Heterocyclic Compounds from Urea Derivatives. Part XII.[1] Ethoxycarbonylhydrazine as a Source of 1,2,4-Triazoles

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Interaction of equimolar quantities of carbodi-imides and ethoxycarbonylhydrazine in dimethylformamide yields 1-(*NN'*-diarylamidino)-2-ethoxycarbonylhydrazines, which are readily cyclised, with loss of ethanol, to 4-aryl-3-arylamino-5-hydroxy-1,2,4-triazoles. Ring-closure to the corresponding 5-ethoxy-heterocycles, with loss of water, occurred in one case.

S-Alkyl 1-ethoxycarbonyl-4-phenyl-3-isothiosemicarbazides, obtained from ethoxycarbonylhydrazine and phenyl isothiocyanate, and subsequent *S*-alkylation, are similarly convertible into 3-alkylthio-5-hydroxy-4-phenyl-1,2,4-triazoles.

Addition of aroyl isothiocyanates to ethoxycarbonylhydrazine yields 4-aroyl-1-ethoxycarbonyl-3-thiosemicarbazides. These are ring-closed in alkaline media, with loss of carbon dioxide and ethanol, to 3-aryl-5-mercapto-1,2,4-triazoles. The isolation of 1-ethoxycarbonyl-3-methylthio-5-phenyl-1,2,4-triazole in one example suggests that compounds of this type are formed intermediately in this cyclisation.

COMPOUNDS containing twinned double bonds, such as carbodi-imides, and iso(thio)cyanate esters, undergo rapid addition reactions with hydrazino [2-4] and amidino groups.[3,5] Applied to aminoguanidine,[6] diaminoguanidine,[7] and diguanide,[8] addition-cyclisations of this type provide a useful general route to heterocyclic compounds, particularly 1,2,4-triazoles, 1,3,4-thiadiazoles, and *s*-triazines. This Paper deals with the extension of this group of reactions to ethoxycarbonylhydrazine, and describes effective syntheses of 3-hydroxy(or mercapto)-1,2,4-triazoles.[9]

Equimolar quantities of ethoxycarbonylhydrazine and aromatic carbodi-imides reacted additively in dimethylformamide to afford 1-(*NN'*-diarylamidino)-2-ethoxycarbonylhydrazines (I). In contrast to comparable addition compounds derived from aminoguanidine,[6c] diaminoguanidine,[7a] and diguanide [8a] (which show an increasing tendency to cyclise *in situ* under the prevailing conditions), the present adducts (I) were isolated as stable solids in good yield. They were readily cyclised, with loss of ethanol, to 4-aryl-3-arylamino-

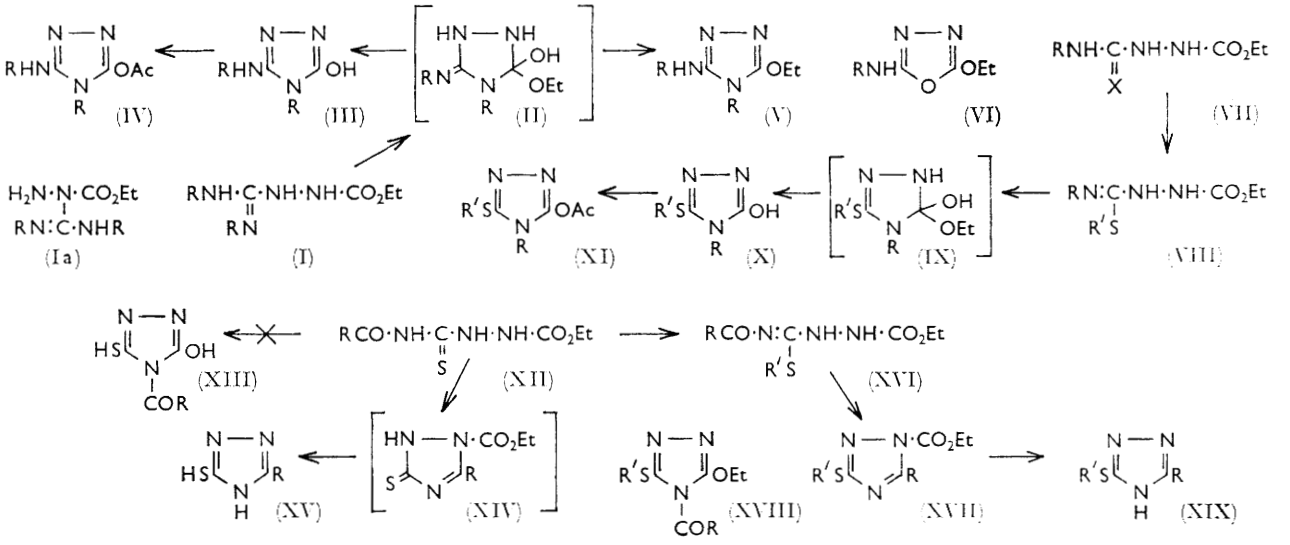
[1] Part XI, F. Kurzer and K. Douraghi-Zadeh, preceding Paper.
[2] H. G. Khorana, *Chem. Rev.*, 1953, **53**, 145, 160.
[3] F. Kurzer and K. Douraghi-Zadeh, *Chem. Rev.*, 1967, **67**, in the press.
[4] E. E. Reid, "Organic Chemistry of Bivalent Sulphur," Chemical Publishing Co., New York, 1963, vol. 5, p. 194.
[5] K. H. Slotta, R. Tschesche, and H. Dressler, *Ber.*, 1930, **63**, 208.
[6] L. E. A. Godfrey and F. Kurzer, *J. Chem. Soc.*, (*a*) 1960, 3437; (*b*) 1961, 5137; (*c*) 1962, 3561.
[7] F. Kurzer and K. Douraghi-Zadeh, *J. Chem. Soc.*, (*a*) 1965, 3912; (*b*) 1965, 4448; (*c*) (*C*), 1966, 1; (*d*) (*C*), 1966, 6.
[8] F. Kurzer and E. D. Pitchfork, *J. Chem. Soc.*, (*a*) 1964, 3459; (*b*) 1965, 6296.
[9] Brief summary, *Chem. and Ind.*, 1966, 1143.

5-hydroxy-1,2,4-triazoles (III). The phenyl homologue (I; R = Ph), for example, though rather stable towards mineral acid, gave the triazole (III; R = Ph) rapidly in excellent yield on pyrolysis or treatment with alkali; small quantities (8—12%) of this triazole arose in fact as a by-product in the preparation of the primary adduct (I). Action of acetic anhydride at 100° on (I; R = Ph) gave the corresponding acetyl derivative [probably (IV)] of the hydroxy-triazole, though in low yield; this was probably due to the relative stability of the adduct (I) in acid media. The structure of the hydroxy-triazoles (III) was established by the identity of the phenyl homologue with authentic material.[10]

Addition of the more stable [2,3,11] cyclohexylcarbodi-imide to ethoxycarbonylhydrazine occurred much less rapidly, a proportion of the reactant being recovered (as *s*-dicyclohexylurea) after 8 hours' interaction at 100°. The primary adduct could not be isolated by the usual technique, but was cyclised *in situ* to (III; R = cycloC_6H_{11}), showing that the reaction proceeded in the usual way.

R = *p*-Br·C_6H_4) arising as a by-product in the preparation of the adduct (I; R = *p*-Br·C_6H_4) from di-*p*-bromophenylcarbodi-imide. Production of 1,3,4-oxadiazoles (VI) by loss of a molecule of amine was not observed.

The addition of iso(thio)cyanate esters to ethoxycarbonylhydrazine has been the subject of previous studies. The appropriate adducts (VII; X = O [13,14] or X = S [14,15]) are synthesised and cyclised without difficulty to 3,5-dihydroxy-[13] and 3-hydroxy-5-mercapto-1,2,4-triazoles,[14,15] respectively (see also ref. 16). As expected, 1-ethoxycarbonyl-4-phenyl-3-thiosemicarbazide (VII; R = Ph, X = S) was readily *S*-alkylated; cyclisation of the resulting *S*-alkylthio-derivatives (VIII; R = Ph, R′ = Me or $PhCH_2$) proceeded entirely as that of their parent compound, resulting in 3-alkylthio-5-hydroxy-4-phenyl-1,2,4-triazoles (X; R = Ph, R′ = Me or $PhCH_2$) in excellent yield. Acids as well as alkalis were effective in promoting this reaction [cf. carbodi-imide adducts (I) above], acetic anhydride providing fair yields of the expected acetyl compound, probably (XI).



The results of the cyclisation exclude the formulation of the primary adducts as (Ia), because such structures cannot give rise to 1,2,4-triazoles; in the initial addition, the carbodi-imides thus react at the free amino group of the ethoxycarbonylhydrazine, an observation that agrees with the general behaviour of substituted hydrazines in this type of reaction.[4,12] The cyclisation (I) ⟶ (III) may be visualised to be initiated by an intramolecular nucleophilic attack of the arylamino group of (I) at the ethoxycarbonyl carbon, the resulting cyclic intermediate (II) yielding 5-hydroxy- (III) or 5-ethoxy-1,2,4-triazoles (V) by loss of the appropriate fragments. The latter elimination was observed in one example only, the substituted ethoxy-1,2,4-triazole (V;

However, the more interesting object of these experiments, *viz.*, the aminolysis and hydrazinolysis of the *S*-alkylthio-intermediates (VIII), was not realised. Although methanethiol was evolved when *S*-methyl 1-ethoxycarbonyl-4-phenyl-3-isothiosemicarbazide was treated with hydrazine, the reagent caused merely the usual cyclisation to the substituted 1,2,4-triazole (X), even under very restrained conditions. Aniline had the same effect.

In conclusion, the use of aroyl isothiocyanates in this reaction has been examined. Their interaction with ethoxycarbonylhydrazine under the usual conditions gave 4-aroyl-1-ethoxycarbonyl-3-thiosemicarbazides (XII; R = Ph, *p*-Cl·C_6H_4, *p*-MeO·C_6H_4) in 75—85% yield. Subsequent cyclisation by alkali differed from

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[11] E. Schmidt, W. Striewsky, and F. Hitzler, *Annalen*, 1948, **560**, 222.
[12] R. A. Reed, "Hydrazine and Its Derivatives," Royal Institute of Chemistry, London, 1957, no. 5, p. 14.
[13] G. Zinner and W. Deucker, *Arch. Pharm.*, 1961, **294**, 370.
[14] D. N. Majumdar and P. C. Guha, *J. Indian Chem. Soc.*, 1933, **10**, 685.
[15] M. Tišler, *Arch. Pharm.*, 1959, **292**, 90.
[16] E. Fromm and E. Nehring, *Ber.*, 1923, **56**, 1370.

that of the related adducts (I) and (VII) in that simple loss of ethanol [*i.e.*, production of 4-aroyl-3-hydroxy-5-mercapto-1,2,4-triazoles (XIII)] did not occur; instead simultaneous elimination of carbon dioxide as well as ethanol gave excellent yields of 3-aryl-5-mercapto-1,2,4-triazoles (XV); their structure followed from the identity of the phenyl homologue (XV; R = Ph) with authentic material.[17]

Some insight into the mechanism of this reaction was gained by observations concerning the *S*-alkylation of the adducts. The *S*-benzyl compound (XVI; R = Ph, R′ = $PhCH_2$) was prepared without difficulty by the conventional procedure, and was ring-closed by alkali to 3-benzylthio-5-phenyl-1,2,4-triazole (XIX; R = Ph, R′ = $PhCH_2$) in the expected manner. *S*-Methylation of (XII), on the other hand, was attended by loss of water, giving a product of possible structure (XVII) or (XVIII) (R = Ph, R′ = Me). Of these, the latter was clearly eliminated by the fact that the product was hydrolysed by alkali nearly quantitatively to 3-methylthio-5-phenyl-1,2,4-triazole (XIX; R = Ph, R′ = Me). The isolation of 1-ethoxycarbonyl-3-methylthio-5-phenyl-1,2,4-triazole (XVII) as an intermediate in this example appears to give some weight to the view that a 1-ethoxycarbonyl compound of this type, (XVII) and (XIV), is generally the initial stage of the cyclisation, which may therefore, in the case of the parent compound, be formulated as (XII) ⟶ (XIV) ⟶ (XV).

EXPERIMENTAL

Light petroleum had b. p. 60—80°. Dimethylformamide was redistilled, and the water-containing fore-run rejected.

Addition of Carbodi-imides

1-(NN′-*Diphenylamidino*)-2-*ethoxycarbonylhydrazine*.—(a) *Preparation*. A solution of ethoxycarbonylhydrazine (5·2 g., 0·05 mole) in dimethylformamide (40 ml.) at room temperature was treated during 1 min. with diphenylcarbodi-imide (9·7 g., 0·05 mole) (slightly exothermic), and the liquid kept at 100° for 1·5 hr. The resulting colourless liquid was stirred into ice–water (500 ml.), the precipitate collected at 0°, air-dried, and crystallised from ethanol–light petroleum (3 and 2 ml. per g.), giving prisms (7·15—9·2 g., 48—62%) of the *product*, m. p. 119—121° (Found: C, 64·0; H, 6·1; N, 19·0. $C_{16}H_{18}N_4O_2$ requires C, 64·4; H, 6·0; N, 18·8%).

The crystallisation filtrates deposited a more soluble fraction which consisted, after crystallisation from ethanol, of 3-anilino-5-hydroxy-4-phenyl-1,2,4-triazole, m. p. and mixed m. p. (see below) 209—211° (1·0—1·5 g., 8—12%) (Found: C, 66·7; H, 4·6. Calc. for $C_{14}H_{12}N_4O$: C, 66·7; H, 4·8%).

(b) *Action of acid*. The reactant (0·005 mole) was recovered (92%) after being boiled in ethanol (8 ml.)–concentrated hydrochloric acid (4 ml.) for 30 min., and reprecipitated with ammonia from the diluted solution.

(c) *Action of alkali*. A solution of the reactant (1·5 g., 0·005 mole) in ethanol (4 ml.) was treated with 3N-sodium hydroxide (8 ml.) and refluxed for 30 min. (transient deep green colour). The yellow liquid was diluted with ice–water (20 ml.) and acidified (to pH 2) with 3N-hydrochloric acid. The precipitate was 3-anilino-5-hydroxy-4-phenyl-1,2,4-triazole, m. p. 210—211°, needles (from ethanol) (1·0 g., 80%) (lit.,[10] 212—213°) (Found: C, 66·6; H, 4·8; N, 22·1. Calc. for $C_{14}H_{12}N_4O$: C, 66·7; H, 4·8; N, 22·2%).

(d) *Pyrolysis*. The finely powdered reactant (1·2 g., 0·004 mole) was kept at 200° (metal-bath) for 5 min. The material melted with effervescence, and resolidified on being set aside at room temperature. Crystallisation from ethanol gave needles (0·79 g., 78%) of 3-anilino-5-hydroxy-4-phenyl-1,2,4-triazole, m. p. and mixed m. p. [with (c)] 209—210°.

(e) *Action of acetic anhydride*. A solution of the reactant (0·005 mole) in acetic anhydride (10 ml.) was kept at 100° for 2 hr., then stirred into water (100 ml.). After prolonged storage, the aqueous phase was decanted from the gum, which was dissolved in boiling ethanol. The solution gradually deposited needles (total, 0·22 g., 15%) of the *monoacetyl derivative* of 3-anilino-5-hydroxy-4-phenyl-1,2,4-triazole, m. p. and mixed m. p. (see immediately below) 193—194° (Found: C, 64·9; H, 4·9; N, 18·6. $C_{16}H_{14}N_4O_2$ requires C, 65·3; H, 4·8; N, 19·05%). Increasing the time of reaction to 6 hr. did not materially improve the yield. The reaction mixture rapidly blackened on being boiled.

3-*Anilino*-5-*hydroxy*-4-*phenyl*-1,2,4-*triazole Monoacetyl Derivative*.—A solution of the 5-hydroxy-compound (0·5 g., 0·002 mole) in acetic anhydride (8 ml.) was kept at 100° for 30 min. (slow separation of crystals), then stirred into water (50 ml.), giving felted needles (0·44 g., 75%) (from ethanol) of the monoacetyl derivative, m. p. 193—194° (Found: C, 65·1; H, 4·6%).

1-(NN′-*Di*-p-*tolylamidino*)-2-*ethoxycarbonylhydrazine*.—A solution of ethoxycarbonylhydrazine (2·1 g., 0·02 mole) in dimethylformamide (25 ml.) was treated with di-*p*-tolylcarbodi-imide (4·45 g., 0·02 mole), then kept at 100° for 1 hr. Addition to water gave a precipitate which was crystallised from methanol—light petroleum (4 and 1 ml. per g.), affording white felted needles (4·7 g., 72%) of the *product*, m. p. 128—129° (Found: C, 66·9; H, 7·4; N, 16·7. $C_{18}H_{22}N_4O_2$ requires C, 66·3; H, 6·75; N, 17·2%).

1-(NN′-*Di*-p-*bromophenylamidino*)-2-*ethoxycarbonylhydrazine*.—This was prepared as the foregoing example, using di-*p*-bromophenylcarbodi-imide (7·0 g., 0·02 mole). Crystallisation of the crude product (9 g.) from ethanol (30 ml.) gave two successive crops (total, 6·55 g., 72%) of the *substituted hydrazine* as felted needles, m. p. 129—131° (from ethanol) (Found: C, 42·3; H, 3·7; Br, 34·1; N, 11·8. $C_{16}H_{16}Br_2N_4O_2$ requires C, 42·1; H, 3·5; Br, 35·1; N, 12·3%).

The filtrates therefrom deposited a more soluble fraction (1·5 g.), which consisted, after crystallisation from acetone–ethanol (4 : 1), of platelets of 3-p-*bromoanilino*-4-p-*bromophenyl*-5-*ethoxy*-1,2,4-*triazole*, m. p. 210—211° (1·05 g., 12%) (Found: C, 43·8; H, 2·9; Br, 36·6. $C_{16}H_{14}Br_2N_4O$ requires C, 43·85; H, 3·2; Br, 36·5%).

A solution of the foregoing substituted hydrazine (0·91 g., 0·002 mole) in ethanol (4 ml.)–3N-sodium hydroxide (8 ml.) was refluxed for 30 min. The liquid was diluted with ice (10 g.) and acidified (to pH 2). The precipitate gave, after crystallisation from ethanol (40 ml. per g.), microprisms (0·62 g., 75%) of 3-p-*bromoanilino*-4-p-*bromophenyl*-5-*hydroxy*-1,2,4-*triazole*, m. p. 238—240° (Found: C, 40·6; H, 2·0; N, 14·0. $C_{14}H_{10}Br_2N_4O$ requires C, 41·0; H, 2·4; N, 13·7%).

4-*Cyclohexyl*-3-*cyclohexylamino*-5-*hydroxy*-1,2,4-*triazole*.—Ethoxycarbonylhydrazine (3·12 g., 0·03 mole) and dicyclo-

[17] E. Hoggarth, *J. Chem. Soc.*, 1949, 1160, 1163.

hexylcarbodi-imide (4·12 g., 0·02 mole) in dimethylformamide (18 ml.) were kept at 100° for 8 hr. The solution was diluted with ethanol (20 ml.), treated with concentrated hydrochloric acid (10 ml.), and the clear yellow liquid refluxed for 30 min. It was stirred into water, and the solidified white gum broken up, collected at 0°, washed with water, and air-dried (4·5 g.). Crystallisation from chloroform (10 ml. per g., recovery 90%) (undissolved residue R) gave white platelets (2·95 g., 56%) of the *substituted triazole*, m. p. 247—249° (Found: C, 63·6; H, 9·2; N, 21·2. $C_{14}H_{24}N_4O$ requires C, 63·6; H, 9·1; N, 21·2%).

The residue R consisted, after crystallisation from ethanol, of flat prisms (0·54 g., 8%) of *s*-di(cyclohexyl)urea, m. p. 226—228° (Found: C, 69·9; H, 10·7. Calc. for $C_{13}H_{24}N_2O$: C, 69·6; H, 10·7%) (lit.,[18] 229—230°).

When equimolar proportions of the reactants were used the yield of triazole was 30% and that of recovered *s*-di(cyclohexyl)urea 25%.

Addition of Isothiocyanates

S-*Methyl* 1-*Ethoxycarbonyl*-4-*phenyl*-3-*isothiosemicarbazide*.—(a) *Preparation*. A solution of 1-ethoxycarbonyl-4-phenyl-3-thiosemicarbazide[14,15] (4·80 g., 0·02 mole) in methanol (50 ml.)–methyl iodide (20 ml.) was refluxed for 20 min., reduced to one-third of its volume in a vacuum, and diluted with water (120 ml.). Basification with 3N-ammonia gave a white precipitate which was collected at 0° and crystallised from methanol (10 ml. per g.), affording needles of the S-*methyl compound*, m. p. 143—144° (3·8—4·05 g., 75—80%) (Found: C, 52·8; H, 6·2; N, 16·6; S, 12·4. $C_{11}H_{15}N_3O_2S$ requires C, 52·2; H, 5·9; N, 16·6; S, 12·65%).

(b) *Action of mineral acid*. A solution of the reactant (1·25 g., 0·005 mole) in methanol (8 ml.) was treated with concentrated hydrochloric acid (3 ml.) and refluxed for 1 hr. (distinct odour of methanethiol). The cooled liquid was basified (to pH 8—9) with 3N-sodium hydroxide, and the white solid collected at 0°. Two crystallisations from ethanol gave needles (0·62 g., 60%) of 3-hydroxy-5-methylthio-4-phenyl-1,2,4-triazole, m. p. 206—208° (Found: C, 52·4; H, 4·7; N, 20·8; S, 15·9. Calc. for $C_9H_9N_3OS$: C, 52·2; H, 4·35; N, 20·3; S, 15·5%) (lit.,[19] 207—208°).

(c) *Action of alkali*. A solution of the reactant (0·005 mole) in ethanol (8 ml.)–3N-sodium hydroxide (12 ml.) was refluxed for 30 min. (slight odour of methanethiol), and the colourless liquid diluted with ice (20 g.) and acidified (to pH 4—6) with 3N-hydrochloric acid. The precipitate was 3-hydroxy-5-methylthio-4-phenyl-1,2,4-triazole, m. p. 206—208° (from ethanol) (0·88 g., 85%) (Found: C, 52·2; H, 5·0; N, 20·2%).

(d) *Pyrolysis*. The reactant (0·005 mole) was kept at 215° (metal-bath) for 20 min., effervescence occurring initially (distinct odour of methanethiol). The solidified melt gave, on crystallisation from ethanol, needles (56%) of 3-hydroxy-5-methylthio-4-phenyl-1,2,4-triazole, m. p. and mixed m. p. [with (c)] 206—208°. After pyrolysis at 200° for 3 min., the starting material was substantially recovered (70%).

(e) *Action of hydrazine*. A solution of the reactant (0·005 mole) in ethanol (15 ml.)–hydrazine hydrate (2·5 ml.) was refluxed for 1 hr. (odour of methanethiol), then set aside at 0° for 24 hr. The separated crystals (0·78 g., 75%) were 3-hydroxy-5-methylthio-4-phenyl-1,2,4-triazole, m. p. and mixed m. p. [with (c)] 206—208° (from ethanol). Substantially the same result was obtained after prolonged stirring of the reaction mixture at room temperature.

(f) *Action of aniline*. A solution of the reactant (0·005 mole) in aniline (10 ml.) was refluxed for 2 hr., and the aniline removed by steam-distillation; the result was the same as in (e) (yield, 72%).

(g) *Action of acetic anhydride*. A solution of the reactant (0·005 mole) in acetic anhydride (8 ml.) was kept at 100° for 1 hr., stirred into water (30 ml.), and the liquid neutralised (to pH 8) with 3N-sodium hydroxide. The solidified precipitate gave, on crystallisation from ethanol (5 ml.), microprisms (0·74 g., 50%) of solvated 3-*acetoxy*-5-*methylthio*-4-*phenyl*-1,2,4-*triazole*, m. p. 115—117° (Found: C, 52·6; H, 5·9; N, 14·5; S, 11·5. $C_{11}H_{11}N_3O_2S,C_2H_5OH$ requires C, 52·9; H, 5·8; N, 14·2; S, 10·85%).

S-*Benzyl* 1-*Ethoxycarbonyl*-4-*phenyl*-3-*isothiosemicarbazide*.—(a) *Preparation*. A solution of 1-ethoxycarbonyl-4-phenyl-3-thiosemicarbazide[14,15] (2·4 g., 0·01 mole) in hot ethanol (20 ml.) was treated successively with benzyl chloride (1·4 g., 0·011 mole) and 3N-sodium hydroxide (3·3 ml., 0·01 mole). The solution, which began to deposit sodium chloride almost immediately, was set aside at room temperature for 3 hr., then stirred into ice–water. The precipitated oil solidified on storage at 0°, and gave, on crystallisation from chloroform–light petroleum (b. p. 40—60°) (2 and 3 ml. per g.), prismatic needles (total, 2·65 g., 80%) of the S-*benzyl-compound*, m. p. 97—100° (Found: C, 62·8; H, 5·3; N, 13·5; S, 10·0. $C_{17}H_{19}N_3O_2S$ requires C, 62·0; H, 5·8; N, 12·8; S, 9·7%).

In some experiments, under precisely identical conditions, the *S*-benzylation was accompanied by ring-closure to 3-benzylthio-5-hydroxy-4-phenyl-1,2,4-triazole [identified by mixed m. p. and ultraviolet spectrum; see (b) below]. This formed the main yield (up to 50%) on crystallisation from chloroform–light petroleum in the usual way, but isolation of the low-melting open-chain *S*-benzyl compound from the filtrates was difficult in such cases.

(b) *Action of alkali*. Alkaline treatment of the *S*-benzylthiol (1·65 g., 0·005 mole) [as described for the methyl analogue in procedure (c) above] gave a white solid on final acidification. Crystallisation from ethanol (20 ml.) afforded needles (1·05 g., 75%) of 3-benzylthio-5-hydroxy-4-phenyl-1,2,4-triazole, m. p. 159—160° (lit.,[16] 158°) (Found: C, 63·35; H, 4·85. Calc. for $C_{15}H_{13}N_3OS$: C, 63·6; H, 4·6%). It had an ultraviolet absorption curve of negative slope (λ 220, 240, 260 mμ; log ε 4·21, 3·76, 3·54).

Addition of Aroyl Isothiocyanates

Aroyl isothiocyanates were prepared by a modified procedure due to Elmore and Ogle.[20] Strict exclusion of moisture throughout is essential. To a stirred refluxing solution of potassium thiocyanate (dried at 80°) (10·7 g., 0·11 mole) in anhydrous acetone (120 ml.), the aroyl chloride (0·1 mole) was added dropwise during 10 min. The resulting yellow suspension was refluxed and stirred for 1 hr., allowed to cool to room temperature, and the precipitated potassium chloride removed by filtration under reduced pressure. The filtrate was treated with benzene (azeotropically dried; 150 ml.), set aside for several hours, and further separated solid filtered off. The filtrate was distilled to approximately one-quarter bulk (reduced pressure; temperature below 50°), stored at 0° for 12 hr., and more yellow solid filtered off at room temperature

[18] A. Skita and H. Rolfes, *Ber.*, 1920, **53**, 1242, 1248.
[19] F. Arndt, E. Milde, and F. Tschenscher, *Ber.*, 1922, **55**, 351.
[20] D. T. Elmore and J. R. Ogle, *J. Chem. Soc.*, 1958, 1141.

and rinsed with very little anhydrous benzene (solid S). Vacuum-distillation of the orange-to-red oil remaining after the removal of the solvent (using a wide receiver adapter to prevent blocking due to solidifying product) gave the products as follows: benzoyl isothiocyanate, b. p. 95—100°/2—3 mm. (7·3—9·0 g., 45—55%) (lit., b. p. 58—62°/0·03 mm.;[20] 119°/10 mm.;[21] *p*-chlorobenzoyl isothiocyanate, b. p. 115—118°/1·5 mm., m. p. 46—48° (13·8 g., 70%) (lit., b. p. 130—133°/2 mm., m. p. 48°[17]) (see also ref. 22); *p*-methoxybenzoyl isothiocyanate, b. p. 148—152°/1 mm. (13·1—14·5 g., 68—75%) (lit., b. p. 116—118°/0·3 mm.;[17] 169—170°/10 mm.[23]).

Solid S (0·4—0·6 g., obtained in the preparation of the benzoyl compound) was washed with water and crystallised from methanol, affording pale yellow needles of polymeric thiocyanic acid (no decomp. to 350°) [Found: C, 20·4; H, 1·9; N, 23·0; S, 53·0. Calc. for $(HCNS)_x$: C, 20·3; H, 1·7; N, 23·7; S, 54·2%].

4-Benzoyl-1-ethoxycarbonyl-3-thiosemicarbazide.—(a) *Preparation*. A solution of ethoxycarbonylhydrazine (5·2 g., 0·05 mole) in dimethylformamide (45 ml.) was slowly treated with benzoyl isothiocyanate (9·0 g., 0·055 mole) (exothermic reaction). The golden-yellow liquid was kept at 100° for 1 hr. (slight odour of hydrogen sulphide), then stirred into ice–water (350 ml.). The resulting granular solid was collected at 0°, washed with water, and crystallised from ethanol (4—5 ml. per g.), giving large prisms (10·0—11·35 g., 75—85%) of the *product*, m. p. 150—151° (Found: C, 49·3; H, 4·7; N, 15·2; S, 11·1. $C_{11}H_{13}N_3O_3S$ requires C, 49·4; H, 4·9; N, 15·7; S, 12·0%).

(b) *Action of alkali*. A solution of the reactant (1·35 g., 0·005 mole) in 3N-sodium hydroxide (16·6 ml.) was refluxed for 20 min., the yellow liquid turning colourless. It was acidified with 3N-hydrochloric acid at 0° (to pH 2—3) (evolution of carbon dioxide). The precipitate (m. p. 256—258°; 0·80 g., 90%) was 3-mercapto-5-phenyl-1,2,4-triazole, m. p. 258—260° (prisms from ethanol) (lit.,[17] 256°) (Found: C, 54·2; H, 4·3; N, 23·6; S, 17·8. Calc. for $C_8H_7N_3S$: C, 54·2; H, 3·95; N, 23·7; S, 18·1%).

S-Benzyl 4-Benzoyl-1-ethoxycarbonyl-3-isothiosemicarbazide.—(a) *Preparation*. A solution of 4-benzoyl-1-ethoxycarbonyl-3-thiosemicarbazide (2·65 g., 0·01 mole) in warm ethanol (20 ml.) was treated successively with benzyl chloride (1·4 g., 0·011 mole) and 3N-sodium hydroxide (3·3 ml., 0·01 mole). The crystallising mixture was set aside at room temperature, then at 0°, and the solid collected, and washed with water. Crystallisation from acetone (10 ml. per g.) gave lustrous prisms (3·0—3·3 g., 85—92%) of the *S-benzyl compound*, m. p. 144—145° (Found: C, 60·25; H, 5·2; N, 12·4; S, 9·4. $C_{18}H_{19}N_3O_3S$ requires C, 60·5; H, 5·3; N, 11·8; S, 9·0%).

(b) *Action of alkali*. *S*-Benzyl 4-benzoyl-1-ethoxycarbonyl-3-isothiosemicarbazide (1·78 g., 0·005 mole) dissolved on being boiled in 2N-sodium hydroxide (20 ml.). The colourless (temporarily deep yellow) liquid was refluxed for 30 min., acidified with 3N-hydrochloric acid (evolution of carbon dioxide), and the precipitate (m. p. 80—85°; 1·20 g., 90%) crystallised from chloroform–light petroleum (b. p. 40—60°), giving platelets of 3-benzylthio-5-phenyl-1,2,4-triazole, m. p. 82—84° or 98—100° (Found: C, 66·6; H, 5·0; N, 16·2; S, 12·0. Calc. for $C_{15}H_{13}N_3S$: C, 67·4; H, 4·9; N, 15·7; S, 12·0%). The identity of the lower and higher melting forms was confirmed by the identity of their ultraviolet and infrared spectra with each other and those of authentic material (see below), and by their conversion (80%) into the 4-acetyl derivative, m. p. and mixed m. p. (see below) 143—145°.

(c) *Action of hydrochloric acid*. A solution of the reactant (0·005 mole) in ethanol (20 ml.)–concentrated hydrochloric acid (5 ml.)–water (4 ml.) was refluxed for 8 hr., distilled to half bulk, and diluted with water (10 ml.). The resulting crystals (0·95 g., 70%) were collected at 0°, and consisted, after crystallisation from chloroform–light petroleum, of 3-benzylthio-5-phenyl-1,2,4-triazole, m. p. and mixed m. p. [with (b)] 82—84°. After refluxing for 1·5 hr. the yield of triazole was reduced to 30%, part of the reactant (30%) being recoverable as a less soluble fraction.

3-Benzylthio-5-phenyl-1,2,4-triazole.—A hot solution of 3-mercapto-5-phenyl-1,2,4-triazole[17] (3·55 g., 0·02 mole) in ethanol (50 ml.)–benzyl chloride (3·2 g., 0·025 mole) was treated with 3N-sodium hydroxide (6·7 ml., 0·02 mole), and kept on a steam-bath for 30 min. Addition to ice–water gave an oily precipitate, which solidified on storage at 0° and stirring. Crystallisation from chloroform–light petroleum (4 ml. each, per g.) gave the white granular *product*, m. p. 98—100° (4·35 g., 82%) (Found: C, 67·4; H, 4·6; N, 16·1; S, 11·8. $C_{15}H_{13}N_3S$ requires C, 67·4; H, 4·9; N, 15·7; S, 12·0%). Ultraviolet spectrum: curve of negative slope (λ 220, 250, 280 mμ; log ε 4·30; 4·10; 3·65). Infrared spectrum: $\nu_{max.}$ (KBr) 690, 730, 780, 980, 1135, 1230, 1330, 1425, 1460, 1540, 2700—3100 (multiple) cm.$^{-1}$.

The antibacterial activity of the compound has been mentioned, but no chemical data were given.[24] The assignment by Fromm *et al.*[25] of the above structure to Young and Eyre's[26] 2-amino-5-phenyl-1,3,4-thiadiazole, m. p. 160°, is incorrect.

4-Acetyl-3-benzylthio-5-phenyl-1,2,4-triazole.—A solution of the foregoing triazole (1·35 g., 0·005 mole) in acetic anhydride (12 ml.) was boiled for 30 min., and the colourless solution stirred into water (120 ml.). The solidified precipitate gave, on crystallisation from ethanol (60 ml. per g.), massive prismatic needles (1·25 g., 80%) of the *acetyl derivative*, m. p. 143—145° (Found: C, 66·5; H, 5·0; N, 13·0; S, 10·3. $C_{17}H_{15}N_3OS$ requires C, 66·0; H, 4·85; N, 13·6; S, 10·4%).

1-Ethoxycarbonyl-3-methylthio-5-phenyl-1,2,4-triazole.—(a) *Preparation*. 4-Benzoyl-1-ethoxycarbonyl-3-thiosemicarbazide (2·67 g., 0·01 mole) was dissolved in methanol (20 ml.) with slight warming, and successively treated with methyl iodide (5 ml.) and (dropwise) 3N-sodium hydroxide (3·7 ml., 0·011 mole). The liquid was set aside at room temperature for 12 hr. (slight odour of methanethiol), then diluted dropwise with water (4—5 ml., just short of turbidity). After further 24—36 hr. storage at room temperature, the large needles (m. p. 115—120°; 2·4 g., 88%) were collected and rinsed with very little methanol. Crystallisation from methanol (15 ml. per g., recovery 70%) gave needles of the *product*, m. p. 110—112° (Found: C, 54·3; 54·5; H, 4·6, 4·9; N, 16·35; S, 12·3. $C_{12}H_{13}N_3O_2S$ requires C, 54·75; H, 4·9; N, 16·0; S, 12·2%).

(b) *Action of alkali*. A solution of the foregoing substituted triazole (1·32 g., 0·005 mole) in 3N-sodium hydroxide

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(12 ml.)–ethanol (2 ml.) was refluxed for 15 min., cooled, and acidified with 3N-hydrochloric acid (evolution of carbon dioxide). The resulting precipitate (m. p. 162—164°; 0·88 g., 92%) gave, on crystallisation from ethanol, needles of 3-methylthio-5-phenyl-1,2,4-triazole, m. p. and mixed m. p.[17] 162—164° (Found: C, 57·0; H, 4·9; N, 21·0; S, 16·0. Calc. for $C_9H_9N_3S$: C, 56·5; H, 4·7; N, 22·0; S, 16·75%).

4-p-*Chlorobenzoyl*-1-*ethoxycarbonyl*-3-*thiosemicarbazide*.—This was prepared from *p*-chlorobenzoyl isothiocyanate (10·85 g., 0·055 mole) as described for the benzoyl analogue (see above). The *substituted thiosemicarbazide* formed needles, m. p. 150—152° (from ethanol; 5 ml. per g.) (total, 11·3 g., 75%) (Found: C, 43·3; H, 4·1. $C_{11}H_{12}ClN_3O_3S$ requires C, 43·8; H, 4·0%).

Treatment of the foregoing compound (3·02 g., 0·01 mole) in warm ethanol (45 ml.)–benzyl chloride (1·52 g., 0·012 mole) with 3N-sodium hydroxide (3·3 ml., 0·01 mole) in four equal portions at ½ hr. intervals, storage at room temperature for 12 hr., and addition to water gave a white gum that solidified gradually. Crystallisation from chloroform–light petroleum (b. p. 40—60°) gave prisms (3·3 g., 84%) of the S-*benzyl compound*, m. p. 122—124° (Found: C, 54·8; H, 4·6; N, 9·9. $C_{18}H_{18}ClN_3O_3S$ requires C, 55·2; H, 4·6; N, 10·7%).

Addition of the alkali in *one* portion precipitated the hydrated *sodium salt* of the reactant [m. p. 220—225° (decomp.); 2·05 g., 60%] (filtrate F) forming microprisms, m. p. 216—218° (from ethanol) (Found: C, 38·65; H, 3·7; N, 12·6; S, 9·1. $C_{11}H_{11}ClN_3O_3SNa,H_2O$ requires C, 38·7; H, 3·8; N, 12·3; S, 9·4%). Filtrate F gave the above *S*-benzyl compound in 24% yield.

3-*Chlorophenyl*-5-*mercapto*-1,2,4-*triazole*.—A solution of 4-*p*-chlorobenzoyl-1-ethoxycarbonyl-3-thiosemicarbazide (1·5 g., 0·005 mole) in 3N-aqueous sodium hydroxide (30 ml.) was refluxed for 30 min., then acidified. The precipitate was crystallised from 85% ethanol (12 ml. per g.), giving crystalline granules of the substituted 1,2,4-triazole, m. p. 289—291° (0·85 g., 80%) (Found: C, 45·2; H, 3·0. Calc. for $C_8H_6ClN_3S$: C, 45·4; H, 2·8%) (lit.,[17] 296—297°).

1-*Ethoxycarbonyl*-4-p-*methoxybenzoyl*-3-*thiosemicarbazide*.—This was prepared from *p*-methoxybenzoyl isothiocyanate (10·6 g., 0·055 mole) as described for the benzoyl analogue (see above). The *substituted thiosemicarbazide* formed massive prisms, m. p. 164—166° (from ethanol; 20 ml. per g.) (total, 12·6 g., 85%) (Found: C, 48·45; H, 5·0. $C_{12}H_{15}N_3O_4S$ requires C, 48·5; H, 5·05%).

The foregoing compound (1·5 g., 0·005 mole), suspended in nearly boiling ethanol (35 ml.), dissolved on addition of 3N-sodium hydroxide (1·7 ml., 0·005 mole). It was treated with benzyl chloride (0·76 g., 0·006 mole), set aside for 24 hr., distilled to one-third bulk, and stirred into ice–water. The solidified oil gave, on crystallisation from ethanol (5 ml. per g.), prisms of the S-*benzyl compound*, m. p. 115—117° (1·55 g., 80%) (Found: C, 58·2; H, 5·35; S, 8·2. $C_{19}H_{21}N_3O_4S$ requires C, 58·9; H, 5·4; S, 8·3%).

3-*Mercapto*-5-p-*methoxyphenyl*-1,2,4-*triazole*.—Alkaline treatment of 1-ethoxycarbonyl-4-*p*-methoxybenzoyl-3-thiosemicarbazide (usual procedure, see above) gave the substituted 1,2,4-triazole, m. p. 252—254° (from ethanol; 30 ml. per g.) (70%) (Found: C, 51·8; H, 4·5; N, 16·6; S, 12·95. Calc. for $C_9H_9N_3OS,C_2H_5OH$: C, 52·2; H, 5·9; N, 16·6; S, 12·65%) (lit.,[17] 257°).

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