Triazines and Related Products. Part XVI.[1] Synthesis of Triazolotriazines by Cyclisation of 3-Hydrazino-1,2,4-triazines and 3-Hydrazino-1,2,4-triazoles

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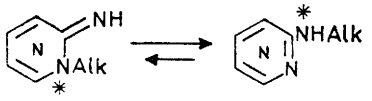
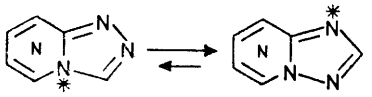
Cyclisation of 3-hydrazino-5,6-diphenyl-1,2,4-triazine with cyanogen bromide afforded 3-amino-6,7-diphenyl-1,2,4-triazolo[4,3-*b*][1,2,4]triazine, whereas interaction of 3-amino-5-hydrazino-1,2,4-triazole and benzil yielded the isomeric 2-amino-6,7-diphenyl-1,2,4-triazolo[5,1-*c*][1,2,4]triazine: both amines were deaminated with amyl nitrite in boiling tetrahydrofuran without rearrangement of the heterocyclic skeleton. 6,7-Diphenyl-1,2,4-triazolo[5,1-*c*][1,2,4]triazine, also formed from 3-hydrazino-1,2,4-triazole and benzil in alcoholic sodium acetate, formed a covalent hydrate which could be detected spectroscopically in solution, and a covalent methanolate and ethanolate which could be isolated. The alcoholates reverted to the aromatic system on being heated, or in hot acetic acid or pyridine.

A FEATURE of the chemistry of *N*-alkyl heterocycles of general structure (1) is their rearrangement to more stable aromatic alkylaminoazines (2).[2] This Dimroth rearrangement, involving the apparent migration of an *N*-alkyl group (labelled with an asterisk) from an endo- to an exo-cyclic position proceeds *via* a ring-opened species (a 'Dimroth intermediate'). Similar transformations complicate the chemistry of those bi- and poly-cyclic systems formed by fusion of a 1,2,4-triazole ring to an azine with a common bridgehead N atom. It has been established empirically that bicyclic systems



(1) (2)



(3) (4)

of type (3) with N-4 of the triazole at the ring junction, which may be prepared by cyclisation of 2-hydrazinoazines with carbon-inserting reagents,[3] readily rearrange *via* ring-opened intermediates to the more thermodynamically stable isomers (4) conjoined at N-1 of the triazole.[4] There appear to be no exceptions.

In a previous paper[5] the chemistry of diphenyl-1,2,4-triazines bearing a fused 1,2,4-triazole or tetrazole ring was explored; we now report an extension of this work.

Reaction of 5,6-diphenyl-3-hydrazino-1,2,4-triazine (5) with cyanogen bromide in methanol afforded the hydrobromide of a weakly basic aminotriazolotriazine. This salt dissociated in water to give a red base which was further characterised as a diacetyl derivative. Although the presumed intermediate cyanohydrazinotriazine (6) can cyclise in two ways, previous experience with this type of cyclisation has established that N-2 of the triazine (rather than N-4) acts in a nucleophilic capacity.[5] The product was therefore assigned structure (7) and proved to be stable to heat, boiling acetic acid, and pyridine. There is no plausible mechanism whereby this aminotriazolotriazine can further rearrange unless one invokes an unlikely fission of the triazine N–N bond. (N–N Bond fission has been observed in 1,2,4-triazolo[4,3-*b*]pyridazine[6] and 1,2,4-triazolo[3,4-*a*]phthalazine[7] but is not mechanistically feasible in the present case.)

In corroboration of this assignment, the amine (7) was deaminated with pentyl nitrite in boiling tetrahydrofuran[8] to 6,7-diphenyl-1,2,4-triazolo[4,3-*b*][1,2,4]triazine (8), which has been synthesised previously from the hydrazinotriazine (5) and carbon-inserting reagents,[5] and from 3,4-diamino-1,2,4-triazole (10; R = H) and benzil.[5,9] Furthermore, the aminotriazolotriazine had physical characteristics in accord with those reported[10] for the amine formed unequivocally from 3,4,5-triamino-1,2,4-triazole (10; R = NH_2) and benzil.

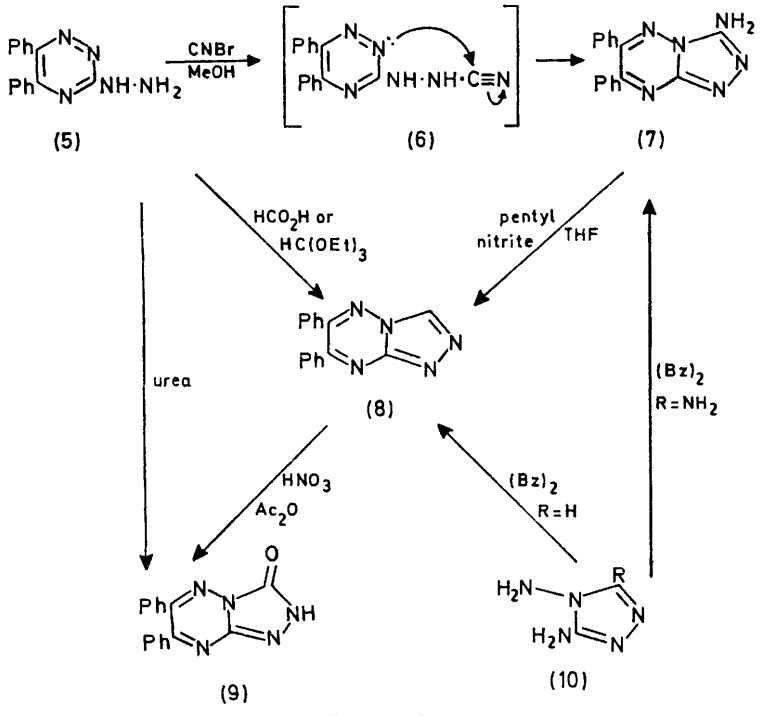
We expected that nitration of the unsubstituted diphenyltriazolotriazine (8), followed by reduction, would provide an alternative synthesis of the amine (7). However, the only nitrating conditions which were examined (nitric acid in acetic anhydride at 0 °C) led, unexpectedly, to the *oxidised* product (9) which was identical with the fused triazolone formed from hydrazine (5) and urea.[11] The inter-relationships of all the aforementioned triazolotriazines are depicted in Scheme 1.

3-Amino-5-hydrazino-1,2,4-triazole (11a), prepared as a dihydrochloride by reduction with tin(II) chloride of diazotised 3,5-diamino-1,2,4-triazole,[12] reacted slowly with benzil in boiling methanol, with or without sodium acetate, to afford a single pale yellow product isomeric with (7); the product formed mono- and di-acetyl

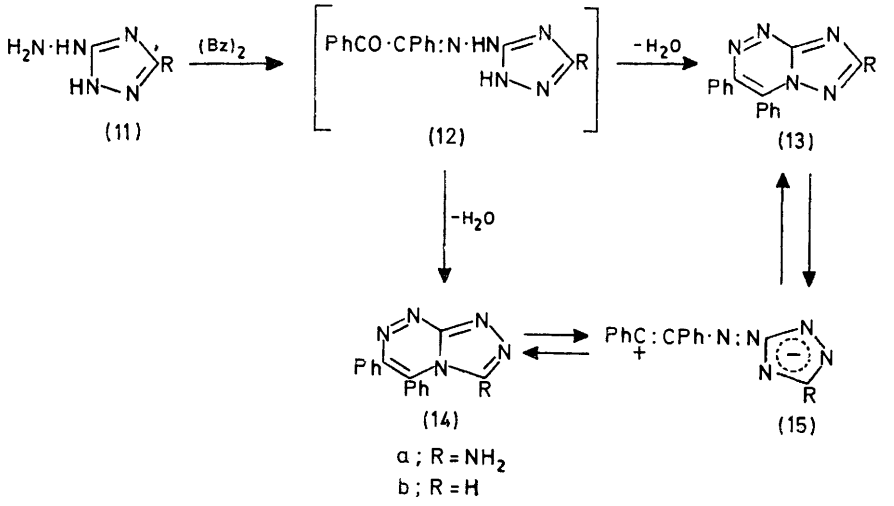
[1] Part XV, T. B. Brown and M. F. G. Stevens, *J.C.S. Perkin I*, 1975, 1023.
[2] D. J. Brown, in 'Mechanisms of Molecular Migrations,' ed. B. S. Thyagarajan, vol. 1, Wiley, New York, 1968, p. 209.
[3] J. Daunis, R. Jacquier, and P. Viallefont, *Bull. Soc. chim. France*, 1969, 3670; J. Daunis and M. Follet, *ibid.*, 1975, 857.
[4] P. Guerret, R. Jacquier, and G. Maury, *J. Heterocyclic Chem.*, 1971, **8**, 643.
[5] M. F. G. Stevens, *J.C.S. Perkin I*, 1972, 1221.
[6] A. Pollak, S. Polanc, B. Stanovnik, and M. Tišler, *Monatsh.*, 1972, **103**, 1591.
[7] K. T. Potts and C. A. Lovelette, *Chem. Comm.*, 1968, 845.
[8] J. I. G. Cadogan and G. A. Molina, *J.C.S. Perkin I*, 1973, 541.
[9] E. Hoggarth, *J. Chem. Soc.*, 1952, 4811.
[10] E. C. Taylor, W. H. Gumprecht, and R. F. Vance, *J. Amer. Chem. Soc.*, 1954, **76**, 619.
[11] A. Dornow, W. Abele, and H. Menzel, *Chem. Ber.*, 1964, **97**, 2179.
[12] R. Stollé and W. Dietrich, *J. prakt. Chem.*, 1934, **139**, 193.

derivatives. Significantly, this new aminotriazolotriazine was stable above its m.p. or in boiling acetic acid, pyridine, or piperidine. The evidence points conclusively to structure (13a), which could be formed (Scheme 2) either directly from the intermediate hydrazone (12a) would hinder development of the transition state leading to the isomer (14a).

We experienced considerable difficulty in preparing the unsubstituted 3-hydrazino-1,2,4-triazole (11b). A conventional procedure based on the diazotisation of



SCHEME 1

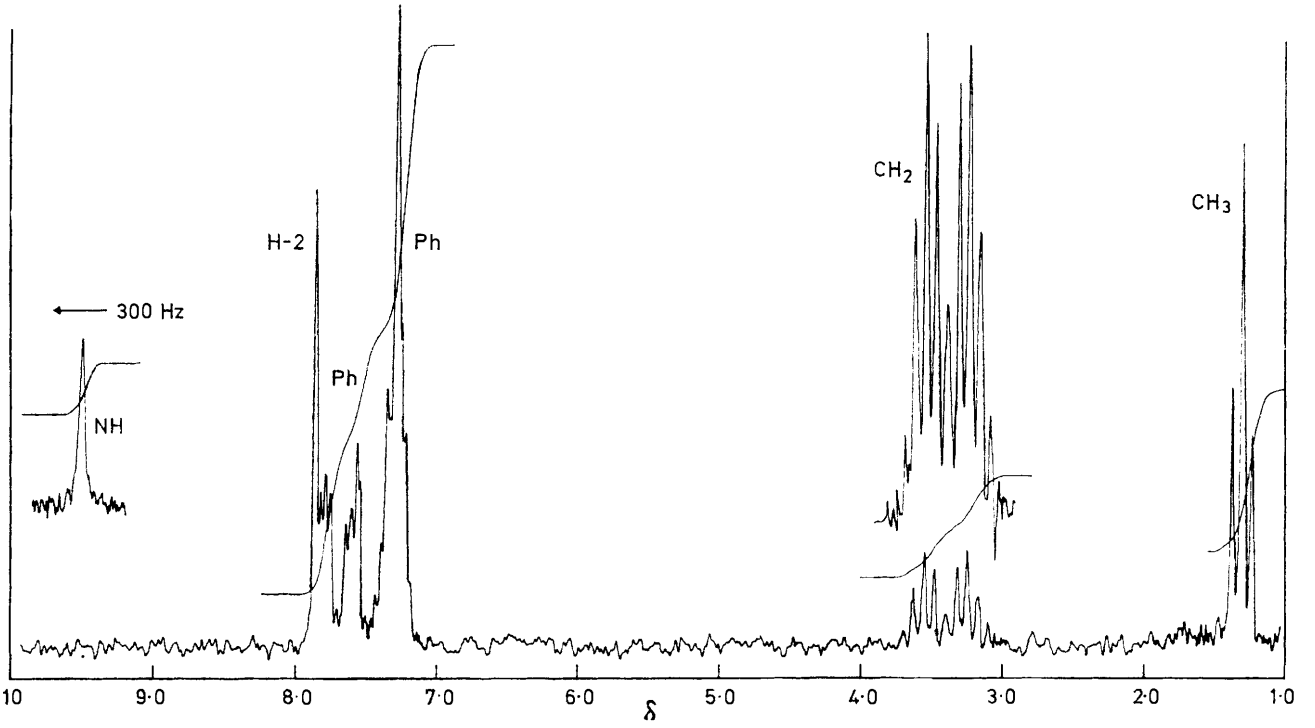


SCHEME 2

by cyclisation at the triazole N-1, or indirectly by Dimroth rearrangement of the isomeric aminotriazolotriazine (14a). Dimroth rearrangements in bicyclic systems are known to be accelerated by electron depletion in the azine ring,[13] and such factors could stabilise a zwitterionic intermediate (15a). Intuitively, we prefer direct cyclisation at the triazole N-1 since steric repulsions between the amino- and phenyl groups 3-amino-1,2,4-triazole in hydrochloric acid, followed by reduction with tin(II) chloride, was unreliable: furthermore 3-chlorotriazoles, 3-nitrosoaminotriazoles, and 1,3-bis(triazol-3-yl)triazenes have been variously reported as products of the diazotisation of 3-amino-1,2,4-triazoles.[14]

[13] K. T. Potts and C. R. Surapaneni, *J. Heterocyclic Chem.*, 1970, **7**, 1019.
[14] R. N. Butler, *Chem. Rev.*, 1975, **75**, 241.

However, reduction with zinc dust and acetic acid of 3-nitroamino-1,2,4-triazole [15] proved an efficient route to the required hydrazine (11b), which was purified as its hydrochloride. Interaction of this hydrochloride and benzil in ethanol containing an excess of sodium acetate gave a single product with a u.v. spectrum typical of a bicyclic system ($\lambda_{max.}$ 349 and 248 nm), and a mass spectrum showing the appropriate molecular ion at *m/e* 273. This product, 6,7-diphenyl-1,2,4-triazolo-[5,1-*c*][1,2,4]triazine (13b) was, as expected, stable to heat and a range of boiling organic acids and bases, and boiled in alcohols in the *absence* of sodium acetate, products were obtained in high yield which afforded analytical figures corresponding to a diphenyltriazolotriazine with incorporation of methanol or ethanol, but which were converted into the aromatic bicyclic system (13b) on heating alone or in boiling acetic acid or pyridine. That the alcohols were *covalently* bound was evident from their mass spectra, which showed molecular ions at *m/e* 305 and 319 for the methanolate and ethanolate, respectively. Conclusive proof of covalent solvation was obtained from the unusual ^{1}H n.m.r.



100 MHz ^{1}H N.m.r. spectrum of 7-ethoxy-4,7-dihydro-6,7-diphenyl[1,2,4]triazolo[5,1-*c*][1,2,4]triazine (18) in deuteriochloroform

was identical with the product formed by deamination (pentyl nitrite–tetrahydrofuran) of the corresponding aminotriazolotriazine (13a), which has been previously deduced to have the same skeletal arrangement of N atoms. The chemical shift of the triazole proton (δ 8.66) in the triazolotriazine (13b) lies within the range expected for this type of fused triazole,[16] and contrasts with the more deshielded proton (δ 9.17) in the isomer (8).

When 6,7-diphenyl-1,2,4-triazolo[5,1-*c*][1,2,4]triazine (13b) was warmed in N-hydrochloric acid the u.v. spectrum underwent a rapid change, and the two peaks were replaced by a single broad band (at 294 nm); these changes were reversed at pH 10. We attribute these shifts to the formation of a covalent hydrate (16) in aqueous acid, and similar spectral changes were noted when methanolic and ethanolic solutions of the triazolotriazine were treated with N-hydrochloric acid. Indeed, when 3-hydrazinotriazole hydrochloride and benzil were

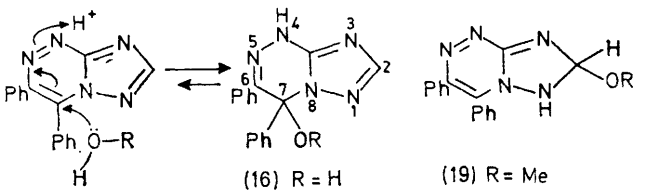
[15] C.-F. Kröger and R. Miethchen, *Z. Chem.*, 1969, **9**, 378.
[16] J. Daunis, R. Jacquier, and P. Viallefont, *Bull. Soc. chim. France*, 1969, 2492.

spectrum of the ethanolate (see Figure): the triazole proton signal had moved upfield (to δ 7.85), and the O·C*H*$_2$·CH$_3$ signal appeared as a complex multiplet centred at δ 3.37, characteristic of the AB part of an ABX$_3$ system; the O·CH$_2$·C*H*$_3$ signal appeared as a conventional triplet at δ 1.28 and the (exchangeable) NH signal at δ −2.5. The methylene protons are magnetically non-equivalent because of the adjacent asymmetric centre.[17] The methoxy-derivative had a similar arrangement of aromatic C–H absorptions and a methoxy-singlet at δ 3.24.

We prefer structures (17) and (18) for the methanolate and ethanolate rather than the isomers (19) and (20) since acid-catalysed nucleophilic attack at the π-deficient triazine ring is more likely than at the π-excessive triazole ring.[18] Nucleophilic addition to the most electrophilic centre (C-7) of the triazolotriazine (Scheme 3) is precisely analogous to the process known to initiate

[17] G. R. Bedford, M. W. Partridge, and M. F. G. Stevens, *J. Chem. Soc.* (*C*), 1966, 1214.
[18] A. Albert, 'Heterocyclic Chemistry,' Athlone Press, London, 2nd edn., 1968, p. 125.

the Dimroth rearrangement in other mono- and bicyclic systems.[2,4] Covalent adducts are only rarely isolated, and addition is normally followed by ring



(16) R = H
(17) R = Me
(18) R = Et
(19) R = Me
(20) R = Et

SCHEME 3

opening and rearrangement. Although the bicyclic water adduct (16) may well exist in equilibrium with its acyclic isomer (12b), recyclisation to the less favoured triazolo[3,4-*c*]triazine isomer (14b) does not occur.

EXPERIMENTAL

U.v. spectra were measured for solutions in ethanol and i.r. spectra for KBr discs. ^{1}H N.m.r. spectra were run on a Varian HA-100D spectrometer for solutions in $CDCl_3$ (Me_4Si as internal standard).

3-*Amino*-6,7-*diphenyl*-1,2,4-*triazolo*[4,3-b][1,2,4]*triazine* (7).—3-Hydrazino-5,6-diphenyl-1,2,4-triazine (2.63 g) [19] and cyanogen bromide (1.16 g, 1.1 mol) were boiled in methanol (125 ml) for 2 h. Addition of cold ether (150 ml) precipitated a hydrobromide salt, which was collected and stirred in aqueous sodium acetate. The red triazolotriazine (73%) crystallised from ethanol with m.p. 263—264° (lit.,[10] 263—264°) (Found: C, 66.7; H, 4.1; N, 29.1. Calc. for $C_{16}H_{12}N_6$: C, 66.7; H, 4.2; N, 29.2%); $\lambda_{max.}$ 420, 335infl, 284, and 243 nm (log ε 3.38, 3.80, 4.17, and 4.17); $\nu_{max.}$ 3 395 (NH), 3 060br (bonded NH), and 1 623 cm^{-1} (C=N). The triazolotriazine was stable to dry heat (270 °C for 1 h) and in boiling acetic acid, pyridine, or piperidine (14 h). The *diacetyl derivative* (92%), from the base and acetic anhydride (1 h at 100 °C), had m.p. 190—191° (from methanol) (Found: C, 64.2; H, 4.2; N, 22.7. $C_{20}H_{16}N_6O_2$ requires C, 64.5; H, 4.3; N, 22.9%); $\lambda_{max.}$ 340 and 229 nm (log ε 3.84 and 4.41); $\nu_{max.}$ 1 740 and 1 723 cm^{-1} (C=O); δ 7.45—7.10 (10 H, m, 2 × Ph) and 2.21 (6 H, s, 2 × Me).

The triazolotriazine (0.12 g) in anhydrous tetrahydrofuran (25 ml) was added dropwise (2 h) to a boiling solution of pentyl nitrite (0.44 g) in tetrahydrofuran (5 ml). The solution was boiled for a further 3 h and evaporated. The The product, purified by column chromatography on neutral alumina with elution by benzene–chloroform, afforded 6,7-diphenyl-1,2,4-triazolo[4,3-*b*][1,2,4]triazine (8) (0.07 g) identical (i.r. and mass spectra) with an authentic sample prepared by treating 3-hydrazino-5,6-diphenyl-1,2,4-triazine with 100% formic acid or triethyl orthoformate.[5]

6,7-*Diphenyl*-1,2,4-*triazolo*[4,3-b][1,2,4]*triazin*-3(2H)-*one* (9).—6,7-Diphenyl-1,2,4-triazolo[4,3-*b*][1,2,4]triazine (5.43 g) in acetic anhydride (12 ml) at −15 °C was treated dropwise (30 min) with a solution of nitric acid (s.g. 1.5; 1.26 g) in acetic anhydride (5 ml). The mixture was allowed to warm to 0 °C and quenched with ice–water. The precipitated triazolotriazinone (2.7 g) crystallised from methanol with m.p. 285—286°, and was identical (i.r. and mass spectra) with an authentic sample prepared from 3-hydrazino-5,6-diphenyl-1,2,4-triazine and urea.[11]

3-*Amino*-5-*hydrazino*-1,2,4-*triazole Dihydrochloride*.—3,5-Diamino-1,2,4-triazole (10.0 g) in 10N-hydrochloric acid (200 ml) was diazotised at 0 °C with sodium nitrite (7.5 g) in water (25 ml). The stirred diazonium solution was treated in portions (over 1 h) with tin(II) chloride dihydrate at 0 °C. The mixture was stirred for a further 1 h at 0 °C, heated to 80 °C, and filtered hot, and the filtrate was saturated with hydrogen chloride gas. The aminohydrazinotriazole dihydrochloride (8.3 g) separated as a white crystalline solid, m.p. 214—216° (efferv.) (lit.,[12] 217°).

2-*Amino*-6,7-*diphenyl*-1,2,4-*triazolo*[5,1-c][1,2,4]*triazine* (13a).—3-Amino-5-hydrazino-1,2,4-triazole dihydrochloride (1.88 g) was boiled in methanol (50 ml) containing benzil (2.10 g) for 2 h. The *triazolotriazine* (94%), deposited from the cooled solution, crystallised from aqueous ethanol as yellow needles, m.p. 272—274° (Found: C, 66.4; H, 4.2; N, 29.6. $C_{16}H_{12}N_6$ requires C, 66.7; H, 4.2; N, 29.2%); $\lambda_{max.}$ 350 and 260 nm (log ε 3.89 and 4.43); $\nu_{max.}$ 3 470 and 3 325 (NH), and 1 620 cm^{-1} (C=N). The *monoacetyl derivative* (85%), formed with boiling acetic acid–acetic anhydride (1 : 1) (1 h) crystallised from ethanol with m.p. 294—295° (Found: C, 65.1; H, 4.5; N, 25.7. $C_{18}H_{14}N_6O$ requires C, 65.5; H, 4.2; N, 25.5%); $\lambda_{max.}$ 325 and 257 nm (log ε 3.94 and 4.45); $\nu_{max.}$ 3 220 (NH) and 1 700 cm^{-1} (C=O). The *diacetyl derivative* (78%) [boiling acetic anhydride (2 h)] had m.p. 195—196° (from aqueous ethanol) (Found: C, 64.6; H, 4.4. $C_{20}H_{16}N_6O_2$ requires C, 64.5; H, 4.3%); δ 7.6—7.2 (10 H, m, 2 × Ph) and 2.26 (6 H, s, 2 × Me).

2-Amino-6,7-diphenyl-1,2,4-triazolo[5,1-*c*][1,2,4]triazine was unchanged after being subjected to dry heat at 300 °C (1 h) or boiling acetic acid, pyridine, or piperidine (10 h).

3-*Hydrazino*-1,2,4-*triazole Hydrochloride*.—This compound was prepared by a process kindly supplied by Professor K. T. Potts. 3-Nitroamino-1,2,4-triazole (20 g) [15] and activated zinc dust (40 g) were moistened with water and ground to a paste. The paste was suspended in water (100 ml) at 10 °C and treated with 50% aqueous acetic acid (200 ml) over 2 h, the temperature being maintained at 10—20 °C. The mixture was stirred at 20 °C for a further 4 h, heated to 60 °C (1 h), and allowed to cool. The excess of zinc was filtered off and the filtrate saturated with hydrogen sulphide (2 h). After removal of zinc sulphide the filtrate and washings were treated with 10N-hydrochloric acid. Evaporation afforded a gum, which was boiled with chloroform (10 ml) for 30 min. 3-Hydrazino-1,2,4-triazole hydrochloride (10 g) separated on addition of absolute ethanol (50 ml); m.p. 225° (lit.,[20] 224°).

6,7-*Diphenyl*-1,2,4-*triazolo*[5,1-*c*][1,2,4]*triazine* (13b).—(i) 2-Amino-6,7-diphenyl-1,2,4-triazolo[5,1-*c*][1,2,4]triazine (13a) (0.24 g) in tetrahydrofuran (60 ml) was added dropwise (2 h) to a boiling solution of pentyl nitrite (0.88 g) in tetrahydrofuran (10 ml). The solution was boiled (3 h) and evaporated. The residue was dissolved in benzene and chromatographically fractionated on a neutral alumina column. Evaporation of the benzene eluate afforded the *diphenyltriazolotriazine* (0.09 g), m.p. 193—195° (from methanol) (Found: C, 70.2; H, 4.3; N, 25.7. $C_{16}H_{11}N_5$ requires C, 70.3; H, 4.0; N, 25.6%); δ 8.66 (s, H-2) and 7.7—7.3 (10 H, m, 2 × Ph); $\lambda_{max.}$ 349 and 248 nm (log ε 3.84 and 4.32).

(ii) 3-Hydrazino-1,2,4-triazole hydrochloride (0.5 g),

[19] P. V. Laakso, R. Robinson, and H. P. Vandrewala, *Tetrahedron*, 1957, **1**, 103.
[20] W. Manchot and R. Noll, *Annalen*, 1905, **343**, 1.

benzil (0.6 g), and sodium acetate trihydrate (2 g) were boiled in methanol (50 ml) for 2 h. The same triazolotriazine (40%) was deposited when the solution was diluted with water.

The triazine was stable at 200 °C (1 h) and in boiling acetic acid, pyridine, or piperidine (10 h).

4,7-Dihydro-7-methoxy-6,7-diphenyl-1,2,4-triazolo[5,1-c]-[1,2,4]*triazine* (17).—3-Hydrazino-1,2,4-triazole hydrochloride (0.5 g) and benzil (0.6 g) were boiled in methanol (6 h) and the solution was evaporated. Crystallisation of the residue from methanol afforded the *methoxytriazolotriazine* (60%), m.p. 211—212° (Found: C, 66.6; H, 5.0; N, 23.4. $C_{17}H_{15}N_5O$ requires C, 66.9; H, 5.0; N, 23.4%); $\lambda_{max.}$ 297 nm (log ε 4.16); δ 7.85 (s, H-2), 7.82—7.25 (10 H, m, 2 × Ph), and 3.24 (s, OMe) (Found: M^+, 305.127 264. $C_{17}H_{15}N_5O$ requires *M*, 305.127 653).

The methoxytriazolotriazine (0.2 g) in boiling acetic acid (3 ml) was converted into 6,7-diphenyl-1,2,4-triazolo[5,1-*c*]-[1,2,4]triazine (i.r. and u.v.) after 2 h, in 90% yield.

7-Ethoxy-4,7-dihydro-6,7-diphenyl[1,2,4]*triazolo*[5,1-c]-[1,2,4]*triazine* (18).—Reaction of 3-hydrazino-1,2,4-triazole hydrochloride and benzil in ethanol as above afforded the *ethoxytriazolotriazine* (65%), m.p. 205—206° (from methanol) (Found: C, 67.6; H, 5.4; N, 21.9. $C_{18}H_{17}N_5O$ requires C, 67.7; H, 5.3; N, 21.9%); $\lambda_{max.}$ 298 nm (log ε 4.16) (Found: M^+, 319.142 546. $C_{18}H_{17}N_5O$ requires *M*, 319.143 302).

The ethoxytriazolotriazine (0.5 g) was boiled in acetic acid (5 ml) for 2 h and the solvent was removed under vacuum. The product (93%) was identical (i.r.) with 6,7-diphenyl-1,2,4-triazolo[5,1-*c*][1,2,4]triazine (13b). The ethoxytriazolotriazine was similarly converted into the triazolotriazine (13b) by heat (1 h at 220 °C) and by boiling pyridine (2 h) (90 and 95% yields, respectively).

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