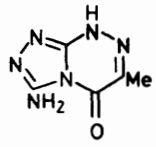


SCHEME 1

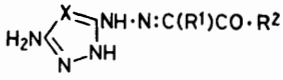
those of the corresponding triazolotriazinone (5) similarly prepared from 3-amino-5-hydrazino-1,2,4-triazole. In the latter case the triazolo[5,1-*c*][1,2,4]triazine arrangement (5) rather than the isomeric triazolo[3,4-*c*][1,2,4]-triazine (6) is preferred by analogy with related cyclisations.[3] (The same argument applies to the other 1,2,4-triazolotriazines mentioned in this paper.) Although



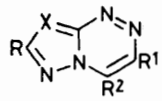
(4) X = CH
(5) X = N



(6)



(7) X = CH; R[1] = R[2] = Me
(8) X = N; R[1] = R[2] = Me
(9) X = N; R[1] = H; R[2] = Me



(10) X = CH; R = NH_2; R[1] = R[2] = Me
(11) X = CH; R = H; R[1] = R[2] = Me
(12) X = CH; R = NH_2; R[1] = R[2] = Ph
(13) X = CH; R = NHAc; R[1] = R[2] = Ph
(14) X = CH; R = H; R[1] = R[2] = Ph
(15) X = N; R = NH_2; R[1] = R[2] = Me
(16) X = N; R = NH_2; R[1] = H; R[2] = Me
(17) X = N; R = NH_2; R[1] = Me; R[2] = H
(18) X = N; R = NH_2; R[1] = R[2] = Ph

insoluble in water and common organic solvents both triazinones were conveniently purified by vacuum sublimation. A feature of the ^1H n.m.r. spectrum of the pyr-

[1] Part 20, A. Gescher, M. F. G. Stevens, and C. P. Turnbull, *J.C.S. Perkin I*, 1977, 2078.
[2] E. J. Gray and M. F. G. Stevens, *J.C.S. Perkin I*, 1976, 1492.
[3] E. J. Gray, M. F. G. Stevens, G. Tennant, and R. J. S. Vevers, *J.C.S. Perkin I*, 1976, 1496.
[4] M. F. G. Stevens, *J.C.S. Perkin I*, 1972, 1221.
[5] T. Sato, *J. Org. Chem.*, 1959, **24**, 963.

azolotriazinone was the highly shielded pyrazole H-3 proton at τ 4.64 (see Table).

^{1}H N.m.r. spectra (τ values) [a] of pyrazolo[5,1-*c*]- and 1,2,4-triazolo[5,1-*c*]-[1,2,4]triazines

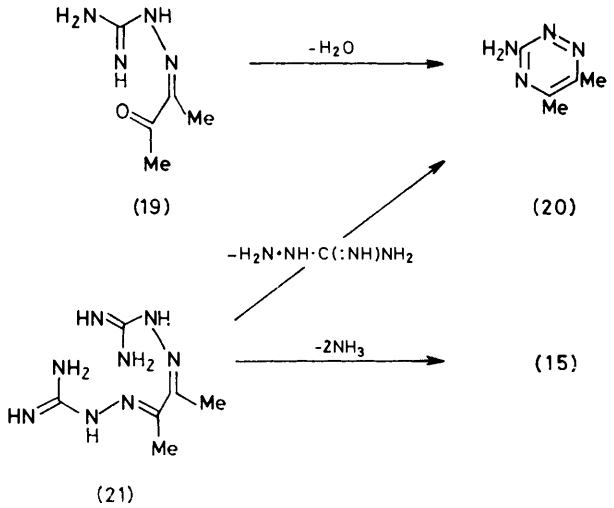
Compound	Solvent	H-2	H-3	Me(6)	Me(7)	Other absorptions
(4)	*b*		4.64(s)	7.78(s)		4.21br (2 H, s, NH_2)
(5)	*b*			7.86(s)		3.76br (2 H, s, NH_2)
(10)	*b*		4.09(s)	—— 7.39(s) ——		3.83br (2 H, s, NH_2)
(11) [c]	*d*	1.75 (d, *J ca.* 2 Hz)	2.78 (d, *J ca.* 2 Hz)	7.16(s)	7.12(s)	
(15)	*b*			—— 7.35(s) ——		3.08br (2 H, s, NH_2)
3-Bromo-6,7-dimethylpyrazolo-[5,1-*c*][1,2,4]triazine [c]	*d*	1.81(s)		7.18(s)	7.13(s)	
6-Acetyl-7-methylpyrazolo-[5,1-*c*][1,2,4]triazine [c]	*d*	1.55 (d, *J ca.* 2 Hz)	2.66 (d, *J ca.* 2 Hz)		7.0(s)	6.76 (3 H, s, $COCH_3$)
Ethyl-7-methylpyrazolo[5,1-*c*]-[1,2,4]triazine-6-carboxylate [c]	*d*	1.57 (d, *J ca.* 2 Hz)	2.64 (d, *J ca.* 2 Hz)		6.77(s)	5.40 (2 H, q, CH_2CH_3) 8.49 (3 H, t, CH_2CH_3)

[a] Recorded on a Varian HA-100 spectrometer. [b] [$^2H_6$]Dimethyl sulphoxide. Ref. 6. [d] Deuteriochloroform.

The unstable hydrazone (7) formed when 3-amino-5-hydrazinopyrazole dihydrochloride was boiled with diacetyl in ethanol rapidly cyclised to 2-amino-6,7-dimethylpyrazolo[5,1-*c*][1,2,4]triazine (10) in water. Again the 2-amino-group exerts a striking shielding influence on the H-3 proton: this absorbs at τ 4.0 in the amino-derivative (10) but at τ 2.78 (doublet) in the unsubstituted analogue (11).[6] An insoluble polymer was isolated from the reaction of the dihydrochloride of (1) and glyoxal in the presence of base. In contrast, reaction with benzil gave directly the aminodiphenylpyrazolotriazine (12) which was characterised by conversion into an acetyl derivative (13) and by reductive deamination (n-pentyl nitrite in boiling tetrahydrofuran) to to the known 6,7-diphenylpyrazolo[5,1-*c*][1,2,4]triazine (14).[6]

The aminohydrazino-1,2,4-triazole dihydrochloride (2) reacted with diacetyl in aqueous sodium acetate to afford a poor yield of the triazolotriazine (15). The same product was formed by spontaneous cyclisation of the intermediate hydrazone (8) produced in the Japp–Klingemann reaction between diazotised 3,5-diamino-1,2,4-triazole and 2-methylacetoacetic acid. A similar crude triazolotriazine was formed from the aminohydrazine (2) and pyruvaldehyde: this product was evidently the 7-methyltriazolotriazine (16) rather than the 6-methyl isomer (17) since the same product was isolated from the spontaneous cyclisation of hydrazone (9) formed by coupling diazotised 3,5-diamino-1,2,4-triazole and acetoacetic acid. Although the monomethyltriazolotriazine (16) could not be purified, it had similar spectroscopic features to the dimethylpyrazolotriazine (10) and dimethyltriazolotriazine (15). The mass spectra of the three derivatives showed abundant molecular ions at *m/e* 150, 163 and 164 respectively as the only significant features.

1,2-Dicarbonyl compounds react with semicarbazide, thiosemicarbazide, or aminoguanidine under non-oxidative conditions to afford 1,2,4-triazines:[7,8] the cyclisation of diacetyl mono[(amidino)hydrazone] (19) to 3-amino-5,6-dimethyl-1,2,4-triazine (20) (Scheme 2) at 200 °C. Ammonia was also evolved from compound (21) in boiling ethylene glycol or nitrobenzene but the only identified product was the monocyclic triazine (20). Under similar reaction conditions diacetyl bis(thiosemicarbazone) evolved both ammonia and hydrogen sulphide: in this case neither (20) nor (15) were detected



SCHEME 2

(t.l.c.) in the complex reaction mixture. Similarly attempted cyclisation of benzil bis(thiosemicarbazone) under a range of conditions failed to yield the corresponding aminodiphenyltriazolotriazine (18) which was available as a reference compound.[2]

EXPERIMENTAL

3-Amino-5-hydrazinopyrazole Dihydrochloride (1).—Malononitrile (6.6 g) in ethanol (30 ml) was treated with a solution of 80% aqueous hydrazine hydrate (10 ml) during 10 min. The mixture was stirred at 20—25 °C for 4 h after which solvent was removed. Addition of 10N-hydrochloric acid (30 ml) gave a brown solid which was collected after 24 h at 0 °C. The *pyrazole dihydrochloride* (7.8 g) crystallised from 5N-hydrochloric acid as buff needles, m.p. 205 °C [lit.,[5] m.p.

[6] M. W. Partridge and M. F. G. Stevens, *J. Chem. Soc.* (*C*), 1966, 1127.

[7] J. Daunis, R. Jacquier, and P. Viallefont, *Bull. Soc. chim. France*, 1969, 3675.

[8] F. Kurzer and L. E. A. Godfrey, *Angew. Chem. Int. Ed.*, 1963, **2**, 459.

[9] J. G. Erickson, *J. Amer. Chem. Soc.*, 1952, **74**, 4706.

205 °C (decomp.) for the compound considered to be 4,6-diamino-2,5-dihydro-1,2,3-triazine dihydrochloride (3)].

2-Amino-6-methylpyrazolo[5,1-c][1,2,4]*triazin-7(4H)-one* (4).—3-Amino-5-hydrazinopyrazole dihydrochloride (1.86 g), ethyl pyruvate (1.16 g), and sodium acetate (1.5 g) were boiled in water for 1 h. The precipitated brown solid (1.0 g) was purified by vacuum sublimation to yield a white sublimate of the *pyrazolotriazinone* (0.7 g), m.p. >350 °C, $\nu_{max.}$ (KBr) 3 400 (NH), 3 200br (NH or OH), and 1 650 cm^{-1} (CO) (Found: C, 43.4; H, 4.1; N, 42.1%; M^+, 165. $C_6H_7N_5O$ requires C, 43.6; H, 4.2; N, 42.4%; *M*, 165).

No product was obtained when the aminohydrazinopyrazole dihydrochloride was treated in similar manner with diethyl oxalate in the presence of sodium acetate.

2-Amino-6-methyl-1,2,4-triazolo[5,1-c][1,2,4]*triazin-7(4H)-one* (5).—3-Amino-5-hydrazino-1,2,4-triazole dihydrochloride (3.7 g),[2] sodium acetate (2.0 g), and ethyl pyruvate (2.3 g) in water (25 ml) were boiled for 1 h. After 6 days a white precipitate was collected (1.1 g) and vacuum-sublimed to afford the pure *triazolotriazinone* (0.8 g), m.p. >350 °C (Found: C, 36.0; H, 3.8; N, 50.1%; M^+ 166. $C_5H_6N_6O$ requires C, 36.15; H, 3.6; N, 50.6%; *M*, 166); $\nu_{max.}$ (KBr) 3 420 (NH), 3 300br (NH or OH), 2 800—2 200br (bonded NH or OH), and 1 695 cm^{-1} (CO).

The same triazolotriazinone (0.4 g) was formed when 3-amino-5-hydrazino-1,2,4-triazole dihydrochloride was treated with ethyl pyruvate in water in the absence of sodium acetate.

2-Amino-6,7-dimethylpyrazolo[5,1-c][1,2,4]*triazine* (10).—3-Amino-5-hydrazinopyrazole dihydrochloride (1.0 g) and diacetyl (0.4 g) were boiled in ethanol (50 ml) for 1 h. The precipitate (0.8 g) collected from the concentrated mixture, had m.p. 230—235 °C, $\lambda_{max.}$ (H_2O) 330 nm and was probably the crude hydrazone hydrochloride (7). The crude hydrazone (0.8 g) was boiled in water (25 ml) for 0.5 h and the solution vacuum-evaporated to furnish a red solid. Basification of the solid with aqueous ammonia gave a yellow solution which was extracted with chloroform (4 × 25 ml). Evaporation of the dried ($MgSO_4$) chloroform layers afforded the *dimethylpyrazolotriazine* as a yellow solid (from light petroleum–toluene), m.p. 202—203 °C (Found: C, 51.7; H, 5.7; N, 42.5. $C_7H_9N_5$ requires C, 51.3; H, 5.5; N, 42.9%); $\lambda_{max.}$ (EtOH) 337 and 254 nm (log ε 3.46 and 4.52); $\nu_{max.}$ (KBr) 3 480, 3 320, and 3 200 cm^{-1} (NH); *m/e* 163 (M^+, 100%), 162(6) 134(4), 120(4), 106(8), 92(14), 82(14), 81(36), 79(14), 78(70), 77(72), 68(10), 67(16), and 66(16).

A dark brown solid (95%) was immediately precipitated when 3-amino-5-hydrazinopyrazole dihydrochloride was boiled with glyoxal (1 mol equiv.) in water containing either an excess of sodium acetate (pH 6) or sodium hydroxide (pH 9): all attempts to purify this polymeric material failed.

2-Amino-6,7-diphenylpyrazolo[5,1-c][1,2,4]*triazine* (12).—The aminohydrazinopyrazole dihydrochloride (1) (0.93 g) and benzil (1.1 g) in boiling ethanol (30 ml) yielded a yellow solid (98%) after 1 h. The *pyrazolotriazine*, m.p. 338 °C (from n-butanol) (Found: C, 70.8; H, 4.6; N, 24.6. $C_{17}H_{13}N_5$ requires C, 71.1; H, 4.5; N, 24.4%) had $\lambda_{max.}$ (EtOH) 353 and 281 nm (log ε 3.48 and 4.45); $\nu_{max.}$ (KBr) 3 430, 3 300, and 3 200 cm^{-1} (NH); *m/e* 287 (M^+, 100%), 286(45), 230(11), 205(8), 202(11), 178(28), 176(9), 165(14), 152(8), 104(9), 103(8), 89(11), 83(10), and 77(22).

The *monoacetyl derivative* (13) (83%) from the pyrazolotriazine and boiling acetic anhydride (1 h) had m.p. 324—326 °C (Found: C, 68.9; H, 4.6; N, 20.9. $C_{19}H_{15}N_5O$ requires C, 69.3; H, 4.6; N, 21.3%); $\lambda_{max.}$ (EtOH) 348 and 271 nm (log ε 3.46 and 4.57); *m/e* 329 (M^+, 78%), 287(31), 286(31), 178(78), 176(12), 165(12), 139(24), 119(42), 111(65), 103(100), 77(60), and 76(56).

6,7-Diphenylpyrazolo[5,1-c][1,2,4]*triazine* (14).—2-Amino-6,7-diphenylpyrazolo[5,1-c][1,2,4]triazine (12) (0.2 g) in anhydrous tetrahydrofuran (125 ml) was added dropwise (2 h) to a boiling solution of n-pentyl nitrite (1.22 g) in tetrahydrofuran (10 ml) and the mixture was boiled for a further 3 h. Removal of solvent yielded a gum which was chromatographically fractionated on a neutral alumina column. A yellow band, eluted with light petroleum, gave the diphenylpyrazolotriazine (0.07 g), m.p. 193—194 °C (lit.,[6] 193—194 °C) with an i.r. spectrum identical to that of an authentic sample prepared by treating 3-hydrazinopyrazole with benzil.[6]

2-Amino-6,7-dimethyl-1,2,4-triazolo[5,1-c][1,2,4]*triazine* (15).—(i) 3-Amino-5-hydrazino-1,2,4-triazole dihydrochloride (0.85 g), diacetyl (0.4 g), and sodium acetate trihydrate (1.0 g) were boiled in water (15 ml) for 1 h and yellow solid (0.55 g) was collected. The *aminodimethyltriazolotriazine* crystallised from n-butanol as yellow micro-rosettes, m.p. >300 °C (decomp.) (Found: C, 43.7; H, 5.1; N, 51.3%; M^+, 164. $C_6H_8N_6$ requires C, 43.9; H, 4.9; N, 51.2%; *M*, 164); $\lambda_{max.}$ (water) 228, 303, and 333infl. nm (log ε 4.51, 3.75, and 3.74).

(ii) 3,5-Diamino-1,2,4-triazole (2.0 g) in 10N-hydrochloric acid (50 ml) was diazotised at 0 °C with a solution of sodium nitrite (1.5 g) in water (5 ml). 2-Methylacetoacetic acid [from ethyl 2-methylacetoacetate (2.88 g) and aqueous potassium hydroxide (1.5 g in 12 ml water) acidified to pH 6 after 24 h] was added to the diazonium solution at 0 °C and buffered to neutral pH (excess sodium acetate trihydrate). After being stirred for 3 h at 0 °C the mixture was extracted with chloroform for 24 h. The evaporated chloroform solution afforded the same aminodimethyltriazolotriazine (0.8 g) (identical m.p., mixed m.p., i.r. spectrum, and t.l.c. R_F value).

2-Amino-7-methyl-1,2,4-triazolo[5,1-c][1,2,4]*triazine* (16).—(i) Interaction of 3-amino-5-hydrazino-1,2,4-triazole dihydrochloride (1.87 g) and pyruvaldehyde (0.72 g) in boiling ethanol (25 ml) containing sodium hydrogen carbonate (1.68 g) for 2 h afforded the crude *triazolotriazine* (1.3 g), m.p. >300 °C (decomp.). All attempts to purify the product by crystallisation or sublimation were unsuccessful. The compound had M^+ 150 ($C_5H_6N_6$ requires *M* 150) and $\lambda_{max.}$ (H_2O) 228, 300, and 330 nm.

(ii) Coupling between diazotised 3,5-diamino-1,2,4-triazole and a solution of acetoacetic acid (prepared by alkaline hydrolysis of ethyl acetoacetate) in the manner described above gave the same crude triazolotriazine (35%) with an i.r. spectrum identical to the aforementioned sample.

Decomposition of Benzil Bis(thiosemicarbazone).—Benzil bis(thiosemicarbazone) [10] (1.0 g) was boiled in ethylene glycol (10 ml) for 1.5 h. An initial evolution of ammonia and hydrogen sulphide was followed by slow evolution of hydrogen sulphide. T.l.c. examination of the dark brown solution [silica gel; methanol–acetic acid (9 : 1) as developing solvent] confirmed that 3-amino- and 3-mercapto-5 6-diphenyl-1,2,4-triazine and 2-amino-6,7-diphenyl-1,2,4-triazolo[5,1-*c*][1,2,4]triazine (18) [2] were not products of the reaction.

Ammonia and hydrogen sulphide were also evolved when

[10] H. Blitz and T. Arnd, *Ber.*, 1902, **35**, 344.

benzil bis(thiosemicarbazone) was boiled in nitrobenzene: no hydrogen sulphide was detected from the bis(thiosemicarbazone) in boiling water or 2N-sodium hydroxide.

Decomposition of Biacetyl Bis(thiosemicarbazone).—Biacetyl bis(thiosemicarbazone) [11] (0.2 g) in boiling ethylene glycol (5 ml) evolved hydrogen sulphide. After 1 h the solution was examined by t.l.c. [silica gel; toluene–acetone (7 : 3) as developing solvent]. 3-Amino-5,6-dimethyl-1,2,4-triazine (20) and 2-amino-6,7-dimethyl-1,2,4-triazolo[5,1-*c*]-[1,2,4]triazine (15) were not products of the reaction.

Decomposition of Biacetyl Bis[(amidino)hydrazone] (21).—Sublimation of the hydrazone [12] *in vacuo* at 200 °C afforded a white sublimate of 3-amino-5,6-dimethyl-1,2,4-triazine (20), identical to an authentic specimen.[9]

Ammonia was evolved when the hydrazone was boiled in either ethylene glycol or nitrobenzene. T.l.c. examination of the solution [silica gel; toluene–acetone (7 : 3) as developing solvent] confirmed the presence of 3-amino-5,6-dimethyl-1,2,4-triazine (20) but the absence of the aminodimethyltriazolotriazine (15).

We thank the 3M Company for a research grant (to E. J. G.).

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[11] T. Posner, *Ber.*, 1901, **34**, 3973.
[12] J. Thiele and E. Dralle, *Annalen*, 1898, **302**, 275.