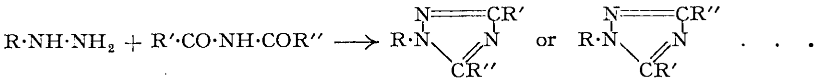
# **657.** *Triazoles. Part I. Unsymmetrical Einhorn–Brunner and Related Pellizzari Reactions.*

By M. R. Atkinson and J. B. Polya.

Reactions of phenylhydrazine with *N*-formylbenzamide, *N*-acetylbenzamide, and *N*-acetylpropionamide in the presence of acid catalysts result in the formation of single triazoles, the substituent derived from the stronger acid related to the diacylamine appearing in the 3-position. The new compounds 3-ethyl-5-methyl-1-phenyl- and 3-methyl-1 : 5-diphenyl-1 : 2 : 4-triazole were obtained, the former through the Pellizzari reaction and the latter through both the Pellizzari and the Einhorn–Brunner reaction, in addition to new compounds (not triazoles) of unknown structure.

Condensation of a hydrazine with a diacylamine as in (1) (R, R′, and R″ = H, alkyl, aryl, etc.), to afford substituted 1 : 2 : 4-triazoles, may be termed the Einhorn–Brunner reaction (Einhorn and Szelinsky, *Annalen*, 1905, **343**, 229; Brunner, *Ber.*, 1914, **47**, 2671; *Monatsh.*, 1915, **36**, 509). If R′ and R″ are different, the reaction is said to be unsymmetrical and could lead to two isomeric triazoles. The only recorded synthesis of this kind is that of 1 : 5-diphenyl-1 : 2 : 4-triazole from phenylhydrazine and



(1)

*N*-formylbenzamide in aqueous acetic acid (Einhorn and Szelinsky, *loc. cit.*; Thompson, *J. Amer. Chem. Soc.*, **1951**, **73**, 5914). A variation of this synthesis, and reactions of *N*-acetylpropionamide and *N*-acetylbenzamide with phenylhydrazine, are summarized in the Table.

*Reaction of unsymmetrical diacylamines with equimolar amounts of phenylhydrazine in the presence of acid.*

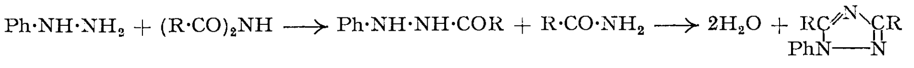
| R'·CO·NH·COR'' | | | | | Substituents in 1 : 2 : 4-triazoles | | | | By-products and yields (%) | |
|---|---|---|---|---|---|---|---|---|---|---|
| R' | R'' | Ph·NH·NH₂ | Solvent | Time (hours) | 1 | 3 | 5 | Yield (%) | | |
| Me | Et | Base | AcOH–NaOAc | 16 | Ph | Me | Et | 45—48 | | |
| Me | Et | Hydrochloride | do. +$H_2O$ | 16 | Ph | Me | Et | 48 | | |
| Me | Et | ,, | Pyridine | 4 | Ph | Me | Et | 65 | Ph·NH·NHAc | 18 |
| Me | Ph | ,, | AcOH–NaOAc | 10 | Ph | Me | Ph | 78 | | |
| Me | Ph | ,, | Pyridine | 4 | Ph | Me | Ph | 35 | $C_{28}H_{31}O_4N_5$ | ? |
| Me | Ph | ,, | Pyridine–$H_2O$ | 5 | — | — | — | 0 | $NH_4Cl$<br>Ph·NH·NH·COPh | 36<br>19 |
| H | Ph | ,, | Pyridine | 4 [a] | Ph | H | Ph | 52 | | |
| H | Ph | Base | 30% AcOH | 1 | Ph | H | Ph | 84 [b] | | |

[a] Main yield in few minutes. [b] Thompson, *loc. cit.*

Careful investigation failed to reveal the presence of more than one triazole in any reaction mixture and the same reactants afforded the same triazole irrespective of the composition of the solvent–catalyst system. The reactions investigated up to the present are not ambiguous and the substituent derived from the stronger acid related to the diacylamine appears in the 3-position of the resulting triazole. Further work is in progress to check the validity of these findings in general. A detailed discussion of the mechanism of the Einhorn–Brunner reaction will be presented in another communication but the following principles may be stated at present.

The participation of diacylamines in the reaction as *N*-acylimidic acid, R'·CO·N:C(OH)·R'', or a related structural form, was postulated by Brunner (*loc. cit.*) and made probable by other evidence (Titherley and Stubbs, *J.*, 1914, **105**, 299; Polya and Spotswood, *Rec. Trav. chim.*, 1949, **68**, 573; 1951, **70**, 146). The reaction takes place in the presence of acidic catalysts only (acetic acid, acidic buffers, pyridine hydrochloride), but excessive acid catalysis reduces the yield of triazole and enhances the formation of acylated hydrazines, ammonium chloride, and occasionally compounds of unknown structure.

Brunner examined and dismissed the possibility of a reaction mechanism illustrated by :



This view has been confirmed, and the proof against such a mechanism has been completed, by showing that the second of these reactions does not occur even in the presence of acid catalysts under the mild conditions of the Einhorn–Brunner reaction. Such reactions occur, however, in the absence of solvents at high temperatures and are termed Pellizzari reactions (Pellizzari, *Gazzetta*, 1911, **41**, II, 20, who gives references to previous work). When the acyl groups of the amide and acylhydrazine are different, the Pellizzari reaction may occur with reacylation (interchange of acyl groups), leading to a mixture of triazoles. This is not always the case, and the formation of a single triazole of the correct molecular formula justifies the assumption of an unambiguous reaction and thus determines the structure of the triazole. This is the case with the hitherto undescribed 3-ethyl-5-methyl-1-phenyl-1 : 2 : 4-triazole, which is formed from acetamide and 1-phenyl-2-propionylhydrazine at temperatures not exceeding 210°; 3 : 5-dimethyl-1-phenyl- and 3 : 5-diethyl-1-phenyl-1 : 2 : 4-triazole are not formed although the former appears as a substantial by-product at higher temperatures. The structure of the new triazole is confirmed by showing it to be different from the unambiguously prepared 5-ethyl-3-methyl-1-phenyl-1 : 2 : 4-triazole (Gastaldi, *Gazzetta*, 1923, **53**, 629). The Pellizzari reaction between benzamide and 1-acetyl-2-phenylhydrazine occurred with reacylation in our experiments and could not be used in itself to determine the structure of the methyldiphenyltriazole obtained in addition to 3 : 5-dimethyl-1-phenyl-1 : 2 : 4-triazole. Since the former is different from the unambiguously prepared 5-methyl-1 : 3-diphenyl-1 : 2 : 4-triazole (Jerchel and Kuhn, *Annalen*, 1950, **568**, 185), it must be the unrecorded 3-methyl-1 : 5-diphenyl-1 : 2 : 4-triazole. When the last-mentioned Pellizzari reaction is carried out at lower temperatures and for shorter times, it is possible to isolate a new substance $C_{15}H_{17}O_2N_3$, apparently an addition compound which is not accompanied by triazoles. Triazoles could not be obtained by replacing amides with nitriles in the Pellizzari reaction. On the contrary, the low yields afforded by most Pellizzari reactions are due to losses through the formation of nitriles which do not participate in the reactions leading to triazoles except in the presence of condensing agents such as sodium (von Walther, *J. pr. Chem.*, 1894, **50**, 91; Engelhardt, *ibid.*, 1896, **54**, 143).

## EXPERIMENTAL

M. p.s corrected. The analysis of triazoles, and particularly of triazole picrates, gives consistently low nitrogen values, whereas no difficulty is experienced with the carbon and hydrogen analyses; this is confirmed by a private communication from Dr. F. Lions.

*N*-Acetylpropionamide and *N*-acetylbenzamide were prepared by Polya and Spotswood's methods (*Rec. Trav. chim.*, 1948, **67**, 927). *N*-Formylbenzamide was prepared by Mr. P. L. Tardrew (Einhorn, Bischkopff, and Szelinsky, *Annalen*, 1905, **343**, 223). 1-Acetyl-2-phenylhydrazine was available as the by-product of the preparation of 3 : 5-dimethyl-1-phenyl-1 : 2 : 4-triazole (Brunner, *loc. cit.*, 1915). Other 1-acyl-2-phenylhydrazines prepared by recorded methods were: formyl (de Vries, *Ber.*, 1894, **27**, 152); propionyl (Leighton, *Amer. Chem. J.*, 1898, **20**, 676); benzoyl (Fischer, *Annalen*, 1878, **190**, 67, 125).

*Phenylhydrazine and* N-*Acetylpropionamide*.—(*a*) Phenylhydrazine hydrochloride (31·5 g.), *N*-acetylpropionamide (25·0 g.), and dry pyridine (100 c.c.) were refluxed for 4 hours. The product was poured into 5% aqueous sodium hydroxide (250 c.c.) and extracted 3 times with ether, the ethereal extracts being combined with the pyridine layer. Removal of ether and pyridine hydrate left an oil (39·1 g.) which was extracted with ether. Fractionation of the extract gave an oil, b. p. 147—155°/12 mm. (21·5 g.), and 1-acetyl-2-phenylhydrazine, m. p. 128—130° (4 g.), as residue. The oil was redistilled, to afford 5-ethyl-3-methyl-1-phenyl-1 : 2 : 4-triazole, b. p. 122—122·5°/2 mm. (18 g., 65%) (Found: C, 70·8; H, 6·9; N, 21·8. Calc. for $C_{11}H_{13}N_3$: C, 70·6; H, 6·9; N, 22·5%).

(*b*) Freshly crystallized phenylhydrazine hydrochloride (7·3 g.), *N*-acetylpropionamide (7·3 g.), glacial acetic acid (1·5 g.), and hydrated sodium acetate (3·5 g.) were refluxed in water (80 c.c.) for 16 hours at initial and final pH 5. The resulting mixture of aqueous phase and oil was treated with 5% mercuric chloride solution, with stirring at 60°, until no further precipitation occurred. Recrystallization from water afforded the mercuric chloride adduct of 5-ethyl-3-methyl-1-phenyl-1 : 2 : 4-triazole, m. p. 148—152° (14·3 g., 62%); it had m. p. 156° on further recrystallization from 1 : 1 ethanol–ether (Found: C, 29·2; H, 2·9; N, 8·6. Calc. for $C_{11}H_{11}N_3,HgCl_2$: C, 28·8; H, 2·8; N, 9·2%). The adduct was dissolved in cold 4N-hydrochloric acid (100 c.c.) and extracted with ether. The extract was discarded and the acid solution treated with hydrogen sulphide, neutralized to pH 5 with ammonia, and precipitated with sodium carbonate. Ether-extraction of the precipitate and filtrate afforded 5-ethyl-3-methyl-1-phenyl-1 : 2 : 4-triazole, b. p. 281—282/760 mm., $d_{20}^{20}$ 1·075, $n_D^{20}$ 1·5450 (4·5 g., 77% recovery from the adduct, 48% overall); this gave a picrate, yellow rhombs, m. p. 139—140·5°, and a hydrochloride, m. p. 205—206°, which did not depress the m. p.s of those prepared from 5-ethyl-3-methyl-1-phenyl-1 : 2 : 4-triazole obtained by Gastaldi's method (*loc. cit.*).

(*c*) Phenylhydrazine (base), *N*-acetylpropionamide, glacial acetic acid, and anhydrous sodium acetate (each 0·1 mole) were heated on the water-bath for 16 hours and worked up as in (*b*), to afford the same triazole, b. p. 151—155°/9—12 mm. (8·3—8·5 g., 45—48%), as shown by the identity of picrates, hydrochlorides, and mercuric chloride adducts.

2-*Phenyl*-1-*propionylhydrazine and Acetamide*.—2-Phenyl-1-propionylhydrazine (3·7 g.) and acetamide (10 g.) were heated at 175° for 9 hours. Much acetonitrile was formed, no triazole could be isolated, and the hydrazine was recovered in a yield of 96%. 2-Phenyl-1-propionylhydrazine (180 g.) and dry, freshly distilled acetamide (60 g.) were heated at 60° for 14 hours; the temperature was raised slowly to 210° and kept thereat for 6 hours while volatile products distilled off. The residual viscous oil was fractionated, giving acetamide, b. p. 108—109°/15 mm. (33 g.), the triazole, b. p. 152—162°/12 mm. (20 g.), and 2-phenyl-1-propionylhydrazine, b. p. 164°/12 mm., m. p. 158—159° (85 g.). The triazole, refractionated, gave a mixture, b. p. 92—110°/2 mm., of acetamide and triazole (1·5 g.), *3-ethyl-5-methyl-1-phenyl-1 : 2 : 4-triazole* (16 g., 17% on unrecovered 1-propionyl-2-phenylhydrazine or 21% on unrecovered acetamide), b. p. 116—118°/2 mm., and a fraction, b. p. 120—134°/2 mm., contaminated with 2-phenyl-1-propionylhydrazine. The pure triazole (Found: C, 70·7; H, 6·9; N, 21·9. $C_{11}H_{13}N_3$ requires C, 70·6; H, 6·9; N, 22·5%) had b. p. 278°/755 mm., $d_{20}^{20}$ 1·058, $n_D^{20}$ 1·5505. When evaporated with excess of hydrochloric acid and dried *in vacuo* on porous plate over solid potassium hydroxide the triazole affords the hydrochloride, m. p. 208—210°, decomp. 220°. The mercuric chloride adduct crystallizes from 50% ethanol in colourless needles, m. p. 138—140°. The picrate, formed in ethanol solution without warming, consists of yellow, monoclinic prisms, m. p. 138—140°; on further recrystallizations from 1 : 2 chloroform–ethanol and then from 90% ethanol, it had m. p. 141—142°; it depressed the m. p. of picrates of 5-ethyl-3-methyl-1-phenyl-1 : 2 : 4-triazole prepared by the Gastaldi or the Einhorn–Brunner method (7—8° for approximately 1 : 1 mixtures). The different crystal forms of the picrates of the closely similar isomeric triazoles in this case may be used for their rapid identification.

*Phenylhydrazine and* N-*Formylbenzamide*.—Phenylhydrazine hydrochloride (14·5 g.) and *N*-formylbenzamide (14·7 g.) in pyridine (50 c.c.) were refluxed for 4 hours although most of the reaction is completed in about 15 minutes, as judged by the volume of oil separating in the reaction. On cooling, prismatic needles of 1 : 5-diphenyl-1 : 2 : 4-triazole, m. p. 89—90°, were obtained (11·5 g., 52%), raised to 90—90·5° after recrystallization from light petroleum (b. p. 60—80°) (Found: C, 76·1; H, 5·1; N, 18·5. Calc. for $C_{14}H_{11}N_3$: C, 76·0; H, 5·0; N, 19·0%). The triazole, its picrate, m. p. 142—143°, and mercuric chloride adduct, m. p. 126—128° (from 80% ethanol), were identical with 1 : 5-diphenyl-1 : 2 : 4-triazole (Young, *J.*, 1895, **67**, 1063) and its derivatives.

1-*Formyl*-2-*phenylhydrazine and Benzamide*.—1-Formyl-2-phenylhydrazine (27·2 g.) and benzamide (25 g.) were heated to 220° for 4 hours, volatile products being allowed to distil off during the reaction (4 g.). The mixture was then poured into 10% potassium hydroxide solution (200 c.c.) and extracted with ether (3 × 50 c.c.), the extract evaporated, and the residue fractionated, giving 1-phenyl-1 : 2 : 4-triazole (2·0 g., 7%), b. p. 144—148°/10 mm.; the picrate had m. p. 156—158° alone or mixed with that of the triazole prepared by Pellizzari and Ferro's method (*Gazzetta*, 1898, **28**, II, 541). A second fraction (1·7 g., 4%), b. p. 158—160°/4 mm., m. p. 60—70° (after sublimation, m. p. 85—90°), was 1 : 5-diphenyl-1 : 2 : 4-triazole; neither this nor its picrate (m. p. 136—138°) depressed the m. p. of authentic material (Young, *loc. cit.*).

*Phenylhydrazine and* N-*Acetylbenzamide*.—(*a*) Phenylhydrazine hydrochloride (14·5 g.), *N*-acetylbenzamide (16·5 g.), glacial acetic acid (30 c.c.), and anhydrous sodium acetate (10 g.) were refluxed for 10 hours. The product was made alkaline with 40% sodium hydroxide solution and extracted with ether. The pale oil obtained from the extract solidified slowly and consisted of *3-methyl-1 : 5-diphenyl-1 : 2 : 4-triazole*, which formed prisms, m. p. 80—81° on recrystallization from 90% ethanol and then light petroleum (b. p. 60—80°) (18·4 g., 78%) (Found: C, 76·6; H, 5·5; N, 17·6. $C_{15}H_{13}N_3$ requires C, 76·6; H, 5·5; N, 17·9%). The hydrochloride is precipitated when an ethereal solution of the triazole is treated with dry hydrogen chloride; it has m. p. 221—223°; the picrate forms yellow prisms (from ethanol), m. p. 152—154°, and the mercuric chloride adduct needles (from 50% ethanol), m. p. 121—124°. The triazole and its derivatives depress the m. p.s of 5-methyl-1 : 3-diphenyl-1 : 2 : 4-triazole (prepared according to Jerchel and Kuhn, *loc. cit.*) and its derivatives.

(*b*) Phenylhydrazine hydrochloride (14·5 g.) and *N*-acetylbenzamide (16·4 g.) in dry pyridine (50 c.c.) were refluxed for 4 hours. After removal of the pyridine in steam, the oil and the aqueous layer were separated. Cooling the aqueous layer gave an unidentified *substance* as colourless needles, m. p. 103° (1·6 g.) (Found: C, 67·1; H, 6·0; N, 14·3. $C_{28}H_{31}O_4N_5$ requires C, 67·2; H, 6·2; N, 14·0%). Recrystallization of the oil from light petroleum (b. p. 60—80°) afforded more of this material (1·4 g.). From the mother-liquors 3-methyl-1 : 5-diphenyl-1 : 2 : 4-triazole was obtained (7·6 g., 35%), having m. p. 78°, identical with the triazole obtained as in (*a*). Repetition with half the quantities in pyridine containing 5% of water did not afford a triazole but gave the following products (yields calc. on unrecovered *N*-acetylbenzamide): ammonium chloride (0·92 g., 52%); phenylhydrazine hydrochloride (4·1 g., 57%); 1-benzoyl-2-

phenylhydrazine, m. p. 167° (2·1 g., 27%). *N*-Acetylbenzamide was recovered in a yield of 2·5 g. (30%).

1-*Acetyl*-2-*phenylhydrazine and Benzamide*.—(*a*) 1-Acetyl-2-phenylhydrazine (10 g.) and benzamide (10 g.) were heated in an oil-bath to 185° during 1 hour, then kept at 175—185° for 4 hours and finally at 200° for 1 hour. The residual pale brown oil solidified on cooling. It was dissolved in water (300 c.c.), boiled with Norite, filtered, brought to pH 8 with ammonia, and cooled, affording a mixture of rhombic prisms and needles, m. p. 96—120° (10·6 g.). When dissolved in warm 0·1N-hydrochloric acid and cooled, this afforded benzamide, m. p. 128—129° (4·6 g.). The acid solution was extracted with ether (2 × 50 c.c.), affording 1-acetyl-2-phenylhydrazide, m. p. 128—130° (2·8 g.). The aqueous solution was brought to pH 10 with ammonia and extracted with ether (3 × 100 c.c.) from which colourless prisms, m. p. 105—107°, were obtained (2·3 g., 18% on unrecovered 1-acetyl-2-phenylhydrazine, 19% on unrecovered benzamide) [Found : C, 66·2; H, 6·3; N, 15·5. $C_{15}H_{17}O_2N_3$ (*i.e.*, Ph·NH·NHAc + Ph·CO·NH$_2$) requires C, 66·4; H, 6·3; N, 15·5%]. The *substance* gave neither picrate nor mercuric chloride adduct; it deteriorated on sublimation or recrystallization from aqueous ethanol.

(*b*) 1-Acetyl-2-phenylhydrazine (11·5 g.) and benzamide (9·1 g.) were heated in an oil-bath at 180° for 4 hours, then at 245° for 4 hours with evolution of ammonia and water. The viscous oil was warmed and poured into 40% aqueous potassium hydroxide (100 c.c.), leaving a little brown oil. The mixture was extracted with ether (3 × 100 c.c.), and the extract was freed from phenylhydrazine and 1-acetyl-2-phenylhydrazine by Brunner's process (Brunner, *loc. cit.*, 1915). Fractionation gave a partly crystallizing forerun (0·8 g.), then 1-acetyl-2-phenylhydrazide, b. p. 158—165°/2—4 mm., m. p. 129—130° (2·9 g.), and 3-methyl-1 : 5-diphenyl-2 : 4-triazole, b. p. 170—195°/2—4 mm., m. p. 79—80° (0·75 g., 5·6% on unrecovered 1-acetyl-2-phenylhydrazine) (Found : C, 76·6; H, 5·5; N, 17·5. Calc. for $C_{15}H_{13}N_3$ : C, 76·6; H, 5·5; N, 17·9%). The triazole and its derivatives were identical with 3-methyl-1 : 5-diphenyl-1 : 2 : 4-triazole and its derivatives obtained by the Einhorn–Brunner reaction and distinct from the triazole and derivatives obtained according to Jerchel and Kuhn. The forerun was separated by filtration into crystalline 1-acetyl-2-phenylhydrazine, m. p. 129° (0·1 g.), and an oil identified as 3 : 5-dimethyl-1-phenyl-1 : 2 : 4-triazole (0·6 g.) through the picrate, m. p. 155—157°.

1-*Benzoyl*-2-*phenylhydrazine and Acetamide*.—(*a*) The reaction between 1-benzoyl-2-phenylhydrazine and acetamide at 140° during 1 hour and then at 175° during 4 hours did not afford triazoles, but 90% of the reactants were recovered.

(*b*) 1-Benzoyl-2-phenylhydrazine (6·0 g.) and dry, freshly distilled acetamide (15 g.) were refluxed in an oil-bath at 250° for 4 hours. The acetamide was distilled off at atmospheric pressure and the residue was extracted with ether (2 × 50 c.c.), leaving undissolved 1-benzoyl-2-phenylhydrazine, m. p. 166° (2·1 g.). The crude triazole extract (3·8 g.) was fractionated to give as main fraction a pale yellow oil, b. p. 210—215°/25 mm., which solidified after several months (2·1 g.). Recrystallization from light petroleum (b. p. 40—60°) removed 1-acetyl-2-phenylhydrazine, m. p. 129° (0·08 g.). The petroleum extract was sublimed at 40°/2 mm., to afford oily crystals, m. p. 80—85°; it gave a *picrate*, flat prisms, m. p. 180—182°, which, recrystallized from ethanol, had m. p. 184—186° (Found : C, 54·6; H, 3·6; N, 17·0. $C_{21}H_{16}O_7N_6$ requires C, 54·3; H, 3·45; N, 18·1%). The substance and its derivative were not identical with the various samples of 3-methyl-1 : 5-diphenyl-1 : 2 : 4-triazole and its picrate but identical with the 5-methyl-1 : 3-diphenyl-1 : 2 : 4-triazole (Jerchel and Kuhn, *loc. cit.*) and its picrate respectively. The triazole from the Pellizzari reaction is somewhat impure since its m. p. is lower than that of the triazole prepared according to Jerchel and Kuhn.

(*c*) 1-Benzoyl-2-phenylhydrazine (95 g.) and acetamide (50 g.) were heated at 260—280° for 3 hours, water and other volatile substances being allowed to distil off (40 g.). The residue was poured into 10% aqueous sodium hydroxide (250 c.c.), and the resulting mixture was extracted with ether (3 × 50 c.c.). The oil (85 g.) from the extract was fractionated, giving a forerun 110—120°/14 mm. (6·1 g.), 3 : 5-dimethyl-1-phenyl-1 : 2 : 4-triazole, b. p. 134—138°/3 mm., 118—124/2 mm. (27·6 g., 70% on unrecovered 1-benzoyl-2-phenylhydrazine) (picrate, m. p. 154—156°; mercuric chloride adduct, m. p. 186—189°), and 1-benzoyl-2-phenylhydrazine, b. p. 172—180°/2 mm., m. p. 167—168° (47 g.).

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UNIVERSITY OF TASMANIA, HOBART.

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