Tetrahedron, Vol. 37, pp. 1429 to 1435, 1981
Printed in Great Britain.

0040-4020/81/071429-07$02.00/0

THE SYNTHESIS AND CYCLISATION OF THIOACYLATED DIAMINOGUANIDINES

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(*Received in UK 5 August 1980*)

Abstract—The thiobenzoylation of 1,2-diaminoguanidine yields 1-amino-2-thioaroylamidoguanidines which are isolable as their stable hydrazones. They are unaffected by alkalis, but are cyclised by mineral acids, with loss of ammonia, to hydrazones of 2-aryl-5-hydrazino-1,3,4-thiadiazoles, or with elimination of hydrazine, to the appropriate 2-amino-5-aryl-1,3,4-thiadiazoles. The action of acetic anhydride effects the same ring-closures, yielding the corresponding acetylated products. 1,2-Diamino-3-phenylguanidine undergoes a comparable series of reactions.

1,2-Diaminoguanidine, in common with aminoguanidine[1] and related structures incorporating a hydrazine-moiety, undergoes addition with a variety of heterocumulenes[2] (including carbodi-imides,[3] aryl iso(thio)cyanates[3] and aroyl isothiocyanates[4]). The resulting linear adducts are readily cyclisable to heterocyclic systems, especially 1,3,4-thiadiazoles and 1,2,4-triazoles. In an extension of this general synthesis, comparable thioacylated aminoguanidines,[5] (thio)semicarbazides,[6] (thio)carbonohydrazides,[7] and amidrazones[8] are similarly ring-closed. The production and cyclisation of thioacylated diaminoguanidines (**5–8**), now described, supplements and concludes our account of this group of heterocyclic syntheses.

Amongst established thioacylating agents, thioaroylthioacetic acids (carboxymethyl dithioates, **2**) are particularly suitable for the thiobenzoylation of amino acids and hydrazines.[9,10] Unlike other reagents[11] used for this purpose, they are readily accessible stable compounds that effect the desired reaction under mild conditions[9] and were employed successfully in the present work.

The monothioacylation of 1,2-diaminoguanidine (**1**) by carboxymethyl dithioates (**2**, Ar = Ph, *p*-ClC_6H_4) in an excess of aqueous alkali produced the thioaroyl-adducts (**3**, **4**) which were rather unstable but were isolable as the stable ketonic derivatives. The isopropylidene- (**5**, **6**) and benzylidene-compounds (**7**), and the hydrazone derived from acetylacetone (**8**) were thus accessible in very good overall yields.

The use of an excess of the thioacylating agent (**2**) under the standard conditions did not afford the symmetrical dithiobenzoyl-derivatives [$(ArCS{\cdot}NHNH)_2$ C:NH], but gave, apart from much resinous material, small yields of 2,5-diphenyl-1,3,4-thiadiazole (**11**, Ar = Ph). As in established precedents,[3,4] the reaction is explicable by visualising the attack of 2 moles of the reagent (**2**) at adjacent nitrogens of the same hydrazino-group, followed by hydrolysis and cyclisation of the unsymmetrical intermediate (**9**). The thiobenzoyl-residue (in **3**) evidently activates the adjacent NH-group making it more receptive than the remaining free hydrazino-group for further thioacylation.

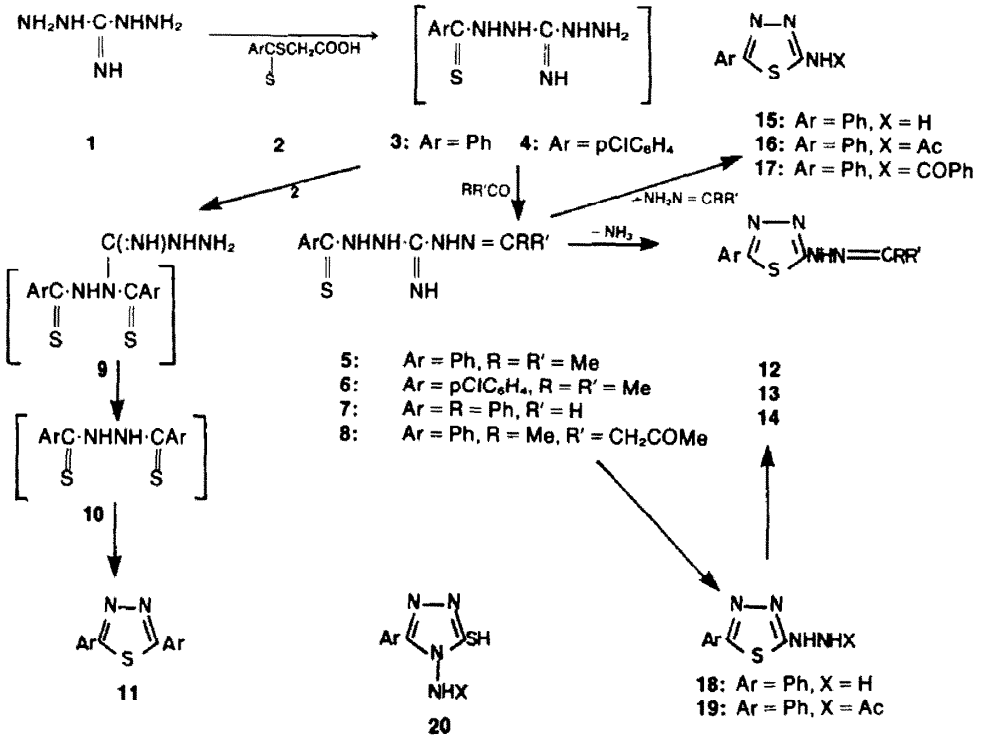
The substituted thiobenzoyl-diaminoguanidines(**5–8**) retained the predominating basic character of their parent guanidine structure and readily formed picrates. Their ability to form S-thioethers was shown in selected examples (Experimental). Their IR spectra included the appropriate peaks attributable to their azine (1600–1660 cm^{-1}), hydrazino- (3000–3300 cm^{-1}), and imino-components (3410–3460 cm^{-1}). The possible assignment of a strong absorption appearing in all the relevant spectra in the 1230–1245 cm^{-1} region to the thiocarbonyl-group is subject to the recognised uncertainties[12] attending this interpretation.

The cyclisation of the linear thioamido-compounds (**5–8**) in acid media produced the appropriate substituted 1,3,4-thiadiazoles. Thus, brief treatment of 1-isopropylideneamino- (**5**, **6**) or 1-benzylideneamino-2-thiobenzamidoguanidines (**7**) with mineral acids gave, by loss of ammonia, the hydrazones (**12–14**) of 2-hydrazino-5-aryl-1,3,4-thiadiazoles. The 2-amino-analogues (e.g. **15**) arose as by-products by the alternative elimination of hydrazine. The formulation of the products was confirmed by their identity with authentic material (**12**, **15**) (see below); their possible 1,2,4-triazole structures, to which 2-amino-[13] and 2-hydrazino-1,3,4-thiadiazoles[14,15] may isomerise (e.g. **18** → **20**) are thus eliminated.

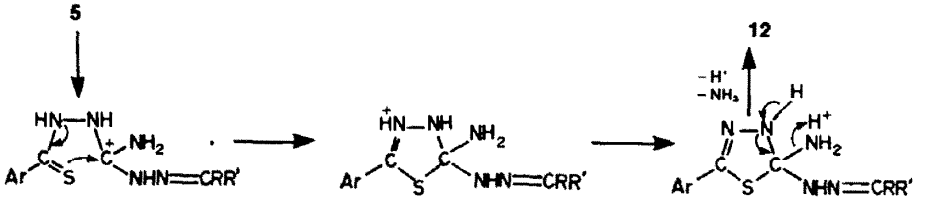
The use of acetic anhydride as cyclising agent gave essentially the same results, affording the thiadiazoles as the acetyl-derivatives. However, loss of hydrazine appeared to occur preferentially, so that the 2-amino- (**16**, Ar = Ph, *p*-ClC_6H_4) rather than the 2-hydrazino-1,3,4-thiadiazoles (**19**) were the main products. Benzoylation of the linear benzylidene-derivative (**7**) similarly gave 2-benzamido-5-phenyl-1,3,4-thiadiazole (**17**), but the isopropylidene-analogue (**5**) gave chiefly 2,5-diphenyl-1,3,4-thiadiazole (**11**), undoubtedly by a sequence of stages analogous to those shown in Scheme 1 (**9** → **11**). The established course of the acidic cyclisation excludes the possible alternative formulation of the reactants (**5–8**) as the branched isomers (e.g. $NH_2(ArCS)N.C(:NH)NHN:CRR'$).

The mechanism of the ring-closure may involve the initial protonation of the imino-group of the reactants (**5–7**): a redistribution of the bonds and charge (see Scheme 2), followed by elimination of either the amino- (shown) or hydrazono-group (not shown), results in the observed products.

Substituted thiosemicarbazides of type **A**, as well as the structurally comparable thioacyl-compounds (**E**) yield 1,3,4-thiadiazoles on acid cyclisation, but vary in their behaviour towards alkalis: the former are ring-closed to 1,2,4-triazoles (**B**, **C**, **D**),[1,16] but the latter[5,7,8] remain generally unaffected. Their cyclisation corresponding to the processes **A** → **C**, **D** is structurally not feasible; that occurring with loss of hydrogen sulphide



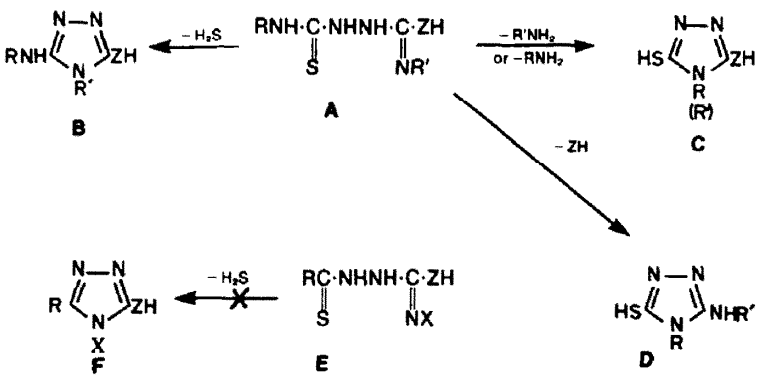
Scheme 1.



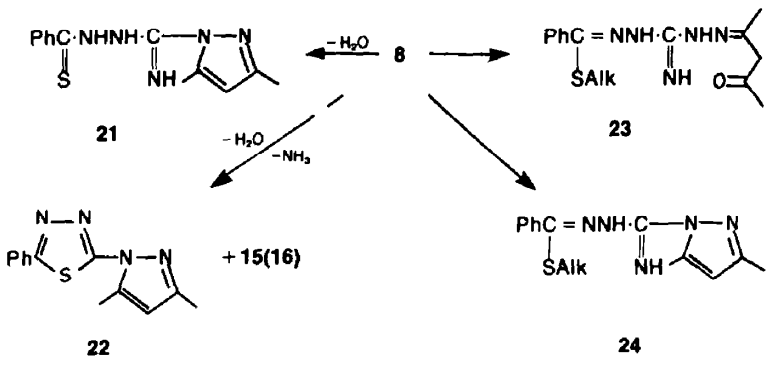
Scheme 2.

(E→F) appears to be inhibited by the stabilisation of their thioacyl-group by alkali salt formation. The thioacyl-diaminoguanidines, as represented by **5**, conformed to this general pattern, being substantially recovered after treatment with aqueous sodium hydroxide under fairly vigorous conditions.

The hydrazone (**8**) derived from acetylacetone (2,4-dioxopentane) incorporates structural moieties that are independently cyclisable to a 1,3,4-thiadiazole and pyrazole ring: under appropriate conditions, these reactions occurred either separately or simultaneously. The action of mineral acid or acetic anhydride (on **8**) gave 2-amino-5-phenyl-1,3,4-thiadiazole (**15**) or its acetyl-derivative (**16**) as main-products, together with the fully cyclised 2-phenyl-5-(3',5'-dimethylpyrazol-1' (H)-yl)-1,3,4-thiadiazole (**22**). The action of alkali resulted in



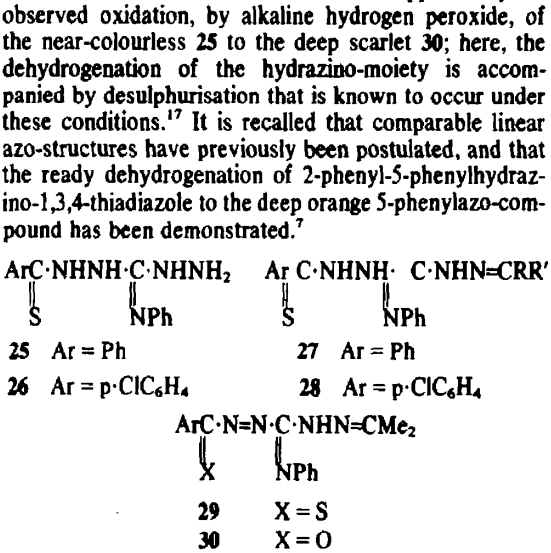
Scheme 3.



Scheme 4.

selective cyclodehydration to 1-thiobenzoyl-(3',5'-dimethylpyrazol-1' (H)-yl)amidrazone (**21**) in fair yield. The same reaction occurred, either wholly or partially, in the S-alkylation of **8** in alkaline media: the action of methyl iodide in sodium methoxide gave the linear S-methylthioether (**23**, Alk = Me) and its pyrazolyl-derivative (**24**, Alk = Me) side by side; S-benzylation in aqueous alkali produced the ring-closed product (**24**, Alk = CH_2Ph) exclusively. Cyclodehydration appears to occur under electron impact also, since the mass spectrum (of **8**) contains no peaks beyond the one corresponding to a molecular ion arising from **8** by loss of 18 mass units (*m/e*, 273).

The foregoing reactions of 1,2-diaminoguanidine (**1**) were also displayed, with minor variations, by its 3-phenyl-analogue. The thiobenzoyl-derivatives (**25, 26**) were sufficiently stable to be isolable, with care, as the free hydrazines. Their production, and that of their hydrazones (**27, 28**) was attended by the formation of deep scarlet to purple by-products. Their composition (specifically that of **29**, Ar = Ph, and of *p*-$ClC_6H_4CS.N{=}N.C(:NPh)NHNH_2$), and their intense colour were indicative of the presence of a system of conjugated unsaturated centres. Accordingly, they are represented as the dehydrogenated linear structures (**29**), and are thought to arise from their precursors by air-oxidation. The pale-yellow thiobenzoylated diaminophenylguanidines and their cyclisation products were in fact almost invariably covered with a pink to red coating attributable to this cause. The formulation is further supported by the observed oxidation, by alkaline hydrogen peroxide, of the near-colourless **25** to the deep scarlet **30**; here, the dehydrogenation of the hydrazino-moiety is accompanied by desulphurisation that is known to occur under these conditions.[17] It is recalled that comparable linear azo-structures have previously been postulated, and that the ready dehydrogenation of 2-phenyl-5-phenylhydrazino-1,3,4-thiadiazole to the deep orange 5-phenylazo-compound has been demonstrated.[7]



The acidic cyclisation of the thiobenzoyl-compounds (**25–28**), proceeding with loss of aniline, gave the same products as the parent bases (**5–8**), but occurred apparently even more readily: ring-closure took place to a variable degree in the thiobenzoylation stage itself, and became predominant when the presence of traces of acid, or delay in the working up promoted it.

Details concerning the authentic 1,3,4-thiadiazoles required for comparison and identification purposes are briefly recorded in the Experimental Part. The key-compound, 2-hydrazino-5-phenyl-1,3,4-thiadiazole (**18**) is accessible, albeit in poor yield, by four distinct methods:[18] the material, now prepared by Sandström's synthesis,[18b] was distinguished from the isomeric triazole (**20**, X = H)[19] by its physical properties, and was characterised by its conversion into known and new derivatives. It seems noteworthy that attempts to prepare its monoacetyl-derivative (and that of **20**) for comparison with the cyclisation product **19** invariably gave the triacetyl-derivative. The condensation of **18** with acetylacetone furnished the authentic pyrazolyl-thiadiazole (**22**).

EXPERIMENTAL

General. M.ps are uncorrected. The IR spectra were determined on a Unicam SP 200 instrument usig KBr discs. Except for compounds **5**, **27** (R = R' = Me), **12**, and **18** unassigned peaks are not listed. The following abbreviations refer to the relative intensities of the absorptions: s, strong; m, medium; w, weak; d, doublet; br, broad. Light petroleum had b.p. 60–80°.

1-Isopropylideneamino-2-thiobenzamidoguanidine (**5**)

A stirred soln of 1,2-diaminoguanidine hydriodide[3,20] (8.68 g, 0.04 mole) in 3N NaOH (40 ml, 0.12 mole)–H_2O (120 ml) was treated at room temp during 8–10 min with 2[21] (8.48 g, 0.04 mole) dissolved in N NaOH (80 ml, 0.08 mole). The turbid liquid was treated with acetone (120 ml) and acidified at 0° (ice) with 2N AcOH (75 ml, 0.15 mole). The copious pale-yellow ppt was collected at 0°, washed with H_2O and finally with a little EtOH. The resulting powder (6.8–7.6 g, 68–76%; pure according to tlc and IR) gave, on crystallisation from EtOH (30 ml per g, recovery 70%) pale-yellow opaque prisms of **5**, m.p. 179–182° (dec). (Found: C, 52.9; H, 5.9; N, 28.45; S, 12.6. $C_{11}H_{15}N_5S$ requires: C, 53.0; H, 6.0; N, 28.1; S, 12.85%). IR: 3420s, 3300vs, 3180vs (NH), 3010vs (arom. CH), 1660–1610vs mult (C=N), 1240s (?CS), 765s, 695vs (Ph), 1490, 1475sd, 1370m, 1315mW, 1130m, 1070m, 1035s, 935s cm^{-1}. The material is soluble in warm N NaOH and is reprecipitated by dilute acetic acid.

The use of 2 molar proportions of **2** in this procedure (scale: 0.005 molar) gave, as crude product, a brown resin which slowly yielded, on crystallisation from EtOH, faintly yellow prisms (0.57 g, 48%) of **11** (Ar = Ph), identified by mixed m.p. 138–140° and IR.[6]

1-Isopropylideneamino-2-thiobenzamidoguanidine (**5**): *Derivatives*

(a) The *picrate* separated slowly from a cold soln of the components (0.001 mole each) in EtOH (10 ml)–acetone (2 ml) as opaque lustrous prisms (40%), m.p. 213–215° (dec, shrinking from 180°). (Found: C, 43.9; H, 3.8; N, 21.6. $C_{11}H_{15}N_5S.C_6H_3N_3O_7.C_2H_5OH$ requires: C, 43.5; H, 4.6; N, 21.4%). Attempted crystallisation of the salt from EtOH causes partial decomposition.

(b) *S-Methylthioether.* A soln of **5** (2.5 g, 0.01 mole) in warm MeOH (30 ml) was treated with MeI (14.2 g, 0.1 mole), the yellow liquid set aside at room temp for 1 hr, evaporated to half volume under reduced pressure at room temp, and gradually diluted with an equal volume of ether. The separated solid (64%) gave clusters of pale-yellow prisms of the *S-methyl-thioether* HI, m.p. 178–180° (dec.) (from EtOH) (Found: C, 37.1; H, 4.5; N, 18.0; S, 8.8; I, 30.5. $C_{12}H_{17}N_5S.HI$ requires: C, 36.8; H, 4.6; N, 17.9; S, 8.2; I, 32.5%). IR: 3370m, 3180s, 3100m (NH), 1660s, 1605vs br (C=N), 770s 730ms, 695s (Ph) cm^{-1}.

Reactions

(c) *Stability to alkali.* The reactant **5** (0.5 g) was recovered (75%) when its soln in 2N NaOH (25 ml) was refluxed for 30 min, cooled, and acidified with HCl.

(d) *Action of hydrochloric acid.* A soln of **5** (1.25 g, 0.005 mole) in 1.5 N HCl (40 ml)–acetone (10 ml) was boiled under reflux for 15 min, allowed to cool and neutralised with conc ammonia. The resulting ppt (filtrate:F) was **12**, m.p. 235–237° (dec, sintering from 220°) (from acetone–EtOH) (0.72 g, 62%), identified by IR (see below). (Found: C, 56.8; H, 5.3; N, 23.8. Calc. for $C_{11}H_{12}N_4S$: C, 56.9; H, 5.2; N, 24.1%). Filtrate F, treated with 0.05M picric acid (50 ml, 0.0025 mole) gave a ppt of **15** picrate, m.p. 254–256° (from EtOH). Lit.[5] m.p. 256–258° (0.24 g, 12%). (Found: C, 41.1; H, 2.7. Calc. for $C_8H_7N_3S$. $C_6H_3N_3O_7$: C, 41.4; H, 2.5%).

(e) *Action of sulphuric acid.* Finely powdered **5** (1.25 g, 0.005 mole) dissolved slowly in conc H_2SO_4 (12 ml) at room temp on stirring. After 1 hr, the brown liquid was added to ice (100 g); the resulting pale-yellow ppt (58%) (filtrate:F) was **12**, m.p. 235–237° (dec, sintering from 200°), identified by IR (see below). Addition of 0.05M picric acid (0.005 mole) to filtrate F gave **12** picrate, as minute plates, mixed m.p. (see below) 180–182° (dec) (from EtOH).

(f) *Action of acetic anhydride.* A soln of **5** (0.005 mole) in Ac_2O (15 ml) was boiled under reflux for 1 hr. The solid separating on cooling was collected at 0° (filtrate:F) and identified as **16** (0.26 g, 24%) by mixed m.p. 274–275°[5,22] (from EtOH) (Found: C, 54.2; H, 4.1; N, 19.6. Calc. for $C_{10}H_9N_3OS$: C, 54.8; H, 4.1; N, 19.2%). IR: 3170m (NH), 3040m (arom CH), 1690vs (CO), 1560vs (C=N), 1440s (C–Me), 1315vs (MeCO), 765s, 685vs (Ph) cm^{-1}.

Addition of filtrate F to H_2O precipitated a discoloured solid which gave minute needles of **19**, m.p. 194–196° (0.26 g, 22%) (from EtOH). (Found: C, 51.6; H, 4.3; N, 24.1. $C_{10}H_{10}N_4OS$ requires: C, 51.3; H, 4.3; N, 23.9%). IR: 3310s, 3210s (NH), 1660, 1640vs (CO, C=N), 1450vs (C–Me), 1300vs (MeCO), 760vs, 685vs, 670s (Ph) cm^{-1}.

(g) *Action of benzoyl chloride.* A soln of **5** (0.005 mole) in pyridine (25 ml) was treated with benzoyl chloride (2.1 g, 0.015 mole), set aside for 4 hr, then stirred into ice-water containing conc HCl (25 ml). The ppt gave microcrystalline **17**, m.p. 229–230° (from EtOH) (0.34 g, 24%). (Found: C, 63.4; H, 4.3; N, 15.1; S, 12.0. Calc. for $C_{15}H_{11}N_3OS$: C, 64.1; H, 3.9; N, 14.9; S, 11.4%). IR: 3150–3100m (NH), 1670s (CO), 1540s (C=N), 760m, 708s, 685vs (Ph), 1315vs cm^{-1}. Lit. m.p.[23] 235°. The ethanolic filtrates therefrom deposited **11** (Ar = Ph) (0.6 g, 50%), identified by IR.[8]

1-p-Chlorothiobenzamido-2-isopropylideneaminoguanidine **6**

This was prepared as **5** (see above) by the use of *p*-chlorothiobenzoylthioacetic acid. Crystallisation from EtOH (with addition of acetone) gave yellow needles (64%) of **6**, m.p. 175–179° (dec, darkening from 162°) (Found: C, 46.4; H, 4.9; Cl, 12.4; N, 24.9; S, 11.0. $C_{11}H_{14}ClN_5S$ requires: C, 46.6; H, 4.9; Cl, 12.5; N, 24.7; S, 11.3%). IR: 3420s, 3320s, 3190s (NH), 3050s (CH arom), 1650–1615vs vbr mult (C=N), 1245, 1235ms d(?CS), 845s, 715mw (1,4-disub. aryl) cm^{-1}.

The *picrate* (25%) had m.p. 220–225° (dec). (Found: C, 40.5; H, 3.7; N, 20.3. $C_{11}H_{14}ClN_5S.C_6H_3N_3O_7.C_2H_5OH$ requires: C, 40.8; H, 4.1; N, 20.05%).

Reactions

(a) *Action of hydrochloric acid.* A soln of **6** (0.85 g, 0.003 mole) in EtOH (30 ml)–conc HCl (5 ml) was boiled under reflux for 15 min, the green liquid reduced to half bulk in a vacuum, and stirred into ice-water. The precipitate (pure by tlc and IR) (0.51 g, 64%) gave **13** as pale-yellow plates, m.p. 223–225° (dec, sintering from 200°) (from a large volume of EtOH containing a little acetone). (Found: C, 49.3, H, 4.4; Cl, 13.5; N, 20.8. $C_{11}H_{11}ClN_4S$ requires: C, 49.5; H, 4.1; Cl, 13.3; N, 21.0%). IR: 3440ms, 3140ms (NH), 3040ms (arom CH), 2920s (CH), 1560vs (C=N), 840s, 725ms (1,4-disub.aryl) cm^{-1}.

The *picrate* (72%) formed felted needles, m.p. 180–182° (dec.) (Found: C, 42.0; H, 3.1; N, 20.2. $C_{11}H_{11}ClN_4S$. $C_6H_3N_3O_7$ requires: C, 41.2; H, 2.8; N, 19.8%).

(b) *Action of acetic anhydride.* Performed as described for **5** in section (f), this gave (36%) ivory silky needles of *2-acetamido-5-p-chlorophenyl-1,3,4-thiadiazole*, m.p. 322–324° (dec) (from EtOH; 150 ml per g). (Found; C, 47.3; H, 3.4; Cl, 13.85; N, 16.2. $C_{10}H_8ClN_3OS$ requires: C, 47.3; H, 3.2; Cl, 14.0; N, 16.6%). IR: 3160m (NH), 3010m (CH arom), 2930–2850ms (CH), 1690vs (CO), 1565vs br (C=N), 1445ms (C–Me), 1320vs (COMe), 835s (1,4-disub.aryl) cm^{-1}.

1-Benzylideneamino-2-thiobenzamidoguanidine **7**

The turbid alkaline soln of **3** (obtained *in situ* on a 0.02 molar scale as described in the preparation of **(5)** was treated with benzaldehyde (2.54 g, 0.024 mole) during 5 min with shaking, which was then continued for 15 min. The orange liquid was decanted from a few droplets of resin (R) and neutralised at 0° (ice) with 2N AcOH (40 ml). The pale yellow ppt was collected, washed well with H_2O and drained, then immediately added to EtOH (*ca* 50 ml at 35°) and quickly hand-stirred until dissolved. Dropwise addition of H_2O (1–2 ml) and scratching or seeding induced crystallisation, which was completed at 0°, producing pale-yellow aggregates (0.42–0.54 g, 28–36%) of microcrystalline **7**, m.p. 159–160°. (Found: C, 59.8; H, 5.1; N, 23.1, S, 10.6. $C_{15}H_{15}N_5S$ requires: C, 60.6; H, 5.05; N, 23.6; S, 10.8%). IR: 3460ms (NH); 3080w (CH arom), 1660vs, 1625vs br (C=N), 1235m (? CS), 760m, 690s (Ph) cm^{-1}. The crystallisation is wasteful. For synthetic purposes, the freshly precipitated air-dried material is suitable (which is pure by IR, though heavily hydrated, m.p. 70° (after shrinking at 55°).

The (hydrated) *picrate* separated from a soln of the components (0.001 mole) in cold EtOH (15 ml), m.p. 214–216° (dec) (35%). (Found: C, 46.25; H, 3.6; N, 19.6. $C_{15}H_{15}N_5S.C_6H_3N_3O_7.H_2O$ requires C, 46.3; H, 3.7; N, 20.6%).

Resin R was dissolved in chloroform–light petroleum; crystals were slowly deposited (0.62 g, 12%), which gave refractive yellow prisms of 1,2-di(benzylideneamino)guanidine, mixed m.p.[3,24] 179–181°. IR: 3480m, 3390m (NH), 3030w (CH arom), 1630vs (C=N), 755s, 695s (Ph), 1590vs, 1435s cm^{-1}.

Reactions

(a) *Action of hydrochloric acid.* The usual method (procedure (a) for **6**) gave yellow prisms (56%) of **14**, identified by mixed m.p. 240–242° and IR (see below). (Found: C, 64.1; H. 4.3; N, 20.15. Calc. for $C_{15}H_{12}N_4S$: C, 64.3; H, 4.3; N, 20.0%).

(b) *Action of acetic anhydride.* A soln of **7** (1.48 g, 0.005 mole) in Ac_2O (15 ml) was refluxed for 1.5 hr, then set aside at 0°. The separated brown crystals (Filtrate: F) gave **16** (0.46 g, 42%), identified by mixed m.p.[5,22] 274–276° (from EtOH), and IR (see f, above). Addition of filtrate F to H_2O precipitated a resin which gave needles (0.45 g, 28%) of the *monoacetyl derivative* of **14**, m.p. 140–142° (from EtOH). (Found: C, 62.8; H, 4.5; N, 17.4; S, 10.0. $C_{17}H_{14}N_4OS$ requires: C, 63.35; H, 4.35; N, 17.4; S. 9.9%).

IR: 1690vs br (CO, C=N), 1445vs (C–Me), 770, 760vs d, 695, 685s d, 660s (Ph) cm^{-1}. The same monoacetyl derivative was obtained (75%) when authentic **14** (see below) was similarly acetylated.

(c) *Action of benzoyl chloride.* Treatment of **7** as described for **5** (section g) gave (56%) **17**, identified as above.

2,4-Dioxopentane 1-amino-2-thiobenzamidoguanidine monohydrazone **8**

The turbid alkaline soln of **3** (obtained *in situ*; 0.002 molar scale, as described in the preparation of **5**) was neutralised with 2N AcOH (*ca* 24 ml) and the resulting yellow ppt redissolved *in situ* by the addition with rapid stirring, of EtOH (60 ml). Treatment with acetylacetone (30 g, 0.3 mole), and storage of the brown liquid at 0° deposited a crystalline solid (m.p. 154–158°, 2.6–3.2 g, 45–65%) (Filtrate: F) which gave faintly yellow platelets of **8**, m.p. 180–182°. (Found: C, 53.7; H, 6.2; N, 24.0; S, 11.0. $C_{13}H_{17}N_5OS$ requires: C, 53.6; H, 5.8; N, 24.0; S, 11.0%). IR: 3380s, 3290s, 3120vs (NH); 1640–1590vs vbr mult (CO, C=N), 1240ms (?CS), 775m, 735m, 700m (Ph), 1485s cm^{-1}. A M.Wt. determination in the mass-spectrometer gave *m/e* 273, corresponding to the cyclodehydrated product **21**, apparently formed under electron impact. In some but not all experiments, filtrate F (and the crystallisation filtrates) deposited needles (up to 0.25 g, 10%) of **22** (from EtOH), identical (mixed m.p., IR) with authentic material (see below).

Reactions

(a) *Action of alkali.* The orange soln obtained on treating a suspension of **8** (0.58 g, 0.002 mole) in EtOH (18 ml) with 3N NaOH (2 ml, 0.006 mole) was kept at 50° for 2 hr, then at room temp for 5 hr. It was reduced to half volume, diluted with ice water (80 ml), and acidified with concentrated HCl. The ppt gave opaque buff microcrystalline (0.30 g, 54%) *1-thiobenzoyl-[3',5'-dimethylpyrazol-1'(H)-yl]amidrazone* (**21**), m.p. 170–172° (darkening from 105°) (from EtOH–H_2O, 1:1, 10 ml). (Found: C, 57.6; H, 5.5; N, 24.2; S, 11.3. $C_{13}H_{15}N_5S$ requires: C, 57.1; H, 5.5; N, 25.6; S, 11.7%). IR: 3400m (NH), 2940w (CH), 1645–1635vs br (C=N/NH), 1260m (? CS), 770ms, 740m, 695ms (Ph) cm^{-1}.

(b) *Action of hydrochloric acid.* A soln of **8** (0.58 g, 0.002 mole) in EtOH (25 ml)–3N HCl (2 ml) was boiled under reflux for 30 min, reduced to half volume under reduced pressure and diluted with H_2O (20 ml). The pale brown ppt (0.04–0.06 g, 8–12%) was **22**, identical with authentic material (see below). The filtrate therefrom was neutralised with 3N ammonia and gave a ppt (0.27 g, 75%) of **15**, m.p. 224–225° (from EtOH), identical with authentic material.[5,22]

(c) *Action of acetic anhydride.* A soln of **8** (0.58 g, 0.002 mole) in Ac_2O (12 ml) was boiled under reflux for 2 hr, then stored at 0°. The separated needles (0.28 g, 65%) were **16**, m.p. 276–278° (from EtOH), identical with authentic material.[5,22] The filtrate therefrom was stirred into H_2O (50 ml); the soft brown resin solidified slowly and gave, on dissolution in EtOH (5 ml), needles (8%) of **22**, identical with authentic material material (see below).

(d) *S-Methylation.* A soln of **8** (2.9 g, 0.01 mole) in MeOH (120 ml) containing Na (0.23 g, 0.01 g-atom)–MeI (28 g, 0.2 mole) was boiled under reflux for 30 min, and reduced to quarter volume under reduced pressure. The resulting solid gave pale-yellow microplatelets (1.40 g, 46%) of the *S-methylthioether* **23** (Alk = Me), m.p. 96–98°. (Found: C, 55.0; H, 5.8; N, 22.1; S, 10.9. M, mass-spectrometrically, 305. $C_{14}H_{19}N_5OS$ requires C, 55.1; H, 6.2; N, 22.95; S, 10.5%. M, 305). IR: 3430s, 3330s (NH), 1645vs, 1620s (CO, C=N), 1330m (? S–Me), 745mw, 725mw, 695mw (Ph) cm^{-1}..

The filtrates slowly deposited yellow platelets (1.20 g, 42%) of the *S-methylthioether* **24** (Alk = Me), m.p. 114–116°. (Found: C, 58.0; H, 6.6; N, 24.4; S, 11.5. $C_{14}H_{17}N_5S$ requires: C, 58.5; H, 5.9; N, 24.4; S, 11.15%). IR:3430s, 3320s, (NH), 3060w(CH *arom*), 2920w (*CH*), 1645*vs br* (*C=N*), 1325*s* (*?S–Me*), 745*ms*, 700ms (Ph), and 1565s, 1445s cm^{-1}.

(e) *S-Benzylation.* The hydrazone **8** (0.58 g, 0.002 mole) dissolved when its suspension in EtOH (20 ml)–benzyl chloride (0.28 g, 0.0022 mole) was treated at 60° with 3N NaOH (0.67 ml, 0.002 mole). The brown liquid which deposited NaCl rapidly, was stirred at 60° for 1 hr, then added to ice-water. The solidified resinous ppt gave needles (0.54 g, 75%) of the *S-benzylthioether* **24** (R=CH_2Ph), m.p. 159–160° (from EtOH). (Found: C, 65.7; H, 5.5; N, 19.1. M, mass-spectrometrically 363. $C_{20}H_{21}N_5S$ requires: C, 66.1; H, 5.8; N, 19.3%. M, 363). IR: 3460s, 3350s (NH), 3050w (CH arom), 2920w (CH), 1645vs (C=N), 750ms, 710–695s mult (Ph), and 1565ms cm^{-1}.

1,2-Diamino-3-phenylguanidine; monothiobenzoylation

Treatment of a stirred soln of 1,2-diamino-3-phenylguanidine HI[25] (2.93 g, 0.01 mole) in N NaOH (0.03 mole) with **2** (0.01 mole) in N NaOH (0.02 mole), followed by acetone (20 ml) and addition of 2N AcOH (20 ml) at 0° (ice), gave a yellow ppt which was collected immediately at 0° (1.45 g, 43%) (Filtrate: F). Crystallisation from acetone–EtOH (1:1, recovery *ca.* 50%) gave faintly yellow prisms of *1-isopropylideneamino-2-phenyl-3-thiobenzamidoguanidine* (**27**, R=R'=Me), m.p. 231–234°. (Found: C, 62.7; H, 6.2; N, 21.4; S, 9.1. $C_{17}H_{19}N_5S$ requires:C, 62.8; H, 5.8; N, 21.5 S, 9.8%). IR: 3370s, 3240s (NH), 3030m(CH arom), 1685s, 1660–1645vs mult, 1610–1580vs mult (C=N), 1230, 1220s d (? CS), 780, 765vs d, 705vs (Ph), 1500ms, 1465vs, 1435s, 1360s, 1120ms cm^{-1}. The crystallisation filtrates deposited **12**, m.p. 235–237°, identified by IR. Delay in the collection of the crude ppt, or its precipitation by HCl, resulted in its substantial conversion into **12**.

Filtrate F slowly deposited dark-red crystals enveloped in dark resinous material. Crystallisation from EtOH–acetone gave scarlet needles (0.39 g, 12%) of **29** (Ar=Ph), m.p. 196–199° (dec, sintering from 185°). (Found: C, 62.8; H, 4.8; N, 20.9; S, 10.1. $C_{17}H_{17}N_5S$ requires: C, 63.2; H, 5.4; N, 21.7; S, 9.9%). IR: 3270ms, 3150s (NH), 3070ms (CH arom), 1630ms, 1610ms, 1580–1560vs mult (C=N, N=N), 1260ms (? CS), 760s, 750s, 690vs (Ph) cm^{-1}.

In an identical experiment, the crude product was precipitated by AcOH *without* the addition of acetone. The orange yellow material was collected at once and washed copiously with H_2O (yield near-quantitative). A sample, stirred in water at 40–50° for 10 min, collected and air-dried gave *1-amino-2-phenyl-3-thiobenzamidoguanidine* (**25**) as an orange powder, m.p. 105–108° (dec, after softening from 90°). (Found: C, 58.2; H, 5.0; N, 23.75; S, 10.5. $C_{14}H_{15}N_5S$ requires: C, 58.95; H, 5.3; N, 24.6; S, 11.2%). Attempted crystallisation from the usual solvents led to partial decomposition.

Reactions

Cyclisation of **25** by HCl in acetone as described for **5** (section d) gave (60%) **12**; it occurred also (56%) when crude **25** was crystallised from acetone with addition of a few drops of 2N acetic acid. The action of acetic anhydride on **25** at 100° for 1 hr gave (25%) the *triacetyl derivative* of **18**, m.p. 138–141° (from EtOH), identical with authentic material (see below).

1-Benzamido-2-isopropylideneamino-3-phenylguanidine: N,N'-*azo-compound* **30**

The stirred alkaline liquid obtained on thiobenzoylating 1,2-diamino-3-phenylguanidine (0.01 mole) as described above (*without* the addition of acetone and AcOH) was treated dropwise at room temp with 6% H_2O_2 (17 ml, 0.03 mole) during 30 min, and stirring continued for 24 hr. The red ppt that separated gradually gave, on crystallisation from EtOH–acetone, deep-scarlet platelets (with a metallic lustre) of **30** (Ar=Ph), m.p. 222–223° (1.2 g, 40%). (Found: C, 66.9; H, 4.4; N, 23.0. $C_{17}H_{17}N_5O$ requires: C, 66.45; H, 5.5; N, 22.8%). IR: 3440m, 3270m (NH), 2900w (CH), 1610s, 1570vs br (C=N, N=N), 760s, 690vs (Ph) cm^{-1}. The filtrate therefrom deposited (up to 15%) of **12**.

1-p-Chlorothiobenzamido-2-isopropylideneamino-3-phenylguanidine **28** (R=R'=Me)

This was obtained in the usual manner by the use of *p*-chlorothiobenzoylthioacetic acid as a yellow ppt. It was collected, washed with H_2O, thoroughly drained, and gave felted needles (3.25–3.75 g, 45–52%) of **28** (R = R'=Me), m.p. 226–228° (dec, darkening from 180°) (from acetone–EtOH). (Found: C,

55.95; H, 5.1; Cl, 9.9; N, 20.1; S, 9.55. $C_{17}H_{18}ClN_5S$ requires: C, 56.75; H, 5.0; Cl, 9.9; N, 19.5; S, 8.9%). IR: 3370s (NH), 3000ms (CH arom), 1650vs br, 1610vs, 1585vs mult (C=N), 1240m (? CS), 845ms (1,4-disub.aryl), 760m, 690mw (Ph) cm^{-1}.

The crystallisation filtrates therefrom deposited successive small crops of red solid (m.p. 206–212°, 0.5–0.8 g, 7–11%), which gave deep scarlet needles of **29** (Ar=*p*-ClC_6H_4), m.p. 215–216° (from EtOH). (Found : C, 52.2; H, 4.1; N, 21.5; S, 9.6. $C_{14}H_{12}ClN_5S$ requires: C, 52.9; H, 3.8; N, 22.05; S, 10.1%). IR: 3480m(NH), 1635m, 1580vs (C=N, N=N), 830m (1,4-disub.aryl), 750w br (Ph) cm^{-1}.

1-p-Chlorothiobenzamido-2-amino-3-phenylguanidine **26**

The crude product obtained in the thioacylation (without the use of acetone; 0.01 molar scale) was rapidly crystallised directly from pure EtOH (20 ml; a little undissolved deep-red by-product being filtered off), giving faintly pink prismatic needles (0.80 g, 25%) of **26**, m.p. 103–105°. (Found: C, 51.8: H, 4.4; Cl, 11.1; N, 22.3; S, 9.6. $C_{14}H_{14}ClN_5S$ requires: C, 52.6; H, 4.4; Cl, 11.1; N, 21.9; S, 10.0%). IR: 3300s br (NH), 1660vs d, 1635, 1625vs d, 1600vs, 1570s (C=N); 1240–1235mw (? CS), 845ms (1,4-disub.aryl), 760–740ms, 700ms (Ph) cm^{-1}.

Reactions of **26**

(a) The action of HCl in acetone (as in section d for **5**) gave (64%) **13**.

(b) The action of boiling Ac_2O (1 hr) gave platelets (50%) of the *monoacetyl derivative* of 2-anilino-5-*p*-chlorophenyl-1,3,4-thiadiazole, m.p. 201–202° (from EtOH). (Found: C, 58.1; H, 3.8; Cl, 10.6; N, 12.7; S, 9.5. $C_{16}H_{12}ClN_3OS$ requires: C, 58.3; H, 3.6; Cl, 10.8; N, 12.75; S, 9.7%). IR: 3080w (CH arom), 1690vs (CO), 1600m (C=N), 1445vs br (C–Me), 845s (1,4-disub.aryl), 750m, 695s (Ph) and 1305vs cm^{-1}.

(c) *Action of benzaldehyde.* A soln of crude **26** (0.64 g, 0.002 mole) in EtOH (12 ml)-benzaldehyde (0.21 g, 0.002 mole)-glacial AcOH (1 drop) was boiled under reflux for 1 hr. The separated orange powder, collected at 0° (46%) gave salmon-pink felted needles of *2-benzylidenehydrazino-5-p-chlorophenyl-1,3,4-thiadiazole*, m.p. 254–256° (from EtOH). (Found: C, 57.2; H, 3.5; Cl, 11.6; N, 17.6; S, 9.9. $C_{15}H_{11}ClN_4S$ requires: C, 57.2; H, 3.5; Cl, 11.3; N, 17.8; S, 10.2%). IR: 3220w (NH), 3020w (CH arom), 1620vs, 1595vs (C=N), 840m, 825m d (1,4-disub.aryl), 755ms, 685ms (Ph) and 1445vs cm^{-1}.

AUTHENTIC COMPOUNDS

2-Isopropylidenehydrazino-5-phenyl-1,3,4-thiadiazole **12**

This was obtained (48–56%) from isopropylidenethiocarbonohydrazide and **2** in boiling pyridine by Sandström's method[18b] and formed needles, m.p. 237–238° (Lit. m.p.[18b] 242–243°). IR: 3140s (NH), 3060m (CH arom), 1570–1560s br (C=N), 765s, 690s (Ph), 2940s, 1450, 1435, 1420m (triplet), 1260ms, 1080ms, 1025m cm^{-1}.

The *picrate* of **12** formed lustrous platelets, m.p. 183–186° (from EtOH–acetone) (65%) (Found: C, 44.5; H, 3.2; N, 21.55; S, 6.8. $C_{11}H_{12}N_4S.C_6H_3N_3O_7$ requires: C, 44.25; H, 3.25; N, 21.25; S, 6.9%).

The *monoacetyl derivative* of **12**, obtained (80%) by the action of boiling acetic anhydride (45 min) on **12**, formed minute prisms, m.p. 121–123° (from EtOH). (Found: C, 56.9; H, 5.4; N, 19.8; S, 11.6. $C_{13}H_{14}N_4OS$ requires: C, 56.9; H, 5.1; N, 20.4; S, 11.7%). IR: 2920–2900m (CH), 1740–1720vs mult (CO), 1635 vs br (C=N), 1365vs (MeCO), 1255vs (C–O–C, ester), 770vs, 760s, 690s (Ph), and 1600vs, 1510vs, 975vs cm^{-1}.

The *monobenzoyl derivative* of **12**, obtained (48%) by the action of benzoyl chloride (2.5 moles) in pyridine at 100° for 30 min on **12**, formed needles, m.p. 118–120° (from EtOH). (Found: C, 63.8; H, 4.7; N, 16.9; S, 10.1. $C_{18}H_{16}N_4OS$ requires: C, 64.3; H, 4.8; N, 16.7; S, 9.5%). IR: 3050m (CH arom), 2880m (CH), 1710vs (CO), 1630s br, 1580s br (C=N), 1455ms (C–Me), 1280vs (C–O–C, ester), 760s, 745m d, 720ms, 700, 690vs d (Ph), and 1325 vs br, 1310vs cm^{-1}.

2-Hydrazino-5-phenyl-1,3,4-thiadiazole **18**

This was obtained (50–60%) by Sandström's method[18b] by acid hydrolysis of **12**. Almost complete hydrolysis occurred on longer refluxing (3–4 hr), no unchanged reactant being recovered (compare ref. 18*b*). **18** formed pale yellow needles, m.p. 178–179° (from EtOH). Lit. m.p. 190–191°[18a,b], 184–186°[18c]. IR: 3370s, 3210s (NH), 3070 (CH arom), 1640s br, 1575s br (C=N), 1515m, 755s (triplet), 680s br (Ph); 2950s, 2900s, 1480m, 1455s br, 1320m, 1260m, 1150, 1130m d, 990s cm^{-1} (see also ref 18*c*).

Triacetyl derivative of **18**. Treatment of **18** with boiling acetic anhydride for 1 hr gave, after the usual working up, small prisms (75%) of the *triacetyl derivative*, m.p. 139–141° (Found: C, 53.2; H, 4.5; N, 18.2; S, 10.1. $C_{14}H_{14}N_4O_3S$ requires: C, 52.8; H, 4.4; N, 17.6; S, 10.1%). IR: 3050, 3020m d (CH arom), 2930m (CH), 1740vs, 1720–1705vs mult (CO), 1455vs (C–Me), 770vs, 695s, 665s (Ph) cm^{-1} and several other high intensity peaks.

2-Benzylidenehydrazino-5-phenyl-1,3,4-thiadiazole (**14**). A boiling soln of **18** (0.002 mole) in EtOH (25 ml), treated with benzaldehyde (0.005 mole), deposited white solid which was collected after 1 hr refluxing. It gave faintly orange felted needles (64%) of **14**, m.p. 250–252° (fromEtOH–acetone). Lit. m.p.[18a,b] 256–257°. IR: 3070m (CH arom), 1620s, 1595s (C=N), 760s d, 685s (Ph) cm^{-1}.

2-Phenyl-5-(3',5'-dimethylpyrazol-1'(H)-yl)-1,3,4-thiadiazole **22**

A soln of **18** (0.38 g, 0.002 mole) in EtOH (12 ml)–acetylacetone (1 g, 0.01 mole)–3N HCl (1 ml) was boiled under reflux for 2 hr. The solid that separated on cooling was **22**, m.p. 170–171° (silky needles from EtOH) (82%). (Found: C, 61.3; H, 5.0; N, 22.6; S, 12.5. $C_{13}H_{12}N_4S$ requires: C, 60.9; H, 4.7; N, 21.9; S, 12.5%). IR: 1580s (C=N), 1525s, 760s, 685s (Ph), and 1475s, 1390s, 1375s, 1000s, 975s cm^{-1}.

REFERENCES

[1] F. Kurzer and L. E. A. Godfrey, *Chem & Indust.* 1584 (1962); *Angew. Chem.* Internat. Edn. **2**, 459 (1963).

[2] H. Ulrich, *Cycloaddition Reactions of Heterocumulenes.* Academic Press, New York (1967).

[3] F. Kurzer and K. Douraghi-Zadeh, *J. Chem. Soc.* 3912, 4448 (1965); *Ibid.* 1, 6 (1966).

[4] F. Kurzer, *Ibid.* 1813 (1970).

[5] F. Kurzer, *Ibid.* 1617 (1961).

[6] K. A. Jensen and J. F. Miguel, *Acta Chem. Scand.* **6**, 189 (1952); A. Lawson and C. E. Searle, *J. Chem. Soc.* 1556 (1957).

[7] R. Esmail and F. Kurzer, *Ibid.* Perkin I, 1781, 1787 (1975).

[8] K. M. Doyle and F. Kurzer, *Tetrahedron* **32**, 1031 (1976).

[9] F. Kurzer, *Chem. & Indust.* 1333 (1961); K. M. Doyle and F. Kurzer, *Ibid.* 803 (1974).

[10] K. A. Jensen and C. T. Pedersen, *Acta Chem. Scand.* **15**, 1097, 1124 (1961); K. A. Jensen, H. R. Baccaro, O. Burchardt, G. E. Olsen, C. T. Pedersen and J. Toft, *Ibid.* **15**, 1109 (1961); K. A. Jensen, U. Anthoni, B. Kagi, C. Larson and C. T. Pedersen, *Ibid.* **22**, 1(1968); K. A. Jensen, U. Anthoni and A. Holm, *Ibid.* **23**, 1916 (1969).

[11] R. N. Hurd and G. DeLaMater, *Chem. Rev.* **61**, 45 (1961): W. Walter and K. D. Bode, *Angew. Chem.* 78, 517 (1966).

[12] L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, p. 355. Methuen, London (1964).

[13] E. Fromm and A. Tranka, *Liebig's Ann.* **442**, 155 (1925).

[14] M. Kanaoka, *J. Pharm. Soc. Japan* **75**, 1149 (1955); *Pharm. Bull. Japan* **5**, 385 (1957).

[15] F. Kurzer and M. Wilkinson, *J. Chem. Soc.* (C), 2099 (1968).

[16] J. F. Willems, *Fortschr. Chem. Forsch.* **5**, 147 (1965).

[17] M. J. Kalm, *J. Org. Chem.* **26**, 2925 (1961).

[18] [a] J. Sandström, *Ark Kemi* **9**, 255 (1956); [b] *Acta Chem. Scand.* **17**, 1595 (1963); [c] K. T. Potts and R. M. Huseby, *J. Org. Chem.* **31**, 3528 (1966); [d] K. Fuji, H. Yoshikawa and M. Yuasa, *J Pharm. Soc. Japan* **74**, 1056 (1954).

[19] E. Hoggarth, *J. Chem. Soc.* 4811 (1952); M. Kanaoka, *J. Pharm*

Soc. Japan **76**, 1133 (1956); F. Kurzer and M. Wilkinson, *J. Chem. Soc.* (C), 1218 (1969).
[20]G. I. Keim, R. A. Henry and G. B. L. Smith, *J. Am. Chem. Soc.* **72**, 4944 (1950).
[21]A. Lawson and F. Kurzer, *Org. Synth.* **42**, 100 (1962).
[22]G. Young and W. Eyre, *J. Chem. Soc.* **79**, 54 (1901).
[23]E. Fromm, *Liebig's Ann.* **447**, 303 (1926); E. Hoggarth, *J. Chem. Soc.* 1164 (1949).
[24]F. L. Scott, D. A. O'Sullivan and J. Reilly, *J. Appl. Chem.* **2**, 184 (1952).
[25]F. Kurzer and K. Douraghi-Zadeh, *J. Chem. Soc.* (C), 742 (1967).