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CHEMISTRY OF AMIDRAZONES—IV

ADDITION–CYCLISATION OF AMIDRAZONES WITH ISOCYANATE ESTERS AND ETHOXYCARBONYL ISOTHIOCYANATE

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Abstract—The interaction of amidrazones and isocyanate esters in dimethylformamide produces good yields of 4-substituted 1-imidoylsemicarbazides. They are unaffected by acids, but are cyclised to 3-alkyl (or aryl)-1,2,4-triazol-3-ones or their 4-substituted analogues in alkaline media. Analogous linear adducts arising in good yields from amidrazones and ethoxycarbonyl isothiocyanates are cyclised to 3-substituted 5-ethoxycarbonamido-1,3,4-thiadiazoles by acids, but are cleaved into small fragments by alkalis.

We conclude our account of addition-cyclisations of amidrazones and heterocumulenes[1] by describing examples involving esters derived from iso(thio)cyanic acid. Originally undertaken to provide data for comparison with our earlier studies of analogous systems, particularly aminoguanidine,[2,3] diaminoguanidine,[3-6] and (thio)carbonohydrazides,[7] the work supplements[8-10] and corrects[9] previous results in this field.

Addition-cyclisation involving isocyanates

The interaction of equimolar quantities of amidrazone salts and isocyanate esters in dimethylformamide, generally at room temperature, gave stable 1 : 1-adducts in very good yield. Their formulation as linear 4-substituted 1-imidoylsemicarbazides **1** is in accord with their mode of formation, involving the nucleophilic attack by the terminal nitrogen of the hydrazino-group on the electron-deficient carbon atom of the isocyanate. It agrees with their properties, particularly their mode of cyclisation. The predominantly basic structure of the adducts **1** accounts for their power of forming stable hydrochlorides and picrates. Their resistance to the action of acids is also ascribed to stabilisation by salt formation.

N^3-Carbamoylamidrazones (e.g. **4**) are isomers of the imidoylsemicarbazides **1** now described, bearing the carbamoyl residue on the imino- instead of the hydrazino-group. Their synthesis[11] and thermal cyclisation[12] have been the subject of recent studies that complement the present work.

The IR spectra of the imidoylsemicarbazides are consistent with their proposed structure (**1**). Intense bands in the region of 3440–3480, 3320–3370 and 3100–3170 cm^{-1} are attributed to the NH-groups, and the strong peak at 1680–1690 cm^{-1} to the carbonyl function. Very intense bands in the region 1640–1665 and 1540–1570 cm^{-1}, indicative of C–N–H vibration,[13,14] are regarded as combination bands due to NH-deformation and C–N stretching vibration,[13-16] and weaker bands appearing at 3100 cm^{-1} may be overtones resulting from the latter. Aromatic and methylene groups give rise to the expected well known absorption characteristics. Amongst the unassigned peaks, moderate to strong bands at *ca.* 1450 and 1320 cm^{-1} appearing in all examples may be of diagnostic value.

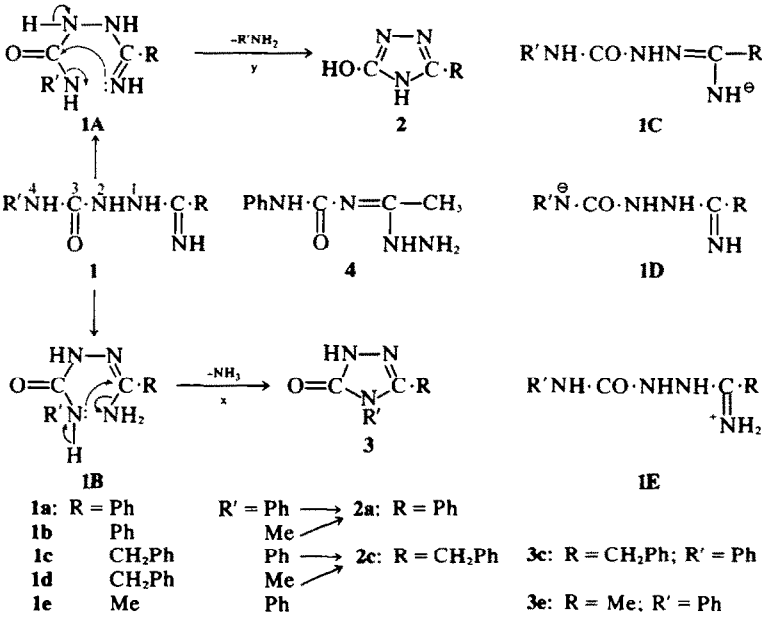
The imidoylsemicarbazides **1** were cyclised by alkalis to 5 - alkyl(or aryl) - 1,2,4 - triazol - 3 - ones **2** or their 4-substituted analogues **3**, with elimination of amine or ammonia, respectively; although reaction did not proceed rapidly, the yields were good. The preferred direction of the cyclisation (path x or y), involving the usual intramolecular nucleophilic mechanism (see previous paper[1]), may here be correlated with the production of the most stable anion in the strongly alkaline medium.

Assuming the imino-nitrogen in **1** to be more nucleophilic than the amido-nitrogen, N-4, and the electron-density at the carbonyl-carbon C-3 to be lower than that at the imidoyl-carbon, the elimination of amine (i.e. path y) should be favoured, with the possible transient production of the anion **1C**. This expected pathway is in fact followed exclusively when substituted 4-methylsemicarbazides **1b**, **1d** are employed (giving **2a**, **2c** in 72 and 56% yield, respectively).

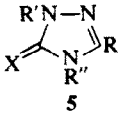
In examples derived from 4-phenylsemicarbazide **1a**, **1c**, **1e** the anion **1D**, being resonance stabilised, is thought to be formed preferentially (see Part III, preceding paper[1]). The amido-nitrogen, in **1D**, is consequently the more effective nucleophilic centre, and the reaction should take path x. Accordingly, 1 - acetimidoyl - 4 - phenylsemicarbazide **1e** is cyclised entirely to **3e** (80%). However, when the substituent R is bulky, steric hindrance inhibits the necessary mutual approach of the groups, accounting for the anomalous cyclisation of the 1-benzimidoyl-compound (**1a**→**2a**; 60%), as well as the "mixed" cyclisation of the 1-phenylacetimidoyl-compound **1c** to **2c** and **3c** (in 30 and 45% yield, respectively).

Under electron impact, the imidoylsemicarbazides **1** appear to be cyclised to **2** in the same manner. Thus, the mass spectra of **1a**, **1c**, and **1d** included peaks of their molecular ion, but displayed more prominent signals corresponding to the loss of the elements of amine ($R'NH_2$). In addition, weak peaks at (M-17) mass units indicated ring closure with elimination of ammonia on a limited scale. The appearance of additional recurring peaks (attributable to $R.C(:NH)NHNH_2$ and smaller fragments, see Experimental) is consistent with a scission of the linear adduct **1**, either directly or after cyclisation.

The prolonged interaction of amidrazone hydrochlorides and iso(thio)cyanates at 200–250° has been reported to afford substituted triazol-3-ones (or thiones) **5** directly in one stage.[8] The invariable loss of ammonia under these conditions is explicable in terms of the



intermediate function of the protonated species **1E**, in which the prevailing nucleophilicity is associated with the amido-nitrogen (N-4). However, the only example derived from an unsubstituted amidrazone, represented as **5** (R = Me, R' = H, R'' = Ph, X = O), lacked the keto-peak in its IR spectrum, failed to yield a picrate,[8] and differs from the material now obtained. The true course of the thermal condensation involving unsubstituted amidrazones thus remains open to doubt.



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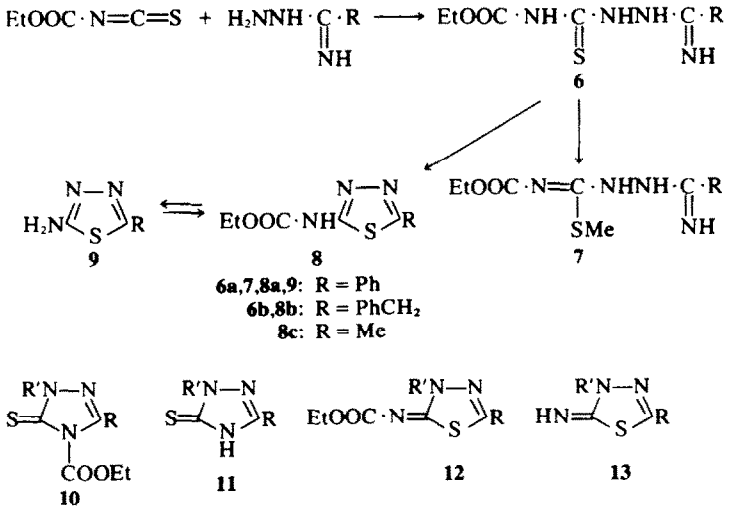
Addition-cyclisations involving ethoxycarbonyl isothiocyanate

In ethoxycarbonyl isothiocyanate,[17] one of the most versatile heterocumulenes,[18] the reactivity of the isothiocyanate function towards nucleophiles is enhanced by the adjacent electron-attracting ethoxycarbonyl group. The interaction of this isothiocyanate with amidrazones in dimethylformamide, in the presence of an equivalent of triethylamine at room temperature gave 1:1 adducts, which are formulated, in agreement with established precedents,[1] as 1-imidoyl-4-ethoxycarbonyl-3-thiosemicarbazides **6**. They were alkali-soluble crystalline solids, and were further characterised, in one example, as the S-methyl thioether **7**. Their structural features (NH, CO, C=N, C–N–H, ester C–O–C, aryl) give rise to familiar absorption bands in their IR spectra. Bands of medium intensity near 1070 cm^{-1} may be assigned to C–O–C symmetrical vibration, or in accordance with previous reasoning,[19] to N–C–S stretching vibration. The medium peak below 835 cm^{-1} that has been associated with C=S vibration in 1-thioaroylamidrazones[19] is not found, but an intense broad absorption appearing at 1250–1260 cm^{-1} (absent in the spectra of the S-methyl ether **7**, and the cyclisation products, **8**) may be a combination band, to which the CS-group makes a significant contribution.[3,20,21]

Compounds incorporating the structural pattern

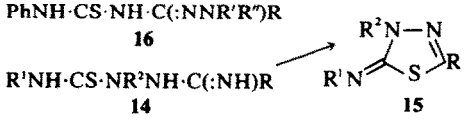


Y.NH.CS.NHNH.C(:NH).Z, of which the present adducts **6** are examples, are normally (though not always) cyclised to 2-amino-1,3,4-thiadiazoles in acidic media, and to 3 - mercapto - 1,2,4 - triazoles in alkaline media.[22,23] In agreement with this general rule, mineral acid converted the substituted thiosemicarbazides **6** into 5-substituted 2 - ethoxycarbonamido - 1,3,4 - thiadiazoles **8** with loss of ammonia. The assigned structure **8** was confirmed by the identity of the 5-phenyl-compound **8a** with material[24] obtained by carbethoxylation of authentic 2 - amino - 5 - phenyl - 1,3,4 - thiadiazole **9**.[25]

In contrast, the adducts **6** failed to yield the isomeric triazoles **10**, **11** (R′ = H) under the influence of alkalis, being merely cleaved hydrolytically into small fragments: from **6a**, benzamide was the only isolable product (70%). It is therefore noteworthy that Bany and Dobosz[9] have reported the production of substituted 1,2,4-triazoline-5-thiones **10** and **11** by the condensation of ethoxy carbonyl isothiocyanate and amidrazone hydrochlorides (10–20 h at 50–110°).

A repetition of their experiments using unsubstituted amidrazones showed (as had seemed likely from the reported[9] physical constants) that the products are in fact identical with the present 1,3,4-thiadiazoles of proved structure. The compounds represented[9] as **10** and **11** (R′ = H, R = Ph, Me) are therefore to be re-formulated as **8** and **9** (R = Ph, Me), and subsequent work[26] based on their use may require re-interpretation. In contrast, the representation[9] as triazoles (**10**, **11**; R = Ph; R′ = Ph, Me) of the examples derived from *substituted* amidrazones appears to be correct: the decarboxylated products **11**, obtainable from **10** by acid hydrolysis, agree in their physical properties with those repeatedly given in the literature for triazoles **11** but differ from those of the isomeric thiadiazoles **13** (see Table 1). The divergent course of this reaction emphasises the uncertainties and need for caution in formulating products arising in cyclisations of this kind, as the isomeric 1,3,4-thiadiazole- or 1,2,4-triazole derivatives (e.g. 2 - amino - 5 - phenyl - 1,3,4 - thiadiazole and 3 - mercapto - 5 - phenyl - 1,2,4 - triazole;[27–29] 2 - hydrazino - 1,3,4 - thiadiazoles and 4 - amino - 3 - mercapto - 1,2,4 - triazoles[30]).

The synthesis of adducts **14** of amidrazones and isothiocyanate esters, their cyclisation to **15**, [10] as well as the direct condensation of the components to substituted triazole-3-thiones (**5**; X = S)[8] have been reported previously. N^3-Thiocarbamoylamidrazones **16** isomeric with **14** are accessible from N^1N^1-disubstituted amidrazones, but do not cyclise readily.[39] The applicability of the present more convenient experimental procedure (using amidrazone salts instead of the free bases) was confirmed by the preparation of two representative examples **14a**, **b**, and their near-quantitative acidic cyclisation to the expected 1,3,4-thiadiazoles **15a**, **b**. The remarkable susceptibility to cyclisation of **14** is reflected in their mass spectra: peaks corresponding to the molecular ion $M^{\cdot+}$ were entirely absent, but prominent peaks indicated the production of particles of molecular weight (M-17). Of the two high-intensity IR absorption maxima of the oxygen analogues **1** at 1680–1695 and 1640–1665 cm^{-1}, only the latter appears in the spectra of **14a**, **b**, thus supporting the assignment in **1** of the former peak to the CO–, and that of the latter to the C=N– grouping. A prominent broad band at 1240–1260 cm^{-1} may be associated with the thiocarbamoyl moiety of **14**.



a: R = Ph, R′ = Me, R² = H
b: R = Ph, R′ = Ph, R² = H

The group of reactions described in this and the foregoing papers[1,19] widens the range of the general synthesis of 1,3,4-thiadiazoles and 1,2,4-triazoles by direct cyclisation of suitable linear precursors, and provides material for instructive comparisons with analogous addition-cyclisations of related bases incorporating the amidinohydrazino-moiety (e.g. (thio)semicarbazides, amino-[2,3] and diaminoguanidines[3–6]). There is scope for varying the course of the reactions by employing variously substituted amidrazones, especially those having their hydrazino-group temporarily blocked by hydrazone formation, thus directing the addition of the heterocumulenes to their imino-group (see Ref. 2).

EXPERIMENTAL

General. M.ps. are uncorrected. The IR spectra were measured on a Unicam SP 200 instrument, using KBr discs. Mass spectra were obtained using an AEI MS-902 instrument, operating at 70 eV. The letters w, m and i refer to weak, medium and intense peaks in the mass spectra.

Addition-cyclisation reactions with isocyanate esters

1-*Benzimidoyl*-4-*phenylsemicarbazide* **1a**

(a) *Preparation.* A stirred solution of benzamidrazone hydriodide[40] (2.89 g, 0.011 mole) in dimethylformamide (15 ml) was treated at room temp. during 1–2 min with phenyl isocyanate (1.2 g, 0.01 mole). After 2 h storage at room temp., the colourless liquid was added to water (60 ml), and any small white precipitate filtered off (solid: S). Basification with concentrated NH_4OH (d, 0.88) gave a white precipitate (m.p. 315–318° decomp, 2.15–2.3 g, 85–90%), which afforded **1a** as microneedles, m.p. 325–327° (decomp, after shrinking at 180–185°) (from EtOH, 40 ml per g, recovery 75%) (Found: C, 66.0; H, 6.0; N, 22.6. $C_{14}H_{14}N_4O$ requires: C, 66.1; H, 5.5; N, 22.05%). IR: 3440s, 3340s, 3170, 3140s (doublet) (NH); 3050m (CH arom.); 1660, 1640s (doublet) (C=N); 1615–1600s br (CO); 1565, 1555, 1540s (triplet) (NH/CN); 1505m, 780m, 690s (Ph); 1685m, 1445m, 1405m, 1315m, 1240m, 1135m and

Table 1. 1-Substituted 3-phenyl-1,2,4-triazole-5-thiones **11** and the isomeric 1,3,4-thiadiazoles **13**

11; R = Ph, R′ = Me		**13**; R = Ph, R′ = Me		**11**; R = R′ = Ph		**13**; R = R′ = Ph	
M.p.°C	Ref.	M.p.°C	Ref.	M.p.°C	Ref.	M.p.°C	Ref.
261–262	9	Oil	27	246–247	9	97	38
265–267	31			248–249	35		
261–264	32			248	36		
264–267	33			253	37		
275–277	34			255–257	34		

745m cm^{-1}. Mass spectrum: *m/e* 254(m, M$^{\cdot+}$), 237 (m, M$^{\cdot+}$–NH$_3$); 161(i, M$^{\cdot+}$–PhNH$_2$); 135(m, ?PhC(:NH)NHNH$_2^{\cdot+}$); 118(i, ?PhC(:NH)N$^{\cdot+}$).

Solid S (*ca.* 0.2 g, 15%) was 1,6-diphenylbiurea, identified by comparison with authentic material[41] by mixed m.p. (252–254°) and IR spectrum (IR: 3300s, 3220s, 3120s (doublet) (NH); 1660s br (CO); 750s, 695s (Ph); 2930m, 1595s, 1545s br, 1445s, 1335m, 1235m cm^{-1}. The product, obtained only occasionally, arose probably from hydrazine retained as an impurity in the amidrazone employed.

The picrate, obtained (70%) from the components in EtOH, formed silky needles, m.p. 188–189° (decomp) (Found: C, 49.5; H, 4.0; N, 19.5. $C_{14}H_{14}N_4O \cdot C_6H_3N_3O_7$ requires: C, 49.7; H, 3.5; N, 20.3%).

(b) *Stability to acid.* A solution of **1a** (1.27 g, 0.005 mole) in 1.5 N HCl (30 ml), boiled under reflux for 2 h, then set aside at 0°, deposited **1a**, as the hydrochloride (72%), forming opaque lustrous platelets, m.p. 154–157° (decomp, somewhat rate dependent) (from EtOH) (Found: C, 56.9; H, 5.4; N, 18.5; Cl, 11.9. $C_{14}H_{14}N_4O \cdot HCl$ requires: C, 57.8; H, 5.2; N, 19.3; Cl, 12.2%).

(c) *Action of alkali.* A solution of **1a** (1.27 g, 0.005 mole) in EtOH (60 ml)–3 N NaOH (10 ml, 0.03 mole) was boiled under reflux for 1.5 h, distilled to smaller volume (20 ml), then stirred into ice-water. The precipitate (0.38 g, 30%) was starting material (IR). The filtrate therefrom gave, on neutralisation with 3 N HCl, a white precipitate (0.48 g, 60%) of **2a**, forming lustrous scales, m.p. 326–328° (from a large volume of EtOH). Lit. m.p. 321–323°[42–44] (Found: C, 59.6; H, 5.6; N, 26.1. Calc. for $C_8H_7N_3O$: C, 59.6; H, 4.35; N, 26.1%). IR: 3200–2800s (multiplet) (NH); 1740 vs br (CO/C=N); 1515m, 730s br, 690, 680s (doublet) (Ph); 1475m, 1090m, 1050m, 965s and 790s cm^{-1}. After a shorter time of boiling (30 min), most of the starting material (72%) was recovered. In aqueous 3 N NaOH, reaction did not occur on account of the insolubility of **1a** therein.

1 - *Benzimidoyl-4-methyl-3-semicarbazide* **1b**

(a) *Preparation.* A solution of benzamidrazone hydriodide (1.58 g, 0.006 mole) in dimethylformamide (10 ml), treated with methyl isocyanate (0.29 g, 0.005 mole), was stirred at room temp. for 20 h, diluted with H_2O (10 ml), and stirred into 0.05 M picric acid (100 ml, 0.005 mole). The crystalline precipitate gave platelets (60%) of **1b** picrate, m.p. 185–186° (decomp.) (from EtOH). (Found: C, 43.0; H, 4.2; N, 22.9. $C_9H_{12}N_4O \cdot C_6H_3N_3O_7$ requires: C, 42.75; H, 3.6; N, 23.3%). The free base was apparently too water soluble to be isolated by the usual procedure.

(b) *Action of alkali.* In the foregoing experiment (a), the resulting dimethylformamide solution was evaporated in a vacuum to small bulk (*ca.* 3 ml), then boiled under reflux with 3 N NaOH (30 ml) for 2 h. Acidification precipitated (72%) **2a**, m.p. 330–332° (decomp) (from EtOH), identified by IR.

4-Phenyl-1-phenylacetimidoylsemicarbazide **1c**

(a) was prepared as **1a**, using phenylacetamidrazone hydriodide[40] (3.05 g, 0.011 mole), and formed needles (70%), m.p. 156–157° (from EtOH) (Found: C, 66.9; H, 5.7; N, 21.0. $C_{15}H_{16}N_4O$ requires: C, 67.2; H, 6.0; N, 20.9%). IR: 3480s, 3370s, 3250m (NH); 3080m, 1540vs br (NH/CN); 2930m (CH_2); 1695s (CO); 1665s (C=N); 760s, 695s (Ph); 1595s, 1455s, 1320m, 1235m, 725ms cm^{-1}. Mass spectrum *m/e* 268(w, M$^{\cdot+}$), 251(m, M$^{\cdot+}$–NH$_3$); 175(i, M$^{\cdot+}$–PhNH$_2$); 149(m, ?PhCH$_2$C(:NH)NHNH$_2^{\cdot+}$), 131i.

The reactant **1c** was substantially recovered after being boiled under reflux in 1.5 N 80% ethanolic hydrochloric acid for 30 min.

The picrate (66%) formed felted needles, m.p. 114–117° (decomp) (from EtOH–light petroleum) (Found: C, 48.7; H, 3.9; N, 18.9. $C_{15}H_{16}N_4O \cdot C_6H_3N_3O_7 \cdot H_2O$ requires: C, 48.9; H, 4.1; N, 19.0%).

(b) *Action of alkali* (as described for **1a** above, but time of refluxing, 45 min) gave, after acidification with 3 N HCl, a white precipitate consisting of two components (TLC). Crystallisation from EtOH (5 ml) gave as the first crop (0.26 g, 30%), 3 - benzyl - 5 - hydroxy - 1,2,4 - triazole **2c**, prisms, m.p. 224–225° (from EtOH). Lit.[43,44] m.p. between 223° and 227° (Found: C, 62.1; H, 5.1; N, 24.1. Calc. for $C_9H_9N_3O$: C, 61.7; H, 5.1; N, 24.0%). IR: 3200ms, 3050ms, 2900m (NH); 2800ms (CH_2), 1710s br (CO); 1590m br (C–N–H); 705s br (Ph); 1480m (doublet), 1015m, 800m cm^{-1}. The filtrates from **2c** slowly deposited prisms (0.56 g, 45%) of 3 - benzyl - 5 - hydroxy - 4 - phenyl - 1,2,4 - triazole **3c**, m.p. 152–155°. Lit. m.p. 159°,[45] 160°.[46] (Found: C, 71.5; H, 5.4; N, 17.45. Calc. for $C_{15}H_{13}N_3O$: C, 71.7; H, 5.2; N, 16.7%). IR: 3180s, 3060s (NH); 2810w (CH_2); 1705, 1695s br (doublet) (CO); 1580s (C–N–H); 1505s, 765s, 695s (Ph); 1425s, 1310s, 1185m, 1060m, 1010m, 835m cm^{-1}. The reactant **1c** was almost insoluble in boiling 3 N aqueous NaOH, and no appreciable reaction occurred in this medium.

4 - *Methyl* - 1 - *phenylacetimidoylsemicarbazide* **1d** formed prisms (58%), m.p. 187–188° (from EtOH, odour of phenylacetic acid). (Found: C, 58.25; H, 6.6; N, 26.9. $C_{10}H_{14}N_4O$ requires: C, 58.25; H, 6.8; N, 27.2%). IR: 3500s, 3430s, 3350, 3290m (doublet) (NH); 3110m, 1560s br (NH/CN); 2960ms (CH_3CH_2); 1690s (CO); 1665s (C=N); 1500m, 760ms, 710ms (Ph); 1425m, 1315s, 1120m, 1075m, 725s cm^{-1}. Mass spectrum: *m/e* 206(i, M$^{\cdot+}$); 189(w, M$^{\cdot+}$–NH$_3$); 175(i, M$^{\cdot+}$–MeNH$_2$); 149(i, ?PhCH$_2$C(:NH)NHNH$_2^{\cdot+}$), 131i. The usual treatment with alkali of **1d** gave **2c** (56%), identified by mixed m.p. and IR spectrum (see above).

1 - *Acetimidoyl* - 4 - *phenylsemicarbazide* **1e**. (a) The standard procedure (addition at 60°) gave a clear liquid, from which the solvent was removed in a vacuum. The residual oil, dissolved in EtOH (25 ml), was treated with conc. HCl (3 ml). The resulting solid (and a second large crop obtained on partial vacuum evaporation) formed opaque microprisms (64%) of **1e** hydrochloride, m.p. 198–200° (Found: C, 46.9; H, 5.3; N, 25.2; Cl, 16.0. $C_9H_{12}N_4O \cdot HCl$ requires: C, 47.3; H, 5.7; N, 24.5; Cl, 15.5%). IR: 3320–3200s (multiplet), 3100–3000s (multiplet) (NH); 1690–1680s (CO); 1640–1605s (multiplet) (C=N); 1510m, 755s br, 695s (Ph); 1570s, 1455m, 1325s, 1245s cm^{-1}. Only *s*-diphenylurea was obtained on performing the reaction in boiling pyridine. The picrate, obtained (80%) from **1e** HCl in 50% aqueous EtOH, formed deep yellow prisms, m.p. 155–158° (decomp) (Found: C, 41.8; H, 3.2; N, 23.3. $C_9H_{12}N_4O \cdot C_6H_3N_3O_7$ requires: C, 42.75; H, 3.6; N, 23.3%). (b) *Action of alkali.* **1e** (1.15 g, 0.005 mole) dissolved within *ca.* 10 min on being boiled under reflux in 1.5 N NaOH (1 h, evolution of NH_3). Acidification (to pH 6) by 3 N HCl precipitated (80%) 3 - hydroxy - 5 - methyl - 4 - phenyl - 1,2,4 - triazole hemihydrate **3e**, m.p. 153–155° (from EtOH) (Found: C, 58.5; H, 5.5; N, 23.2. $C_9H_9N_3O \cdot \frac{1}{2}H_2O$ requires: C, 58.7; H, 5.4; N, 22.8%). IR: 3370s br, 3200m (doublet), 3100m (doublet) (NH); 2860m (CH_3); 1690vs br (CO); 1510s, 775s, 700m (Ph); 1590s, 1420s, 1300m, 815m, 745m, 720m cm^{-1}. Desolvation at 110°/4 mm (Hg) gave anhydrous **3a**, with the same m.p. and IR spectrum as the hemihydrate. (Found: C, 61.1; H, 5.2; N, 23.6. $C_9H_9N_3O$ requires: C, 61.7; H, 5.1; N, 24.0%).

Addition-cyclisations with ethoxycarbonyl isothiocyanate

1 - *Benzimidoyl* - 4 - *ethoxycarbonyl* - 3 - *thiosemicarbazide* **6a**

(a) *Preparation.* A stirred solution of benzamidrazone hydriodide[40] (2.63 g, 0.01 mole) in dimethylformamide (10 ml)-NEt$_3$ (1.0 g, 0.01 mole) was treated at room temp. during 2 min with ethoxycarbonyl isothiocyanate (1.05 g, 0.008 mole) (slightly exothermic). After 2 h storage at room temp., the pale orange liquid was stirred into ice water. The white precipitate (72%) gave, on rapid crystallisation from EtOH (3–5 ml per g; odour of hydrogen sulphide; recovery 75%), pale yellow prisms of **6a**, m.p. 149–150° (decomp). (Found: C, 49.9; H, 5.4; N, 20.9; S, 11.8. $C_{11}H_{14}N_4O_2S$ requires: C, 49.6; H, 5.3; N, 21.05; S, 12.0%). IR: 3440s, 3300–3200s (multiplet); 3000ms (NH); 1720vs br (CO); 1655s (C=N); 1550s (C–N–H); 1255s (?CS); 1230–1205s (multiplet) (C–O–C); 1080m (N–C–S); 780ms, 690s (Ph); 1605, 1595s (doublet); 1485, 1475s (doublet); 1460–1440s (multiplet); 1325m, 1045s cm^{-1}. Mass spectrum: *m/e* 266 (w, M$^{\cdot+}$), 249(i, M$^{\cdot+}$-17); 178(vi, ?PhC(:NH)NHNHCS$^{\cdot+}$).

(b) *S-Methyl-thioether* **7**. To a solution of Na (0.115 g, 0.005 g atom) in MeOH (15 ml), **6a** (1.33 g, 0.005 mole) and MeI (14.2 g, 0.01 mole) was added. The liquid was boiled under reflux for 1 h, its volume reduced to one-third, then stirred into ice water. The solidified product gave **7** as prisms, m.p. 97–98° (from EtOH) (0.85 g, 60%) (Found: C, 51.8; H, 5.7; N, 19.8; S, 11.6. $C_{12}H_{16}N_4O_2S$ requires: C, 51.4; H, 5.7; N, 20.0; S, 11.4%). IR:

3480s, 3390s, 3330s (NH); 2970w (CH, arom.); 2900w (CH_2); 1725s br (CO); 1625m br (C=N); 1575s br (C–N–H); 1210s br (C–O–C ester), 1075s br (N–C–S); 775m, 690m (Ph); 1470s br cm^{-1}.

(c) *Action of alkali.* A solution of **6a** (1.33 g, 0.005 mole) in N NaOH (15 ml) was boiled under reflux for 30 min (odour of benzonitrile). The filtered solution deposited crystalline solid, which was collected after partial evaporation, and extracted with ether. Removal of the solvent gave benzamide (0.42 g, 70%), m.p. 126–128°, identified by its IR spectrum.

(d) *Action of hydrochloric acid.* To a suspension of finely powdered **6a** (1.33 g, 0.005 mole) in H_2O (25 ml), 3 N HCl (25 ml) was added, effecting complete solution, before a white crystalline precipitate reappeared. The mixture was boiled under reflux for 10 min, and the solid collected at 0°, giving needles (1.0 g, 80%) of 2 - ethoxycarbonamido - 5 - phenyl - 1,3,4 - thiadiazole **8a**, m.p. 198–200° (from EtOH). Lit. m.p.[24] 199–200°. (Found: C, 52.7; H, 4.55; N, 17.4; S, 12.2. Calc. for $C_{11}H_{11}N_3O_2S$: C, 53.0; H, 4.4; N, 16.9; S, 12.85%). IR: 3170m, 2880s (doublet), 2750s br (NH); 1720s (CO); 1570s br (C–N–H); 1235s br (C–O–C); 770s, 690ms (Ph); 1365m, 1325s, 1130m and 1060m cm^{-1}. The compound was soluble in cold N NaOH, and was reprecipitated by HOAc or HCl.

The picrate of **8a**, obtained (75%) from the components in EtOH, formed prismatic needles, m.p. 167–168° (from EtOH). (Found: C, 42.8; H, 3.1; N, 17.4. $C_{11}H_{11}N_3O_2S{\cdot}C_6H_3N_3O_7$ requires: C, 42.7; H, 2.9; N, 17.6%).

The structure of **8a** was confirmed: (i) By its identity (m.p., IR spectrum) with a specimen obtained[24] (70%) by the action of ethyl chloroformate on authentic 2 - amino - 5 - phenyl - 1,3,4 - thiadiazole **9** (see below) in pyridine -triethylamine. (ii) By alkaline hydrolysis to **9**: A solution of **8a** (1.25 g, 0.005 mole) in 1.5 N NaOH was boiled under reflux for 1 h. The crystalline solid that separated on cooling was 2 - amino - 5 - phenyl - 1,3,4 - thiadiazole **9** (0.16 g, 18%), m.p. 222–224° (Lit. m.p.[25,27] 222–224°), identified by its IR spectrum (see below). Acidification of the filtrate with 3 N HCl precipitated starting material (75%). 2 - Amino - 5 - phenyl - 1,3,4 - thiadiazole **9**, prepared from thiobenzamidoguanidine,[25] had IR 3300s, 3100s (NH); 1520vs (C=N); 760s, 690s br (Ph); 1635ms, 1470m, 1260m, 1135m, 1055m cm^{-1}. (e) The condensation of benzamidrazone hydrochloride[40] and ethoxycarbonyl isothiocyanate under the conditions (8 h at 100°) specified by Bany and Dobosz[9] gave a crude product affording, after two crystallisations from chloroform-light petroleum (b.p. 60–80°), platelets (52%) of **8a**, identical (mixed m.p. 198–200°; IR spectrum) with the material obtained in (d) above. The authors[9] report m.p. 199.5–200.5°, picrate m.p. 173–174°.

4 - *Ethoxycarbonyl* - 1 - *phenylacetimidoyl* - 3 - *thiosemicarbazide* **6b**

(a) *Preparation.* The use of phenylacetamidrazone hydriodide[40] (2.77 g, 0.01 mole) (procedure a, above) gave prisms (48%) of **6b**, m.p. 143–145° (decomp.) (from EtOH–light petroleum). (Found: C, 51.3; H, 5.8; N, 19.4; S, 11.4. $C_{12}H_{16}N_4O_2S$ requires: C, 51.4; H, 5.7; N, 20.0; S, 11.4%). IR: 3440m, 3310m, 3170s br (NH); 2980m (CH_2); 1720vs br (CO); 1660s (C=N); 1555s br (C–N–H); 1250s br (?C=S); 1220, 1200s br (doublet) (C–O–C); 1050ms (N–C–S); 740m, 700m (Ph); 1470–1460s (doublet) cm $^{-1}$.

(b) Cyclisation of **6b** by HCl (as described for **6a**) gave opaque felted needles of **8b**, m.p. 138–140° (56%). (Found: C, 54.2; H, 5.15; N, 16.2. $C_{12}H_{13}N_3O_2S$ requires: C, 54.75; H, 4.9; N, 16.0%). IR: 3170m, 2910ms (NH); 2780ms (CH_2); 1725s (CO); 1570s br (C–N–H); 1255s br (C–O–C); 770ms, 705ms (Ph); 1325s, 1105m and 1055m cm^{-1}.

2 - *Ethoxycarbonamido* - 5 - *methyl* - 1,3,4 - *thiadiazole* **8c**

A solution of acetamidrazone hydrochloride (2.63 g, 0.024 mole) in hot dimethylformamide (70 ml) was cooled, treated at 25° with ethoxycarbonyl isothiocyanate (2.6 g, 0.02 mole) during 2 min, then set aside for 3 h. The precipitate was collected, and more material (total, *ca.* 3.2 g) was obtained by partial vacuum evaporation, affording needles (62%) of **8c**, m.p. 176–179°. Lit.[47] m.p. 177°. (Found: C, 38.4; H, 4.9; N, 22.6; S, 16.9. Calc. for $C_6H_9N_3O_2S$: C, 38.5; H, 4.8; N, 22.5; S, 17.1%). IR: 3160m, 2980ms, 2900s (NH); 2780s (CH_3); 1715vs (CO); 1585s br (C–N–H); 1240ms (C–O–C); 1325s, 1260s, 1115m, 1065m, 820m, 760s, 705m cm^{-1}. The picrate of **8c** formed felted needles (55%), m.p. 147–148° (from EtOH). (Found: C, 34.7; H, 3.2; N, 20.4. $C_6H_9N_3O_2S{\cdot}C_6H_3N_3O_7$ requires: C, 34.6; H, 2.9, N, 20.2%). The condensation of the components under the conditions (8 h at 100°) employed by Bany and Dobosz[9] gave (44%) **8c**, identical (mixed m.p., IR spectrum) with the above material. The authors[9] give m.p. 179.5–180°, picrate m.p. 148–149°.

Use of isothiocyanate esters

1 - *Benzimidoyl* - 4 - *methyl* - 3 - *thiosemicarbazide* **14a**

(a) The use of methyl isothiocyanate (0.01 mole) [in the procedure (a) described for the preparation of **6a**] gave prisms (0.93 g, 43%), m.p. 124–126° (decomp) (from EtOH). (Found: C, 52.2; H, 5.6; N, 26.1; S, 15.3. $C_9H_{12}N_4S$ requires: C, 51.9; H, 5.8; N, 26.9; S, 15.4%). IR: 3450s, 3310s, 3170s (NH); 2970w (CH_3); 1635s (C=N); 1570, 1560s (doublet) (C–N–H); 1260s vbr (?CS); 1070, 1060m (doublet) (N–C–S); 1500s, 785s, 695s (Ph); 1000m cm^{-1}. Mass spectrum: *m/e* 191(i, M^{+}–NH_3); 118(i, ?PhC(:NH)N^{+}).

(b) *Action of acid.* A solution of the reactant (0.005 mole) in N HCl (15 ml) was refluxed for 30 min, then made alkaline yielding (92%) 2 - methylamino - 5 - phenyl - 1,3,4 - thiadiazole, m.p. 183–185° (prisms, from EtOH). Lit.[27] m.p. 183–184°. IR: 3220s (doublet), 2990s (NH); 1575s (br, doublet) (C–N–H); 770s, 695s (Ph); 1515, 1510ms (doublet); 1470ms, 1410s, 1265w, 1165m br and 1070m br cm^{-1}.

1 - *Benzimidoyl* - 4 - *phenyl* - 3 - *thiosemicarbazide* **14b**, similarly obtained (56%), formed pale yellow minute needles, m.p. 128–129° (from very little EtOH). (Found: C, 62.3; H, 5.3; N, 20.7; S, 11.6. $C_{14}H_{14}N_4S$ requires C, 62.2; H, 5.2; N, 20.7; S, 11.85%). IR: 3350s br, 3080s (NH); 1660, 1655s (doublet) (C=N); 1600s br (C–N–H); 1240ms br (?C=S); 775ms, 695s (Ph); 1535s, 1485s, 1430s, 1320ms, 1190, 1180ms br (doublet) cm $^{-1}$. The compound dissolved in 3 N NaOH on warming and gave a pale yellow stable precipitate on addition of lead acetate in aqueous acetic acid. A small (15–20%) less soluble fraction was identified as 3 - mercapto - 4,5 - diphenyl - 1,2,4 - triazole, m.p. 284–286° (from EtOH). Lit. m.p. 281°[48], 287°.[49] (Found: C, 66.5; H, 4.5; N, 16.2. Calc. for $C_{14}H_{11}N_3S$: C, 66.4; H, 4.35; N, 16.6%). IR: 3110s, 2920s, 2740ms (NH); 1545s (C=N); 1500s, 770s, 700s, 690s (Ph); 1445s, 1405s, 1335s, 1275s, 970s cm^{-1}. The action of ethanolic HCl on **14b** gave (80%) 2 - anilino - 5 - phenyl - 1,3,4 - thiadiazole, m.p. 198–200° (from acetone–EtOH). Lit. m.p.[25,27] 199–200°. IR: 3290m, 3220m, 2950s br (NH); 1625s (C=N); 1575s (C–N–H); 1510s, 765m, 750s, 690s (Ph); 1460s, 1440s, 1220m cm^{-1}.

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