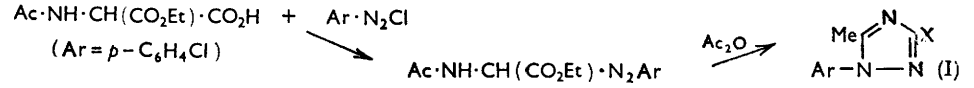
991. *Triazoles. Part VII.* Syntheses of Substituted 1,2,4-Triazoles.*

By (Mrs.) E. J. Browne and J. B. Polya.

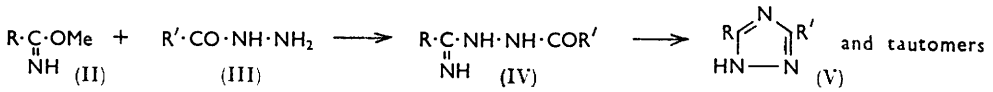
Acetals of *N*-unsubstituted 1,2,4-triazole-3-aldehydes have been prepared by condensation of imidic esters with dimethoxyacethydrazide. Free aldehydes could not be isolated on hydrolysis of the acetals, or on oxidation of propenyl-1,2,4-triazoles. Condensation of imidic esters and acid hydrazides is satisfactory for the preparation of bitriazolyls and methoxymethyl- and cyanomethyl-1,2,4-triazoles.

The preparation of 1,5-diaryl-1,2,4-triazole-3-aldehydes from the corresponding esters or acid hydrazides (Part VI *) is not a general method. Although the Sawdey rearrangement [1] which has been used to obtain the esters and hydrazides [2] is limited to the synthesis of derivatives of 1,5-diaryl-1,2,4-triazoles, the preparation of 1-*p*-chlorophenyl-5-methyl-1,2,4-triazole-3-aldehyde (I; X = CHO) illustrates a convenient synthetic route in some cases. In the reaction illustrated conversion of the ethoxycarbonyl into the aldehyde group by way of an alcohol group follows normal routine.



Reduction of *N*-*p*-nitrophenyl-1,2,4-triazoles to the *N*-*p*-aminophenyl derivatives followed by oxidative removal of the *N*-aryl group could not be used to prepare *N*-unsubstituted triazole-aldehydes, since the conversion of 5-aryl-1-*p*-nitrophenyl-1,2,4-triazole-3-carboxylic acid derivatives into the aldehydes could not be effected.[2] In any case the aldehyde group would have to be protected during oxidation, and the main problem, the liberation of the unstable *N*-unsubstituted triazole-aldehydes from their derivatives without protracted exposure to acid, alkali, or polar solvents would remain unsolved.

Derivatives of *N*-unsubstituted 1,2,4-triazole-3-aldehydes, or triazoles (V) with substituents which in many other series would be readily converted into aldehydes, were



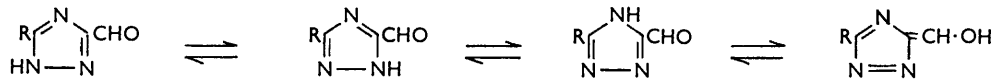
obtained by condensation of imidic esters (II) with acylhydrazines (III), which had been used before for the preparation of alkyl- and aryl-1,2,4-triazoles.[3] The intermediate acylamidrazones (IV) cyclise spontaneously or under moderate conditions (mild heating or treatment with dilute alkali). The use of methyl formimidate (II; R = H) is impracticable, and products from methyl acetimidate (II; R = Me) are difficult to purify. The hydrazides of gluconic [4] or ethoxalic acid [5] failed to form triazoles.

Dimethoxyacethydrazide [III; R' = $(MeO)_2CH$] was used to prepare the dimethyl acetals of triazole-aldehydes shown in Table 2. These acetals are not hydrolysed by weak acid; heating with mineral acids rapidly destroys the free aldehydes, but the expected 2,4-dinitrophenylhydrazones are obtained from fresh hydrolysates. The acetals could not be converted into Girard-T derivatives.

* Part VI, *J.*, 1962, 575.

[1] Sawdey, *J. Amer. Chem. Soc.*, 1957, **79**, 1955.
[2] Cf. Browne and Polya, *Chem. and Ind.*, 1960, 1086.
[3] Postovskii and Vershchagina, *Zhur. obshchei Khim.*, 1959, **29**, 2139.
[4] Van Marle, *Rec. Trav. chim.*, 1920, **39**, 540.
[5] Stollé, *Ber.*, 1911, **44**, 776.

Complete acid-hydrolysis of the acetals, followed by neutralisation, affords syrups which are soluble in water and lack the reactions of aldehydes or common aldehyde derivatives. Rapid polymerisation of the free aldehydes appears probable. Fast removal of aldehydes as they are liberated from their acetals has been attempted by chromatography and various techniques of extraction, but the relatively high solubility in water and the amphoteric properties of the compounds defeated these attempts. If the analogy of imidazole-aldehydes [6,7] is applicable, these difficulties are linked with shifts of tautomeric equilibria:

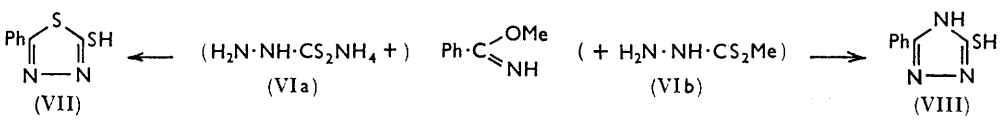


3-Methoxymethyl- (V; R′ = CH_2·OMe) and 3-cyanomethyl-1,2,4-triazoles (V; R′ = CH_2·CN) (Table 1) have been prepared by us, usually without isolation of the intermediate acylamidrazones. One example of the former (R = H) which had been previously prepared from the thiol [8] was prepared by deamination of 5-amino-3-methoxymethyl-1,2,4-triazole.

Formamide and cyanoacethydrazide give a red, insoluble product with a high melting point, which has been regarded as cyanomethyl-1,2,4-triazole.[9] The product is different in type from both the cyanomethyltriazoles and the intermediate acylamidrazones, but it is possibly related to the red polymers obtained when cyanomethyltriazoles or the acylamidrazone intermediates are overheated.

Condensation of the imidic ester (II; R = CH_2·CO_2Et) and formhydrazide gave 3-amino-5-hydroxypyrazole, identical with the product of reaction of cyanoacethydrazide with methanolic potassium hydroxide; [10] no triazole was formed.

Salts (*e.g.*, VIa) and the methyl ester (VIb) of hydrazinedithiocarboxylic acid [11] give different products on condensation with methyl benzimidoate, namely, the thiadiazole [12] (VII) and the 1,2,4-triazole [13] (VIII), respectively. Coloured acyclic intermediates were



isolated. Methyl phenylacetimidoate and the ester (VIb) gave the expected benzyltriazolethiol,[14] but reaction with either the ammonium (VIa) or the potassium salt gave phenylacetamide instead of a thiadiazole.

The expected bitriazolyls (Table 1) were obtained by condensing imidic esters with 1,5-diphenyl-1,2,4-triazole-3-carboxyhydrazide.[2]

Triazoles with unsaturated side chains were prepared in the hope that hydroxylation to glycols followed by Malaprade oxidation would afford the desired aldehydes under mild conditions. Cyclisation of aminoguanidine [15] does not appear feasible with crotonic, cinnamic, or maleic acid. The hydrazides of crotonic [16] and cinnamic [16] acid do not give triazoles with imidic esters: the former afforded amidrazones which failed to cyclise when heated alone or with dilute alkali. The amidrazones R·C(=NH)·NH·NHPh (R = Ph,

[6] Hubball and Pyman, *J.*, 1928, 21.
[7] Turner, *J. Amer. Chem. Soc.*, 1949, **71**, 3472.
[8] Jones and Ainsworth, *J. Amer. Chem. Soc.*, 1955, **77**, 1538.
[9] Klosa, *Arch. Pharm.*, 1955, **288**, 452; *Chem. Abs.*, 1956, **50**, 16,789d.
[10] Ishimaru, *Yakugaku Zasshi*, 1957, **77**, 796; *Chem. Abs.*, 1957, **51**, 17,892i.
[11] Losanitch, *J.*, 1921, **119**, 763.
[12] Sandstrom, *Arkiv Kemi*, 1952, **4**, 297; *Chem. Abs.*, 1953, **47**, 9271h.
[13] Hoggarth, *J.*, 1949, 1160.
[14] Sugii, *Yakugaku Zasshi*, 1959, **79**, 100; *Chem. Abstr.*, 1959, **53**, 10,033i.
[15] Manchot and Noll, *Annalen*, 1905, **343**, 1.
[16] Muckermann, *Ber.*, 1909, **42**, 3449.

CH_2Ph,[17] or *p*-C_6H_4Me) with crotonyl chloride [18] gave the expected 3-substituted 1-phenyl-5-propenyl-1,2,4-triazoles (Table 1), which were, however, not oxidised by performic acid or selenium dioxide. Hydroxylation by treatment with iodine and silver benzoate [19] or acetate [20] was also unsuccessful, and though unchanged material was recovered glycols were not found among the products of oxidation by potassium permanganate.

TABLE 1.

Substituted 1,2,4-triazoles.

Subst.* at posn.				Yield	Found (%)				Required (%)		
1	3	5	M. p.	(%)	C	H	N	Formula	C	H	N
p-C_6H_4Cl	CO_2Et	Me	113—114·5° †	60	52·6	4·1	16·0	$C_{12}H_{12}N_3ClO_2$	54·2	4·6	15·8
p-C_6H_4Cl	CH_2·OH	Me	125·5—127 ‡	46	53·3	4·6	18·5	$C_{10}H_{10}N_3ClO$	53·7	4·5	18·8
p-C_6H_4Cl	CHO	Me	143—146 ‡	27	54·2	3·7	18·8	$C_{10}H_8N_3ClO$	54·2	3·6	19·0
p-C_6H_4Cl	A	Me	268—269 §	—	48·0	3·4	24·1	$C_{16}H_{12}N_7ClO_4$	47·8	3·0	24·4
Ph	Ph	B	125—126·5 ¶	16	78·0	5·8	16·3	$C_{17}H_{15}N_3$	78·1	5·8	16·1
Ph	CH_2Ph	B	64—65 ‡	—	78·6	6·1	15·1	$C_{18}H_{17}N_3$	78·5	6·2	15·3
Ph	*p*-C_6H_4Me	B	130—131 ¶	—	78·4	6·1	15·3	$C_{18}H_{17}N_3$	78·5	6·2	15·3
H	CH_2·OMe	Me	110—111·5 †	80	48·1	7·2	33·4	$C_5H_9N_3O$	47·3	7·1	33·1
H	CH_2·OMe	Ph	107—109 †	42	64·0	5·9	21·9	$C_{10}H_{11}N_3O$	63·5	5·9	22·2
H	CH_2·OMe	CH_2Ph	87—88 †	40	64·8	6·5	20·8	$C_{11}H_{13}N_3O$	65·0	6·5	20·7
H	CH_2·CN	Me	133—134·5 ‖	37	50·0	5·2	44·1	$C_5H_6N_4$	49·2	5·0	45·9
H	CH_2·CN	Ph	161—163 ‡	30	65·3	4·4	30·4	$C_{10}H_8N_4$	65·2	4·4	30·4
H	CH_2·CN	CH_2Ph	147—148 ‡	68	66·5	5·1	28·3	$C_{11}H_{10}N_4$	66·7	5·1	28·3
H	C	Ph	238—239 †	57	71·6	4·5	22·9	$C_{22}H_{16}N_6$	72·5	4·4	23·1
H	C	CH_2Ph	146—147 §	—	64·4	5·2	19·6	$C_{23}H_{18}N_6,3H_2O$	63·8	5·6	19·4
H	C	CH_2Ph	264—266 §	—	71·1	4·7	21·5	$C_{23}H_{18}N_6,\frac{1}{2}H_2O$	71·3	4·9	21·7

* A = 2,4-$(NO_2)_2C_6H_3$·NH·N=CH. B = Propenyl. C = 1,5-Diphenyl-1,2,4-triazol-3-y (*i.e.*, compounds are bitriazolyls). † From benzene–light petroleum. ‡ From ether–light petroleum. § From chloroform–light petroleum. ¶ From light petroleum. ‖ From benzene.

TABLE 2.

Derivatives of *N*-unsubstituted 1,2,4-triazole-3-aldehydes.

5-Subst.	M. p.	Solvent † for crystn.	Yield (%)	Found (%) C	H	N	Formula	Required (%) C	H	N
Dimethyl acetals										
Me	96—101°	C_6H_6–Pet	50	44·0	7·1	25·8	$C_6H_{11}N_3O_2,\frac{1}{2}H_2O$	46·4	7·3	25·3
Ph	102—103	,,	60	60·0	6·0	19·3	$C_{11}H_{13}N_3O_2$	60·3	6·0	19·2
CH_2Ph	102—103	,,	70	61·8	6·5	17·6	$C_{12}H_{15}N_3O_2$	61·8	6·5	18·0
p-C_6H_4Me	127—128	Et_2O–Pet	40	62·2	6·5	17·6	$C_{12}H_{15}N_3O_2$	61·8	6·5	18·0
p-C_6H_4·NO_2	168—169	MeOH–Et_2O	50	47·2	5·1	20·0	$C_{11}H_{12}N_4O_4,H_2O$	46·8	5·0	19·9
2,4-*Dinitrophenylhydrazones*										
Me	254—256	Aq. MeOH	—	40·7	3·4	31·9	$C_{10}H_9N_7O_4,\frac{1}{2}H_2O$ ‡	40·0	3·3	32·7
Ph	286—288 *	Aq. C_5H_5N	—	51·3	3·3	27·3	$C_{15}H_{11}N_7O_4$	51·0	3·1	27·8
CH_2Ph	243—245 *	,,	—	52·6	3·7	26·4	$C_{16}H_{13}N_7O_4$	52·3	3·6	26·7
p-C_6H_4Me	279—281 *	,,	—	56·2	4·2	25·6	$C_{16}H_{13}N_7O_4,C_5H_5N$	56·5	4·1	25·1
p-C_6H_4·NO_2	290—293	Aq. EtOH	—	43·3	3·3	26 §	$C_{15}H_{10}N_8O_6,H_2O$	43·3	2·9	26·9

* With decomp. † Pet = light petroleum. ‡ Found: O, 23·8. Required, O, 24·0%. § Approximate analysis on small sample.

EXPERIMENTAL

Representative experiments are described; further details and analyses appear in the Tables. Light petroleum had b. p. 40—60°. Analytical difficulties in the triazole series have been noted; [21] major differences between theoretical and empirical values, if present, affect either the values of nitrogen or those of carbon and hydrogen.

Ethyl hydrogen acetamidomalonate [22] and diazotised *p*-chloroaniline gave [23] the unstable

[17] Voswinckel, *Ber.*, 1903, **36**, 2483.
[18] Snyder and Putnam, *J. Amer. Chem. Soc.*, 1954, **76**, 33.
[19] Prevost, *Compt. rend.*, 1933, **196**, 1129.
[20] Ginsberg, *J. Amer. Chem. Soc.*, 1953, **75**, 5746.
[21] Browne and Polya, *Analyt. Chem.*, 1962, **34**, 298.
[22] Hellmann, Teichmann, and Lingens, *Chem. Ber.*, 1958, **91**, 2427
[23] Cf. Hellmann and Schwiersch, *Chem. Ber.*, 1961, 1868.

ethyl ester of *N*-acetyl-α-*p*-chlorophenylazoglycine, m. p. 142—145° (decomp.), which was cyclised with acetic anhydride [23] to *ethyl* 1-p-*chlorophenyl*-5-*methyl*-1,2,4-*triazole*-3-*carboxylate* (I; X = CO_2Et). The latter was converted into the *alcohol* (I; X = CH_2·OH) and aldehyde (I; X = CHO) by the methods described in Part VI.

Dichloroacetic acid (26 g.) was converted into methyl dimethoxyacetate [24] which was not isolated. Its solution in methanol (120 ml.) was cooled in ice and salt, and 100% hydrazine (15 g.) was added dropwise with stirring. After 30 min. at room temperature the solution was filtered and then boiled for 18 hr. The solvent was removed in a vacuum and the residue extracted with chloroform (4 × 30 ml.). Concentration of the extracts left *dimethoxyacethydrazide* as needles (9·4 g.) which, on recrystallisation from benzene and drying in a vacuum over silica gel and paraffin, had m. p. 73—75° (Found: C, 36·2; H, 7·4; N, 20·9. $C_4H_{10}N_2O_3$ requires C, 35·8; H, 7·5; N, 20·9%).

Ethyl chloroacetate (30·6 g.) was converted into ethyl methoxyacetate.[25] This was not isolated but its methanolic solution (100 ml.) was boiled with 100% hydrazine hydrate (15 g.) for 18 hr. After removal of the solvent in a vacuum the residue was washed with ether, then extracted with chloroform. Addition of light petroleum to the chloroform solution gave plates of *methoxyacethydrazide* (13 g.), m. p. 58—59° (Found: C, 34·6; H, 7·5; N, 26·8. $C_3H_8N_2O_2$ requires C, 34·6; H, 7·7; N, 26·9%).

A mixture of ethyl phenylacetimidate hydrochloride [26] (3·7 g.) and sodium hydroxide (0·8 g.) in methanol (25 ml.) was filtered, immediately added to dimethoxyacethydrazide (2·7 g.), boiled for 1 hr., and evaporated. The residual syrup was extracted with ether. The material extracted was crystallised from benzene–light petroleum (charcoal) and dried in a vacuum over phosphorus pentoxide at 40°, affording 5-*benzyl*-1,2,4-*triazole*-3-*aldehyde dimethyl acetal* (3·1 g.), plates, m. p. 102—103°.

Methyl phenylacetimidate hydrochloride (3·7 g.) and sodium hydroxide (0·8 g.) in dry methanol (20 ml.) with, later, methoxyacethydrazide (2·1 g.) similarly gave a syrup whence warm benzene (2 × 20 ml.) removed 5-*benzyl*-3-*methoxymethyl*-1,2,4-*triazole* (1·6 g.), needles, m. p. 87—88° (from benzene–light petroleum or ether–light petroleum).

Methyl phenylacetimidate hydrochloride (6·2 g.) was treated similarly with sodium hydroxide (1·35 g.) in dry methanol (60 ml.) and then with cyanoacethydrazide (3·3 g.) in boiling methanol (10 ml.) for 40 min. The solution was concentrated to 20 ml. and treated with ether (10 ml.), a cream powder (1·2 g.), m. p. 205—206° (decomp.), being precipitated. Repeated recrystallisation from methanol–ether gave 5-*benzyl*-3-*cyanomethyl*-1,2,4-*triazole*, the bulk of which (4·5 g.) was obtained by evaporation of the methanol–ether solution filtered from the cream powder. The crude residue was recrystallised from ether–light petroleum containing a few drops of methanol (charcoal) as white needles, m. p. 147—148° (after drying in a vacuum over silica gel).

Methyl phenylacetimidate hydrochloride (2·1 g.) and sodium hydroxide (0·5 g.) in methanol (20 ml.) with, later, 1,5-diphenyl-1,2,4-triazole-3-carboxyhydrazide (3·2 g.) in methanol (20 ml.) (boiling for 30 min.) gave an oil. Treatment of this with chloroform and light petroleum gave a cream powder (4·0 g.), m. p. 114—117° (decomp.). Repeated recrystallisation of this intermediate from chloroform–light petroleum gave white needles of the 5′-*benzyl*-1,5-*diphenyl*-3,3′-*bi*-1,2,4-*triazolyl trihydrate*, m. p. 146—147°. The melt resolidified to form the *hemihydrate*, m. p. 263—265°. The latter was obtained also by heating the intermediate just above its m. p. for 2—3 min.

Amidrazones were prepared from imidic ester hydrochlorides and hydrazines in dry pyridine.[27] To crude, freshly liberated benzimidoylphenylhydrazine (12·0 g.) crotonyl chloride [18] (8·0 g.) was added with cooling. The mixture was heated on a water-bath for 5 hr., then treated with water (100 ml.), made alkaline (litmus) with sodium carbonate, and extracted with benzene (3 × 50 ml.). The extracts were treated with charcoal, filtered, and evaporated on a water-bath. Extraction of the oily residue (6·5 g.) with light petroleum (2 × 80 ml.), concentration, and cooling gave 1,3-*diphenyl*-5-*propenyl*-1,2,4-*triazole*, white needles (from ether–light petroleum), m. p. 125—126·5°.

CHEMISTRY DEPARTMENT, UNIVERSITY OF TASMANIA,
HOBART, TASMANIA.

[*Received, June 26th*, 1962.]

[24] Royals and Robinson, *J. Amer. Chem. Soc.*, 1956, **78**, 4161.
[25] Pratt and Robinson, *J.*, 1925, **127**, 166.
[26] Wheeler, Walden, and Metcalf, *J. Amer. Chem. Soc.*, 1898, **20**, 64.
[27] Atkinson and Polya, *J.*, 1954, 3319.