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CHEMISTRY OF BIUREAS—II

SYNTHESIS AND CYCLISATION OF THIOBIUREAS DERIVED FROM (THIO)CARBONOHYDRAZIDES AND ETHOXYCARBONYL ISOTHIOCYANATE

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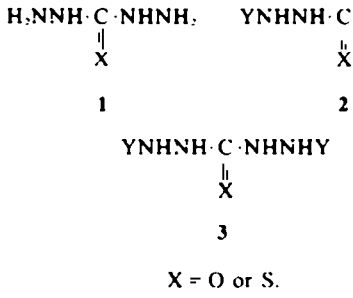
Abstract—Carbonohydrazide and its thio-analogue undergo di-addition with ethoxycarbonyl isothiocyanate. The reaction terminates at the mono-addition stage when one of the hydrazine moieties of the (thio)carbonohydrazide is blocked. The resulting 6-(substituted)amino-1-ethoxycarbonyl-thiobiureas and bithioureas are cyclised to the appropriate 1-ethoxycarbonamido-1,3,4-thiadiazoles by acids, and to mercapto-1,2,4-triazoles by alkalis.

In conjunction with our study of addition-cyclisations of ethoxycarbonyl isothiocyanate with compounds incorporating the hydrazine structure,[1-3] we have examined the behaviour of (thio)carbonohydrazides (**1**, X = O, S) and their substitution products in this general reaction.



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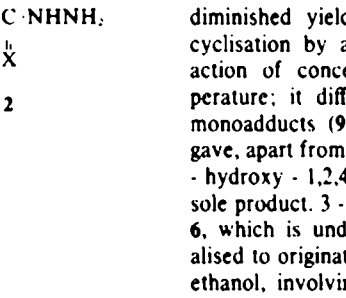

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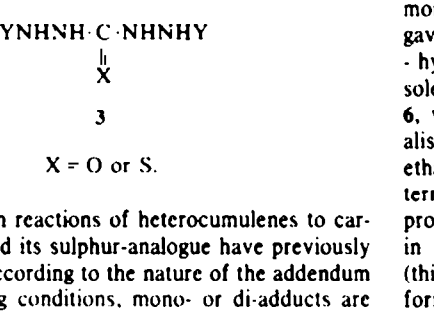


3

X = O or S.

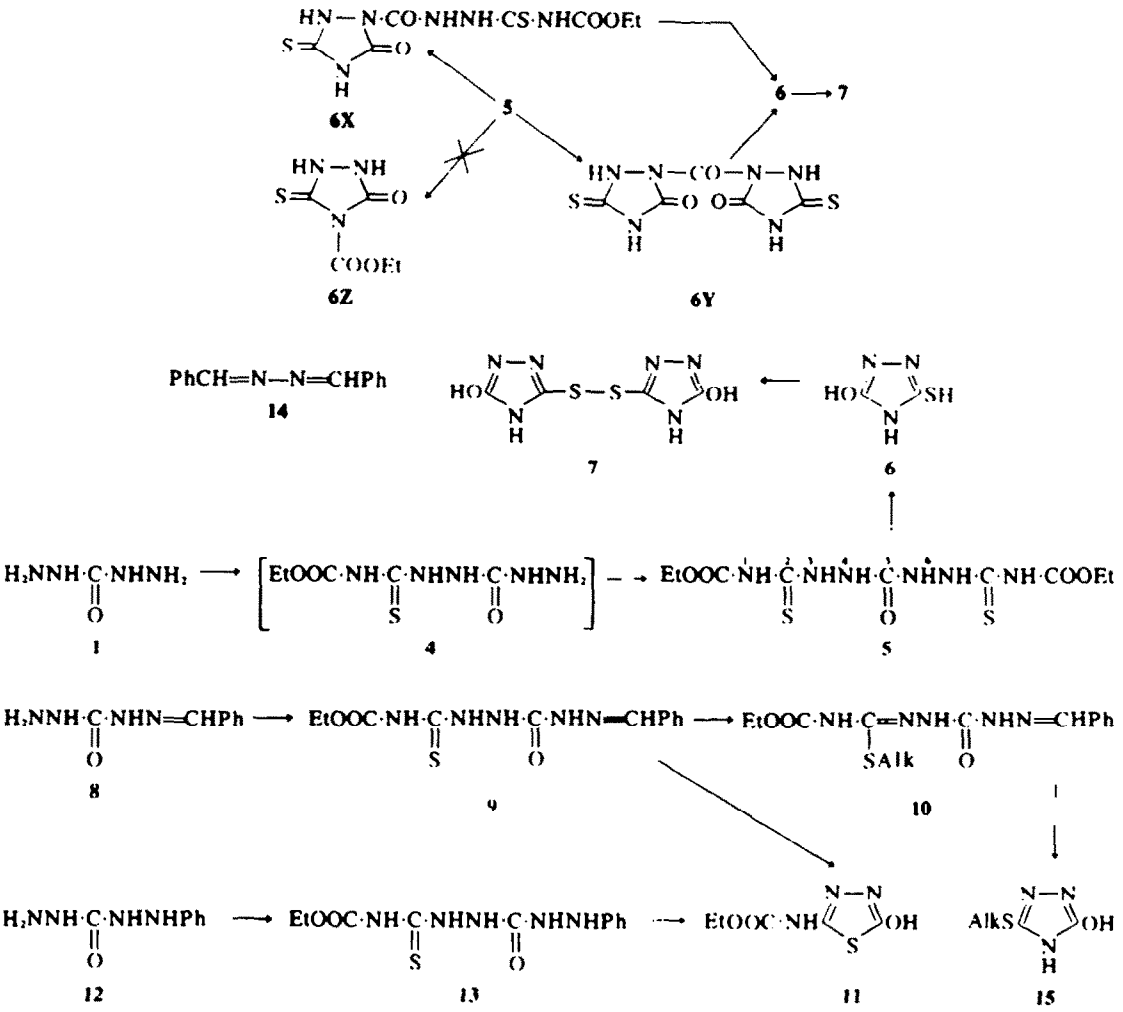
Several addition reactions of heterocumulenes to carbonohydrazide and its sulphur-analogue have previously been explored. According to the nature of the addendum and the prevailing conditions, mono- or di-adducts are produced, which may be isolable or may cyclise spontaneously to heterocyclic products. It is difficult to account consistently for these differences on the basis of the information at present available. Cyanic[4-6] or thiocyanic acid[4,7,8] are added to (thio)carbonohydrazide **1** in stages, yielding successively mono (**2**; Y = $CONH_2$, $CSNH_2$) and diadducts (**3**; Y = $CONH_2$, $CSNH_2$). Isocyanate[4,9] and isothiocyanate esters[10] yield diadducts (**3**; Y = RNHCO, RNHCS), even when an excess of (thio)carbonohydrazide is employed. Distinct mono- and di-addition is observed in the case of aroyl isothiocyanates.[11] Adducts derived from carbodiimides[9,12,13] cyclise spontaneously to substituted 1,2,4-triazoles under the conditions of their formation. Exclusive monoaddition is the rule when the heterocumulene reacts with (thio)carbonohydrazide having one of its hydrazino-moieties blocked by a suitable substituent.[11,13]

The linear adducts thus obtained may be regarded either as substituted (thio)carbonohydrazides or (thio)biureas, and be named accordingly. We adopt the latter nomenclature to emphasise the unity of the material described in this and the foregoing[1] paper.

Thiobiurea Derivatives. Ethoxycarbonyl isothiocyanate reacted readily with carbonohydrazide **1** in dimethyl sulphoxide at room temperature, or in dimethylformamide at 90–100° to produce the symmetrical diadduct, 1 - ethoxycarbonyl - 6 - (ω - ethoxycarbonylthio - ureido)thiobiurea **5** (80%). Monoaddition affording **4** (or cyclisation products arising therefrom) was not observed: the use of equimolar quantities of the reactants, or an excess of carbonohydrazide, also gave **5**, albeit in diminished yields. The thiobiurea **5** was resistant to cyclisation by acid reagents, being unaffected by the action of concentrated sulphuric acid at room temperature; it differs, in this respect, from the related monoadducts (**9**, **13**, see below). The action of alkali gave, apart from carbon dioxide, moderate yields of bis(3 - hydroxy - 1,2,4 - triazol - 5 - yl) disulphide **7**[14-16] as the sole product. 3 - Hydroxy - 5 - mercapto - 1,2,4 - triazole **6**, which is undoubtedly the primary product, is visualised to originate from the starting material **5** by loss of ethanol, involving the formation and hydrolysis of intermediates such as **6X** or **6Y**. An alternative mechanism proceeding via **6Z** is excluded for reasons already given in the case of the analogous biureas derived from (thio)semicarbazides,[1] i.e. because of the demonstrated formation, in suitable examples, of intermediates of type **6X** (see **29**, below, and Ref. 1: **11**, **20**).

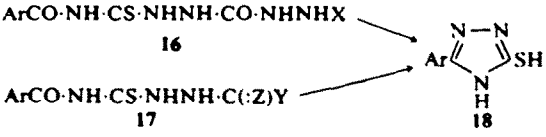
With 1-benzylidene- **8** or 1-phenylcarbonohydrazide **12**, ethoxycarbonyl isothiocyanate underwent smooth monoaddition, affording 6-benzylideneamino (or anilino) - 1 - ethoxycarbonyl - 2 - thiobiurea **9**, **13** in 85–90% yield. Like the diadduct **5**, these are acidic, being soluble in dilute sodium hydroxide, and reprecipitated by acid. They are readily alkylated at their sulphur function, as illustrated by the conversion of **9** into the S-methyl or S-benzyl-derivatives (**10**; Alk = Me, CH_2Ph).

Though stable towards dilute mineral acids, the adducts **9**, **13** were cyclised by concentrated sulphuric acid at room temp. to 2-ethoxycarbonamido - 5 - hydroxy - 1,3,4 - thiadiazole **11** with loss of the appropriate substituted hydrazine. Polyphosphoric acid at 120–130° effected the same cyclisation of **13**, but completely cleaved the benzylidene-analogue **9**, yielding dibenzylidenehydrazine (**14**, 64%) as the only isolable product. Except for the severe conditions required, the reaction is a variant of the usual acidic cyclisation of comparable linear structures[17] to substituted 1,3,4-thiadiazoles and is explicable by the same general mechanism.[1] 2 - Ethoxycarbonamido - 5 - hydroxy - 1,3,4 - thiadiazole **11** was not a suitable precursor for the production of the parent amine; its ethoxycarbonamido-grouping proved resistant to



hydrolysis by alkalis, which readily converts phenoxycarbonamido-heterocycles into the free bases (PhOOC·NHHet → H_2NHet).[18]

The action of alkalis on the monoadducts follows the established cyclisation pattern in furnishing 1,2,4-triazoles by the elimination of ethanol and simultaneous hydrolysis: thus *S*-benzyl 6 - benzylideneamino - 1 - ethoxycarbonyl - 2 - thiobiurea (**10**, Alk = $PhCH_2$) gave 3 - benzylthio - 5 - hydroxy - 1,2,4 - triazole (**15**, Alk = CH_2Ph)[1] in 80% yield. Although the expected 3 - hydroxy - 5 - mercapto - 1,2,4 - triazole **6** escaped isolation when the parent adducts **9**, **13** were treated with alkali, the formation of the hydrolytic cleavage products was apparent from the production of dibenzylidenehydrazine (**14**, 76%) from **9**, and of phenylhydrazine (43%, as picrate) from **13**. Organic bases (including hydrazine hydrate, phenylhydrazine, and aniline), failed to effect cyclisation to 1,2,4-triazoles, causing extensive decomposition in each case. It is recalled that analogous adducts **16**[11] of carbonohydrazides and aroyl isothiocyanates similarly afford 3 - aryl - 5 - mercapto - 1,2,4 - triazoles **18** in alkaline media, as do 1-substituted 4-aroyl

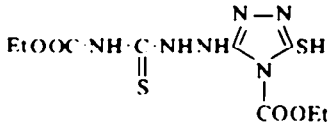


- 3 - thiosemicarbazides **17** derived from aminoguanidines[19] (**17**; Z = NH, Y = NH_2, NHR), diaminoguanidines[19] (**17**; Z = NH, Y = $NHNH_2$) and ethoxycarbonylhydrazine[20] (**17**; Z = O, Y = OEt), all of which yield the same product **18**.

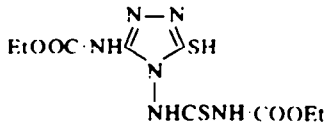
Bithiourea derivatives. Parallel work using thiocarbonohydrazides was concerned with the production and cyclisation of comparable bithioureas. It revealed closer analogies between the oxygen and sulphur series than have been observed in related structures.[17]

The interaction of ethoxycarbonyl isothiocyanate with the parent thiocarbono-hydrazide **19** resulted, as in the case of its oxygen analogue **1**, in rapid diaddition, but was accompanied, in this instance, by ring-closure with loss of hydrogen sulphide. The same reaction occurred invariably under a variety of conditions, but required careful control to afford reasonable yields. If vicinal diaddition (see below), and the possible formation of a tetrazine system, are discounted, the cyclisation product may have one of three possible structures **21**, **21A**, **21B**. Of these, **21A** may reasonably be rejected, since 4 - ethoxycarbonyl - 1,2,4 - triazoles are not formed in any of the comparable cyclisation processes. Structure **21** is favoured on the grounds of analogy, but requires final confirmation.

1-Substituted thiocarbonohydrazides **22**, **25** gave excellent yields of the linear monoadducts **23**, **26**, which were stable and readily isolated. In this respect, they



21A



21B

resemble their analogues derived from thiosemicarbazides,[1] and substituted bithioureas in general,[21] but differ from the closely related bisthioamides of type **32**, which tend to decompose spontaneously with loss of hydrogen sulphide.[22] The IR spectra of both the thiobiurea- **5**, **9**, **13** and bithiourea derivatives **23**, **26** display characteristic bands attributable to their chief structural features: the assignments follow closely those of the analogous (thio)semicarbazide derivatives.[1] In accordance with their thioamide-structure, the substituted bithioureas **23**, **26** are acidic. Both their sulphur functions may be alkylated by the standard methods, as shown by the ready production of a di-*S*-benzyl-derivative **24** from **23**.

a product formulated as the 1H-thiohydrazido - 1,2,4 - triazole **29**. Both the acidic and alkaline cyclisations are thought to occur by the mechanisms proposed for such processes involving the corresponding (thio)semicarbazide derivatives (see Ref. 1; **3A**, **4A** → **5**; **3B**, **4B** → **7**). The triazole **29** was remarkably stable towards acids, and unlike comparable 1H - (thio)amido - 1,2,4 - triazoles,[1] was practically unaffected by more prolonged treatment with alkali. However, hydrolytic removal of its 1H-substituent did occur on *S*-alkylation in alkali: the action of *p*-nitrobenzyl chloride in ethanolic sodium hydroxide (on **29**) gave moderate yields of **30** (Alk = *p*-$NO_2C_6H_4CH_2$), confirming at the same time the structure assigned to **29**. The action of dimethyl sulphate (on **29**)

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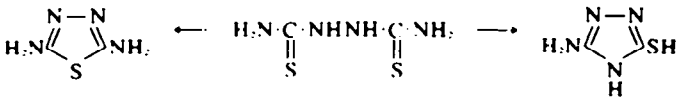
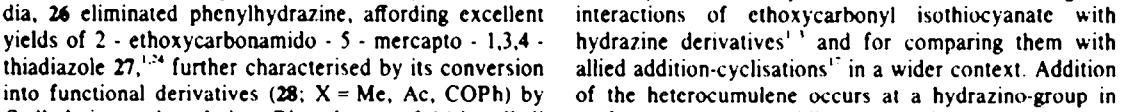
R = Alk, Ar.
R' = R, NH_2, $NHNH_2$, NHNHCSR.



34 33 35

Bithiourea **33** is cyclised to 2,5 - diamino - 1,3,4 - thiadiazole **34** by acids, and to 3 - amino - 5 - mercapto - 1,2,4 - triazole **35** by alkalis, with loss of hydrogen sulphide in each case.[14,23] The ring-closure of the bithiourea derivative **26** proceeded differently. In acid media, **26** eliminated phenylhydrazine, affording excellent yields of 2 - ethoxycarbonamido - 5 - mercapto - 1,3,4 - thiadiazole **27**,[1,24] further characterised by its conversion into functional derivatives (**28**; X = Me, Ac, COPh) by *S*-alkylation and acylation. Ring-closure of **26** by alkali or sodium carbonate occurred with loss of ethanol giving a trimethyl-derivative, which, because of the likelihood of preferred *S*-alkylation, and the persistence in its IR spectrum of a band assignable to a ring-carbonyl group, is formulated as **31**.

The present work provides data for correlating the interactions of ethoxycarbonyl isothiocyanate with hydrazine derivatives[1-3] and for comparing them with allied addition-cyclisations[1-7] in a wider context. Addition of the heterocumulene occurs at a hydrazino-group in preference to an amidino- or (thio)amido-group, as shown by the behaviour of amidrazones[1] and (thio)se-



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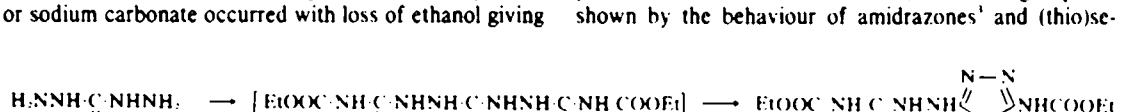

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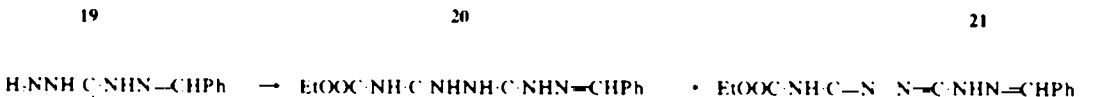
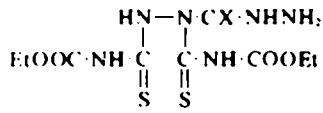


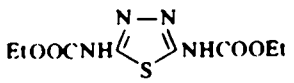
25 26 27

30 29 31 28

micarbazides[1] in this group of reactions. In undergoing immediate symmetrical diaddition with (thio)carbonohydrazide, ethoxycarbonyl isothiocyanate resembles iso(thio)cyanate esters[4,9,10] rather than the more closely related aroyl isothiocyanates.[11] *Vicinal* diaddition (at adjacent nitrogen atoms of the same hydrazine-group) is known to occur when carbodiimides react with (thio)carbonohydrazides,[9,12] (thio)semicarbazides,[25] or (di)aminoguanidines,[25,26] resulting in 3,5-dianilino-5-phenyl - 1,2,4 - triazole in all cases; thiobenzoylation of (thio)carbonohydrazide[27] yields 2,5 - diphenyl - 1,3,4 - thiadiazole by a comparable pathway. That such vicinal diaddition does not occur in the present reactions is shown by the absence of its presumed products (**5A** or **5B**, formed consecutively), and by the failure of the diadduct **5** to react additively with a third molecule of ethoxycarbonyl isothiocyanate (compare ref. 25). These differences may be ascribed to changes in the electron availability at the penultimate nitrogen of the hydrazine-group: its depletion by the electron-withdrawing ethoxycarbonyl-group, or enhancement by an adjacent guanidino-residue (arising in the carbodiimide-addition) influences the power of this centre of attacking the isothiocyanate-carbon nucleophilically.



5A



5B

The course of the alkaline ring-closure common to thiobiurea-derivatives that incorporate an ethoxycarbonyl-group (**5**, **10**, **26**, and Part I[1]: **10**, **14**) merits brief comment. Cyclisation involving the usual loss of hydrogen sulphide (or H_2X) would convert compounds of type **36** into **38** or **39**, but occurs in fact with elimination of ethanol and the formation of 1H - (thio)amido - 1,2,4 - triazoles **37**. The resemblence of this cyclisation and that of comparable aroyl isothiocyanate-adducts[11,19] (e.g. **16**, **17** → **18**) is apparent, but the former is of added interest, in that the 1H-substituted 1,2,4-triazoles **37** are in some cases sufficiently stable to be isolated. We have previously considered a possible explanation for the preferred direction of this type of cyclisation;[19] as the behaviour of an increasing number of structural variants is elucidated, the task of accounting for all the observations by one unifying interpretation becomes more difficult.

EXPERIMENTAL

For general procedures, remarks and abbreviations, see foregoing paper.[1]

Thiobiurea derivatives

1 - *Ethoxycarbonyl* - 6 - (*ω* - *ethoxycarbonylthioureido*) - 2 - *thiobiurea*. (1,5 - *Bis*(*ethoxycarbonylthiocarbamoyl*)*carbonohydrazide*) **5**. (a) *Preparation*. A stirred soln of **1** (0.90 g, 0.01 mole) in dimethyl sulphoxide (30 ml) was treated dropwise with ethoxycarbonyl isothiocyanate (2.62 g, 0.02 mole) during 5 min (temp. rise to *ca.* 40°), the clear liquid stirred for 3 h, then added to ice-water. The precipitate (m.p. 199–200°, 2.65–2.8 g, 75–80%, pure by IR) gave, on crystallisation from boiling pyridine (5 ml per g, recovery 75%), white opaque microcrystalline **5**, m.p. 205–206° (Found: C, 30.9; H, 4.7; N, 24.6; S, 18.3. Calc. for $C_9H_{14}N_6O_5S_2$: C, 30.7; H, 4.5; N, 23.9; S, 18.2%) IR: 3300s, 3220m (NH); 1720s (ester CO); 1675s (amide CO); 1555, 1540s d (NH/CN); 1260s (?CS); 1210, 1200s br (C–O–C); 1045s (C–O–C; ?NCS); 1375ms, 1350ms, 1170w, 770m cm^{-1}. Lit.[28] m.p. 209° (decomp).

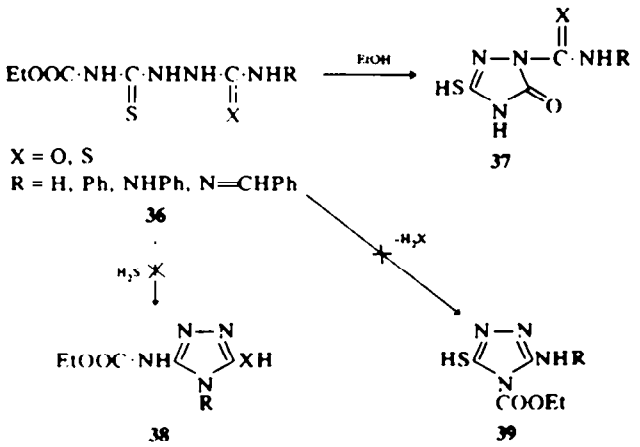
The use of a 0.9 molar proportion of ethoxycarbonyl isothiocyanate in the foregoing procedure also gave **5** (86%, based on the isothiocyanate), as did the interaction of equimolar quantities of the reactants (0.005 mole each) in dimethylformamide (5 ml) at 90–100° for 1 h (32%).

The compound was almost insoluble in the usual organic solvents; it dissolved in cold 3N NaOH and was reprecipitated by acids. It gave a negative "plumbite test". Its attempted *S*-benzylation under standard conditions gave only 3 - benzylthio - 5 - hydroxy - 1,2,4 - triazole, m.p. 182–184°,[1,15] in very low yield.

(b) *Action of sodium hydroxide*. A solution of **5** (0.002 mole) in 3N NaOH (15 ml) was boiled under reflux for 30 min, then acidified (effervescence of CO_2). The needles (0.08 g, 18%) separating on prolonged storage were di(3 - hydroxy - 1,2,4 - triazol - 5 - yl) disulphide, identical (mixed m.p. and IR spectrum) with authentic material.[1,15,23]

(c) The diadduct **5** was recovered (90%) after its soln in dimethyl sulphoxide (0.002 mole in 10 ml) was treated with ethoxycarbonyl isothiocyanate (0.002 mole), kept at room temp. (3 h), and stirred into H_2O.

6 - *Anilino* - 1 - *ethoxycarbonyl* - 2 - *thiobiurea* **13**. (a) *Preparation*. A stirred soln of **12** (3.32 g, 0.02 mole) in dimethylformamide (50 ml) was treated dropwise at room temp. with ethoxycarbonyl isothiocyanate (2.62 g, 0.02 mole), the (warm) liquid set aside for 3 h, then added to ice-water. The finely divided precipitate coagulated on being stirred and gave, on



crystallisation from EtOH (30 ml) lustrous platelets (4.45–4.85 g, 75–82%) of **13**, m.p. 172–174° (Found: C, 43.9; H, 5.0; N, 23.3; S, 10.2. $C_{11}H_{14}N_4O_4S$ requires: C, 44.4; H, 5.1; N, 23.6; S, 10.8%). IR: 3310–3250s br (NH); 3060, 3000w, 770s, 675–670s (Ar); 1725s (ester CO); 1690–1680s br (amide CO); 1560–1520s br (NH/CN); 1255s (?CS); 1200–1190s (C–O–C); 1045s (C–O–C; ?NCS); 1605s, 1485s, 1380ms, 1310ms, 715m cm $^{-1}$. Soluble in 2N NaOH on slight warming, and reprecipitated by dilute HCl.

(b) *Stability to hydrochloric acid.* A soln of **13** (1 g) in EtOH (12 ml)–conc. HCl (4 ml), when refluxed for 30 min, distilled to smaller bulk, and diluted with H_2O, gave the starting material (75%). The use of 3N HCl (6 ml) in this procedure (5 h boiling) also gave unchanged reactant (43%).

(c) *Action of sulphuric acid.* Powdered **13** (0.6 g, 0.002 mole) was stirred into conc. H_2SO_4 (5 ml), the pale-yellow soln set aside at room temp. for 3 h, then stirred into ice-water (75 ml). The white precipitate was 2-ethoxycarbonamido - 5 - hydroxy - 1,3,4 - thiadiazole **11**, forming prisms (64%), m.p. 262–264° (from EtOH), identical with authentic material (mixed m.p.,[24] IR[1]).

(d) *Action of polyphosphoric acid.* Powdered **13** (0.005 mole) was added to polyphosphoric acid (20 g), and the dark brown liquid kept at 120–140° for 30 min. The cooled liquid was stirred into H_2O, giving a precipitate of **11**, m.p. 256–258° (from EtOH) (28%).

(e) *Action of sodium hydroxide.* A soln of **13** (1.5 g, 0.005 mole) in 3N NaOH (10 ml) was refluxed for 30 min. The separated oily globules redissolved on acidification with conc HCl. The (filtered) liquid which deposited nothing on storage, was treated with 0.05M picric acid, and gave phenylhydrazine picrate, m.p. 147–149° (from EtOH) (43%) (Found: C, 43.0; H, 3.8. Calc. for $C_6H_8N_2$, $C_6H_3N_3O_7$: C, 42.7; H, 3.3%). Lit. m.p. 151–152°.[25]

6 - *Benzylideneamino* - 1 - *ethoxycarbonyl* - 2 - *thiobiurea* **9**. (a) *Preparation.* This was obtained from **8** (3.56 g, 0.02 mole) like the 6-anilino-analogue **13**, and formed, after crystallisation from acetone (40 ml per g, recovery 75%) or EtOH (60 ml per g, recovery 70%), prismatic needles (total, 5.4 g, 76%) of solvated **9**, m.p. 184–185°. (Found: C, 47.25; H, 5.4; N, 21.7; S, 9.5. $C_{12}H_{15}N_3O_3S$, C_2H_5OH requires: C, 47.3; H, 5.9; N, 19.7; S, 9.0%). Desolvation at 110°/2 mms for several hours gave opaque needles, m.p. 184–185°. (Found: C, 46.2; H, 4.9; N, 22.35; S, 10.2. $C_{12}H_{15}N_3O_3S$ requires: C, 46.6; H, 4.85; N, 22.65; S, 10.4%); IR: 3320s, 3250s (NH); 3010m, 760ms, 695ms (Ar); 1725s (ester CO); 1690s (amide CO); 1540s–1455m mult. (NH/CN); 1245–1225ms d (C–O–C, ?CS); 1055s (C–O–C, ?NCS); 1710s, 1370m, 1325m, 1290m, 1195s, 960w cm $^{-1}$. Soluble in 2N NaOH on slight warming, and reprecipitated by dilute HCl.

(b) *Action of mineral acids.* The thiobiurea **9** was recovered (65%) when its solution in ethanol–conc. HCl (4:1; 20 ml per g) was boiled under reflux for 30 min. Treatment of **9** with conc. H_2SO_4 as described for the foregoing 6-anilino-analogue **13** gave **11**, m.p. 262–264°, in 84% yield.

The action of polyphosphoric acid under the standard conditions (see above) gave only (64%) dibenzylidenehydrazine, m.p. 90–91° (from EtOH), Lit.[26a] m.p. 93°, identified by its IR spectrum.[11]

(c) *Action of alkali.* A soln of **9** (0.70 g, 0.002 mole) in 3N NaOH (15 ml) was refluxed for 30 min, the (temporarily orange) liquid depositing oily globules (odour of benzaldehyde). Acidification and storage gave yellow crystalline dibenzylidenehydrazine (0.16 g, 76%) identified as in (b, above).

(d) *S-Methyl-derivative* **10** (Alk = Me). The thiobiurea **9** (1.54g, 0.005 mole) dissolved in a soln of Na (0.115 g, 0.005 g atom) in MeOH (25 ml), on being warmed, and was treated with MeI (14.2 g, 0.1 mole). The liquid was boiled under reflux for 30 min, evaporated to quarter volume in a vacuum, and diluted with ice-water. The resulting precipitate gave **10** (Alk = Me), as prisms (0.90 g, 56%), m.p. 137–139° (from MeOH, 15 ml). (Found: C, 47.8; H, 5.6; N, 21.5. $C_{13}H_{17}N_3O_3S$ requires: C, 48.3; H, 5.3; N, 21.7%). IR: 3200ms, 3100ms (NH); 2970ms (Alk); 1705–1690s (mult) (ester CO, amide CO); 1550–1505s (mult) (NH/CN); 1250ms (C–O–C); 1055ms (C–O–C, ?NCS); 750, 745ms, 685ms (Ar); 1360m, 1120ms, 940w cm $^{-1}$.

(e) *S-Benzyl-derivative* **10** (Alk = $PhCH_2$). A stirred suspension of **9** (0.71 g, 0.002 mole) in EtOH (12 ml)—benzyl chloride (0.28 g, 0.0022 mole) was treated at *ca.* 50° with 3N NaOH (0.73 ml, 0.0022 mole) and stirring at 50–60° continued for 45 min. The temporarily clear liquid soon deposited white solid; addition to ice–water gave a white precipitate (0.56 g, 70%) of **10** (Alk = $PhCH_2$), forming prisms, m.p. 172–176° (from EtOH). (Found: C, 57.8; H, 5.4; N, 18.1. $C_{19}H_{21}N_3O_3S$ requires C, 57.1; H, 5.3; N, 17.5%). IR: 3210m (NH); 2950w (Alk); 1740ms (ester CO); 1695s (amide CO); 1550ms br (NH/CN); 1235s (C–O–C); 1060m (C–O–C; ?NCS); 775–750m t; 695ms (Ar); 1660m, 1520m, 1475ms, 1380w d, 1140m cm $^{-1}$.

10 (Alk = CH_2Ph) (0.8 g, 0.002 mole) dissolved slowly (30 min) on being boiled under reflux in EtOH (15 ml)—3N NaOH (3.3 ml) for 2 h. Half of the solvent was removed in a vacuum; dilution of the residual liquid with H_2O gave a precipitate (0.32 g, 80%) of **15** (Alk = CH_2Ph), m.p. 181–183° (from EtOH–H_2O), identified by its IR spectrum.[1]

Bithiourea derivatives

1 - (5 - *Ethoxycarbonylamino* - 1,3,4 - *thiadiazol* - 2 - *yl*) - 4 - *ethoxycarbonylthiosemicarbazide* **21**. A stirred suspension of **19** (2.1 g, 0.02 mole) in dimethylformamide (50 ml) was treated dropwise at room temp. with ethoxycarbonyl isothiocyanate (5.24 g, 0.04 mole) during 5–6 min. The clear liquid (temp. rise to 40°) was kept at room temp. for 3 h, then stirred into ice-water (400 ml). The precipitate gave, on crystallisation from acetone–EtOH (1:1, *ca.* 250 ml), opaque prisms (4.3–5.0 g, 65–75%) of **21**, m.p. 188–189° (decomp.) (Found: C, 31.7; H, 4.25; N, 24.6; S, 18.8. $C_9H_{14}N_6O_4S_2$ requires C, 32.3; H, 4.2; N, 25.15; S, 19.2%). IR: 3250s d, 3200s (NH); 3000m (Et); 1725s (ester CO); 1245–1210s mult (C–O–C, ?CS); 1050s (C–O–C, ?NCS); 1540, 1530s d, 1485, 1480s d, 915w, 855w, 775m, 720w, 675w cm $^{-1}$. There was a significant difference in the IR spectra of the crude and recrystallised material; cyclisation may be completed only in the crystallisation process. The compound is soluble in 1.5N sodium hydroxide and reprecipitated by acids.

Essentially the same results were obtained when the reaction was performed in dimethyl sulphoxide at room temp. or 100° (thus starting with a *soln* of **19**), but the product was less uniform, apt to be contaminated with sulphur, and yields were lower and variable.

The product **21** was recovered (64%) after treatment with an excess of methyl iodide in boiling sodium methoxide (1 eqult.) for 0.5 h.

1-*Anilino-6-ethoxycarbonylbithiourea* **26**. (a) *Preparation.* This was obtained by the usual procedure from **25** (3.64 g, 0.02 mole) as a white precipitate (m.p. 168–170°; 5.4 g; 85%) which gave lustrous blades of **26**, m.p. 172–174° (from acetone–EtOH) (Found: for a specimen dried at 110°/2 mm: C, 42.7; H, 4.95; N, 21.5; S, 20.1. $C_{11}H_{13}N_3O_2S_2$ requires C, 42.2; H, 4.8; N, 22.4; S, 20.45%). IR: 3310m, 3200s (NH); 3000w, 775s, 685ms (Ar); 1720s (ester CO); 1550–1450s (complex mult) (NH/CN); 1240–1225s br (C–O–C, ?CS); 1050s (C–O–C, ?NCS); 1605s, 1375m, 1190s br, 1095m, 915w, 755s cm $^{-1}$.

(b) *Action of hydrochloric acid.* To a refluxing soln of **26** (3.15 g, 0.01 mole) in EtOH (100 ml), conc. HCl (20 ml) was added dropwise, followed by H_2O (10 ml). The pale yellow liquid was boiled for 1.5 h (evolution of H_2S), then distilled to small volume, giving crystalline (1.45–1.65 g; 70–80%) 2 - ethoxycarbonamido - 5 - mercapto - 1,3,4 - thiadiazole **27**, m.p. 204–206° (from H_2O). (Found: C, 29.35; H, 3.25; N, 20.7. Calc. for $C_5H_7N_3O_3S_2$: C, 29.3; H, 3.4; N, 20.5%), further identified by its IR spectrum.[1]

2 - *Ethoxycarbonamido* - 5 - *methylthio* - 1,3,4 - *thiadiazole* (**28**, X = Me). A soln of **27** (0.21 g, 0.001 mole) in one of Na (0.001 g atom) in MeOH (5 ml) was treated with MeI (2 ml), boiled for 30 min, distilled to half bulk and added to H_2O. The precipitate gave **28** (X = Me) as needles, (0.18 g, 80%), m.p. 158–160° (from $CHCl_3$–light petroleum). (Found: C, 33.0; H, 4.4; N, 18.8; S, 28.9. Calc. for $C_6H_9N_3O_3S_2$: C, 32.9; H, 4.1; N, 19.2; S, 29.2%). IR: 3180w, 3070w (NH); 2920m (Alk); 1725s, 1715m sh (ester CO); 1590–1580s v br (C=N); 1260s, 1070, 1055m d (C–O–C); 2770w, 1330s, 1110w, 800w, 770m, 695w cm $^{-1}$. Lit.[26a] m.p. (for a specimen synthesised by the condensation of EtOOC·C(:NOH)Cl and $NH_2NHCSSMe$) 163–165°.

2 - *Ethoxycarbonamido* - 5 - *acetylthio* - 1,3,4 - *thiadiazole* (**28**; X = Ac), obtained (45%) by the action of acetic anhydride at 100° (2 h) on **27**, formed needles, m.p. 151–152° (from benzene). (Found: C, 34.4; H, 4.5; N, 16.9. $C_7H_9N_3O_3S_2$ requires C, 34.0; H, 3.6; N, 17.0%). IR: 3130m, 3030m (NH); 2940m (Alk); 1755ms, 1720s (ester, acetyl CO); 1610s (C=N); 1230–1210s br, 1085m (C–O–C); 1500m, 1370ms, 1260m, 1015m, 980m, 845m, 770m, 710m, 690w cm $^{-1}$.

2 - *Ethoxycarbonamido* - 5 - *benzoylthio* - 1,3,4 - *thiadiazole* (**28**; X = COPh). A soln of **27** (0.002 mole) in pyridine (8 ml)–triethylamine (2 ml), treated with benzoyl chloride (0.0025 mole), was kept at 50° for 1 h, then added to ice–conc. HCl (10 ml). The solidified gum gave pale yellow needles (0.38 g, 62%) of **28** (X = COPh), m.p. 166–167° (from EtOH). (Found: for a specimen kept at 110°/4 mm for 6 h): C, 46.3; H, 3.85; N, 13.8; S, 21.2. $C_{12}H_{11}N_3O_3S_2$ requires C, 46.6; H, 3.6; N, 13.6; S, 20.7%). IR: 3175w, 3075w (NH); 2925m (Et); 1720s, 1675s (ester, acyl CO); 1580m br (C=N); 1255s (C–O–C); 770m, 690ms (Ar); 2725w, 1455w, 1330m br, 1235m, 1205s, 910s cm $^{-1}$.

3 - *Hydroxy* - 5 - *mercapto* - 2(*H*) - *anilinothiocarbamoyl* - 1,2,4 - *triazole* **29**. (a) *Preparation*. A soln of **26** (3.13 g, 0.01 mole) in 3N NaOH (60 ml) was boiled under reflux for 30 min, cooled, and acidified with conc. HCl. The white precipitate (m.p. 140–142°, 2.15–2.4 g, 80–90%) gave on crystallisation from MeOH (25 ml per g) or from EtOH–H_2O (20 + 0.5 ml per g), platelets (1.60–1.92 g, 60–72%) of **29**, m.p. 142–143°. (Found: C, 40.4; H, 3.65; N, 26.2; S, 24.1. $C_9H_9N_5OS_2$ requires C, 40.45; H, 3.4; N, 26.2; S, 24.0%). IR: 3270s br (NH); 1735vs (CO); 1610m (C=N); 1285s (?CS); 760s, 690s (Ar); 1505s br, 1420–1400m mult., 1360s, 1180m, 980m, 805m, 660s cm $^{-1}$.

The use of 3N Na_2CO_3 also gave **29** in somewhat diminished yields (64%).

(b) *Stability to acid*. **29** (0.002 mole) was recovered (90%) after its boiling soln in EtOH (10 ml) was treated dropwise with conc. HCl (3 ml) and refluxed for 1 h.

(c) *Stability to alkali*. **29** (0.002 mole) was recovered (90 and 70% respectively) (by acidification) after (a) its soln in 3N NaOH (15 ml) was boiled for 1 h, (b) its soln in 0.3N 90% ethanolic NaOH was boiled for 1 h.

(d) *Methylation*. A soln of **29** (0.54 g, 0.002 mole) in 3N NaOH (10 ml, 0.03 mole) was shaken with dimethyl sulphate (1.0 g) The precipitated brown gum solidified very slowly on being occasionally stirred with water. Crystallisation from EtOH (3 ml) gave flat prisms (0.24 g, 38%) of **31**, m.p. 138–139°. (Found: C, 46.75; H, 4.9; N, 22.9; S, 20.6. M$^+$, mass-spectrometrically 309. $C_{12}H_{15}N_5OS_2$ requires: C, 46.6; H, 4.85; N, 22.65; S, 20.7%. M$^+$, 309). IR: 3450m, 3260m (NH), 2920w (Me); 1704vs (CO); 1603s (C=N); 755s, 700ms (Ar); 1525s, 1500m, 1450, 1440s d, 1380s, 1255s, 1130s, 955m, 790m, 655m cm $^{-1}$.

(e) *Action of* p-*nitrobenzyl chloride*. A suspension of **29** (0.54 g, 0.002 mole) in EtOH (25 ml) was treated with *p*-nitrobenzyl chloride (0.77 g, 0.0027 mole); to the stirred suspension at 45°, 3N NaOH (1.5 ml, 0.0045 mole) was added dropwise. The yellow soln was stirred at 50–60° for 30 min, reduced to one-third bulk, diluted with H_2O, and acidified with 3N HCl, when the finely divided precipitate coagulated (0.60 g, pure by IR). It was crystallised with some difficulty from $CHCl_3$–light petroleum, then EtOH–H_2O, giving pale-yellow microcrystalline (0.24 g, 48%) **30** (Alk = *p*-$NO_2C_6H_4CH_2$), identical with authentic material described immediately below.

3 - *Hydroxy* - 5 - p - *nitrobenzylthio* - 1,2,4 - *triazole*. **30** (Alk = *p*-$NO_2C_6H_4CH_2$). A soln of ethoxycarbonylthiosemicarbazide[15] (0.82 g, 0.005 mole) in N-NaOH (12 ml, 0.012 mole) was treated with *p*-nitrobenzyl chloride (1.03 g, 0.006 mole), and the liquid boiled under reflux for 10 min. The brown soln containing a little oil was cooled and acidified with 3N HCl; the resulting precipitate gave, after crystallisation (see above), pale-yellow **30** (Alk = *p*-$NO_2C_6H_4CH_2$), m.p. 210–212° (1.0 g, 80%). (Found: C, 43.0; H, 3.5; N, 21.4; S, 12.2. $C_9H_8N_4O_3S$ requires: C, 42.9; H, 3.2; N, 22.2; S, 12.7%). IR: 3440ms br, 3180ms, 3080ms (NH); 2850m (Alk); 1720vs br (amide CO); 1605m (C=N); 1525s, 1350s (NO_2); 780m, 705ms (Ar); 1110m, 980m, 865m cm $^{-1}$. The method is that given by Fromm and Nehring[15] for preparing the 5-benzylthio-analogue.

1-*Benzylideneamino*-6-*ethoxycarbonylbithiourea* **23** was obtained from **22** (3.88 g, 0.02 mole) by the general procedure, as a finely divided precipitate. Crystallisation from acetone–EtOH (*ca.* 25 and 5 ml per g) slowly gave massive prismatic needles (4.85–5.5 g, 75–85%) of **23**, m.p. 191–192°. (Found: C, 44.55; H, 4.8; N, 21.2; S, 19.7. $C_{12}H_{15}N_5O_2S_2$ requires; C, 44.3; H, 4.6; N, 21.5; S, 19.7%). IR: 3150s (NH); 3000ms, 770ms, 690ms (Ar); 1720s (ester CO); 1535s br (NH/CN); 1220s br (C–O–C, ?CS); 1040ms (C–O–C, ?NCS); 1480–1460s t, 1380m, 1190ms, 755ms, 715w cm $^{-1}$.

Dibenzyl derivative **24**. The bithiourea **23** (1.0 g, 0.003 mole), suspended in stirred EtOH (15 ml)–benzyl chloride (1.0 g, 0.008 mole) at 40°, dissolved on addition of 3N NaOH (2.7 ml, 0.008 mole), but white solid quickly reappeared from the bright yellow soln. After 10 mins' continued stirring at 40°, the whole was added to H_2O (100 ml). The emulsion deposited a pale-yellow precipitate which gave prismatic columns (0.91 g; 60%) of **24**, m.p. 153–155° (from acetone–EtOH). (Found: C, 62.3; H, 5.2; N, 13.8; S, 12.8. $C_{26}H_{27}N_5O_2S_2$ requires: C, 61.8; H, 5.35; N, 13.9; S, 12.7%). IR: 3350ms, 3300ms (NH); 2950w, 2900w (Alk); 1735s (ester CO); 1560vs (NH/CN); 1200s (C–O–C); 1070s (C–O–C, ?NCS); 755m, 690ms (Ar); 1460s, 1395w, 710s cm $^{-1}$.

REFERENCES

[1] F. Kurzer and J. L. Secker, *Tetrahedron* **33**, 1999 (1977).
[2] R. Esmail and F. Kurzer, *Synthesis* 301 (1975).
[3] K. M. Doyle and F. Kurzer, *Tetrahedron* **32**, 2347 (1976).
[4] F. Kurzer and M. Wilkinson, *Chem. Rev.* **70**, 111 (1970).
[5] P. C. Guha and S. C. De, *J. Indian Chem. Soc.* **1**, 141 (1924).
[6] G. Pellizzari and F. Roncagliolo, *Gazz. chim. Ital.* **37 I**, 434 (1907); L. F. Audrieth and E. B. Mohr, *Inorg. Synth.* **4**, 36 (1953).
[7] E. S. Scott and L. F. Audrieth, *J. Org. Chem.* **19**, 742 (1954).
[8] A. W. Lutz, *J. Org. Chem.* **29**, 1174 (1964); H. Beyer and C. F. Kröger, *Ann.* **637**, 126 (1960).
[9] F. Kurzer and M. Wilkinson, *J. Chem. Soc.* (C) 19 (1970).
[10] P. C. Guha and S. C. De, *J. Chem. Soc.* **125**, 1215 (1924); A. Dornow and H. Paucksch, *Chem. Ber.* **99**, 81, 85 (1966); N. P. Buu-Hoi, T. B. Loc and N. D. Xuong, *Bull. Soc. Chim. Fr.* 694 (1955); R. S. McElhinney, *J. Chem. Soc.* (C), 1256 (1966).
[11] F. Kurzer, *J. Chem. Soc.* (C), 2927, 2932 (1971).
[12] F. Kurzer and M. Wilkinson, *J. Chem. Soc.* (C), 2099 (1968).
[13] F. Kurzer and M. Wilkinson, *J. Chem. Soc.* (C), 26 (1970).
[14] F. Arndt, E. Milde and F. Tschenscher, *Ber. Dtsch. Chem. Ges.* **55**, 341, 347 (1922); P. C. Guha and P. C. Sen, *J. Indian Chem. Soc.* **4**, 43, 50 (1927).
[15] E. Fromm and E. Nehring, *Ber. Dtsch. Chem. Ges.* **56**, 1370 (1923).
[16] G. Cipens, R. Bokalders and V. Grinstein, *Khim. Geterotsikl. Soedin.* 110 (1966) [*Chem. Abs.* **65**, 705 (1966)].
[17] R. Esmail and F. Kurzer, *J. Chem. Soc. Perkin I* 1781 (1975); and preceding papers in this series.
[18] J. Goerdeler and J. Gnad, *Chem. Ber.* **99**, 1618 (1966); J. Goerdeler, *Quart. Rep. Sulphur Chem.* **5**, 169 (1971).
[19] F. Kurzer, *J. Chem. Soc.* (C), 1805, 1813 (1970).
[20] F. Kurzer and D. R. Hanks, *J. Chem. Soc.* (C), 746 (1967).
[21] *Beilstein's Handbuch Org. Chem.* 4th Edn, Vol. 3, p. 116, 196 and Supplements.
[22] F. Kurzer, *Chem. Indust. (London)* 1333 (1961); K. M. Doyle and F. Kurzer, *Ibid.* 803 (1974).
[23] F. Arndt and E. Milde, *Ber. Dtsch. Chem. Ges.* **54**, 2089 (1921); F. Arndt and F. Bielich, *Ibid.* **56**, 2276 (1923).
[24] V. Petrow, O. Stevenson, A. J. Thomas and A. M. Wild, *J. Chem. Soc.* 1508 (1958).
[25] L. E. A. Godfrey and F. Kurzer, *J. Chem. Soc.* 3561 (1962).
[26] F. Kurzer and K. Douraghi-Zadeh, *J. Chem. Soc.* 3912 (1965).
[27] M. Giua and M. Giua, *Gazz. Chim. Ital.* **51 I**, 313 (1921).
[28] Th. Curtius and R. Jay, *J. Prakt. Chem.* **39**, 27, 44 (1899).
[29] A. Dornow and K. Fischer, *Chem. Ber.* **99**, 72 (1966).