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CYCLIZATION OF 4-SUBSTITUTED 1-AMIDINOTHIOSEMICARBAZIDES TO 1,2,4-TRIAZOLE AND 1,3,4-THIADIAZOLE DERIVATIVES

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Abstract—A number of 4-substituted 3-amino-5-mercapto-1,2,4-triazoles and 2-amino-5-alkyl (or aryl)amino-1,3,4-thiadiazoles are synthesized by cyclization of 4-substituted 1-amidinothiosemicarbazides in alkaline or acid media, respectively. Amongst the intermediates required in these syntheses, the three isomeric (trifluoromethyl)phenyl-thioureas and isothiocyanates are described.

THE readily accessible 4-substituted 1-amidinothiosemicarbazides (I) have recently been shown to be useful starting materials in heterocyclic syntheses: their cyclization in alkaline or acid media yields 4-substituted 3-amino-5-mercapto-1,2,4-triazoles (II)[1,2] and 2-amino-5-alkyl(or aryl)amino-1,3,4-thiadiazoles (IV),[2] respectively. This paper reports the observations made on applying this group of reactions to the synthesis of further members of these series of compounds (I–IV).

The required intermediates (I) were obtained in excellent yield by the condensation of aminoguanidine hydrochloride with the appropriate isothiocyanate esters in dimethylformamide and conveniently isolated as the highly crystalline toluene-*p*-sulphonates. (cf. Table 1). The less reactive aliphatic isothiocyanates underwent addition more slowly than their aromatic analogues, but almost equally good yields were realized by extending the time of reaction.

Boiling aqueous sodium hydroxide cyclized the 4-substituted 1-amidinothiosemicarbazides (I), to 4-substituted 3-amino-5-mercapto-1,2,4,-triazoles (II), usually in yields exceeding 80% (cf. Table 2). The same triazoles (II) were obtainable even more conveniently by a procedure (cf. B, Experimental), which avoided the isolation of the intermediates. The mercapto-triazoles (II) were readily converted into the S-benzylthiol-derivatives (III) by the usual method.[2] Amongst the 1-amidinothiosemicarbazides (I) examined, the 4-(*o*-trifluoromethyl)phenyl-derivative (I, R = *o*-$F_3C{\cdot}C_6H_4$.) was the only one that failed to undergo cyclization under the usual conditions. Both sodium hydroxide and carbonate converted its toluene-*p*-sulphonate merely into the base, which resisted further action even on prolonged boiling, and was the only member of the series to be isolated in the free state. Its exceptional resistance to loss of ammonia (involving the hydrogen of the N(4)-atom, and part of the amidino-group of I) may be due to steric factors: the shielding effect of the adjacent *o*-trifluoromethyl-group may prevent the ready elimination of the N(4)-hydrogen atom, and thus stabilize the molecule. Purely electronic influences of the trifluoromethyl-group, though possibly contributing to the observed stability, are unlikely to be entirely responsible, since

[1] D. J. Fry and A. J. Lambie, *Brit. P.P.* 741280; 741228 (1955).
[2] L. E. A. Godfrey and F. Kurzer, *J. Chem. Soc.* 5137 (1961).

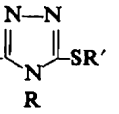
TABLE 1. 4-SUBSTITUTED 1-AMIDINOTHIOSEMICARBAZIDE TOLUENE-*p*-SULPHONATES (I)

R	Time (hr)	Solvent	Yield %	m.p.	Formula	Found		Required	
						C	H	C	H
$(CH_3)_2CH$	5·5	EtOH	80	216–217	$C_5H_{13}N_5S{\cdot}C_7H_8O_3S$	40·8	6·1	41·5	6·05
$(CH_3)_3CHCH_2$	5·0	EtOH	72	199–200	$C_6H_{15}N_5S{\cdot}C_7H_8O_3S$	42·8	6·7	43·2	6·4
cyclo-C_6H_{11}	5·0	50% EtOH	64	192–194	$C_8H_{17}N_5S{\cdot}C_7H_8O_3S$	46·8	6·5	46·5	6·5
p-$MeOC_6H_4$	1·0	90% EtOH	82	169–170	$C_9H_{13}N_5OS{\cdot}C_7H_8O_3S$[a]	46·7	5·5	46·7	5·1
p-ClC_6H_4	1·0	EtOH	82	164–166	$C_8H_{10}ClN_5S{\cdot}C_7H_8O_3S{\cdot}EtOH$	44·0	4·9	44·2	5·2
o-$F_3C{\cdot}C_6H_4$	1·0	EtOH	70	188–190	$C_9H_{10}F_3N_5S{\cdot}C_7H_8O_3S$	42·5	4·0	42·8	4·0
m-$F_3C{\cdot}C_6H_4$	1·0	H_2O	80	185–187	$C_9H_{10}F_3N_5S{\cdot}C_7H_8O_3S$[b]	42·4	4·2	42·8	4·0
p-$F_3C{\cdot}C_6H_4$	1·0	EtOH-P.E.[c]	55	192–194	$C_9H_{10}F_3N_5S{\cdot}C_7H_8O_3S$	43·1	4·3	42·8	4·0

[a] Found: N, 16·2. Calc. N, 17·0%.

[b] Found: N, 15·25. Calc. N, 15·6% Specimen analysed after 30 mins drying at 120–130°.

[c] Crude material rinsed with ether (P.E. = light petroleum, b.p. 60–80°).

TABLE 2. 4-SUBSTITUTED 3-AMINO-5-(ARALKYL)THIOL-1,2,4-TRIAZOLES 

R	R′	Procedure	Solvent	Yield %	m.p.	Formula	Found		Required	
							C	H	C	H
$(CH_3)_2CH$	H	C	EtOH	75	189–191	$C_5H_{10}N_4S$	37·7	6·1	38·0	6·3
$(CH_3)_2CHCH_2$	H	C	EtOH	80	195–197	$C_6H_{12}N_4S$[a]	42·4	6·8	41·9	7·0
$(CH_3)_2CHCH_2$	$PhCH_2$	D	$CHCl_3$-P.E.	60	103–105	$C_{13}H_{18}N_4S$	60·0	6·6	59·5	6·9
cyclo-C_6H_{11}	H	C	EtOH[b]	85	240–241	$C_8H_{14}N_4S$	48·7	7·0	48·5	7·1
cyclo-C_6H_{11}	$PhCH_2$	D	$CHCl_3$-P.E.	82	127–128	$C_{15}H_{20}N_4S$	62·2	6·8	62·5	6·9
p-$MeOC_6H_4$	H	B	GEE-P.E.[c]	80	257–259	$C_9H_{10}N_4OS$	48·4	4·9	48·65	4·5
p-$MeOC_6H_4$	H	C	GEE-P.E.	90	257–259	—	—	—	—	—
p-$MeOC_6H_4$	$PhCH_2$	D	$CHCl_3$-P.E.	85	130–132	$C_{16}H_{16}N_4OS$	61·3	5·1	61·5	5·1
p-ClC_6H_4	H	B	EtOH	75	288–290	$C_8H_7ClN_4S$	42·8	3·2	42·4	3·1
p-ClC_6H_4	H	C	EtOH	90	288–290	—	—	—	—	—
p-ClC_6H_4	$PhCH_2$	D	$CHCl_3$-P.E.	60	124–126	$C_{15}H_{13}ClN_4S$	56·85	4·3	56·9	4·1
p-BrC_6H_4	H	B	GEE-P.E.	75	290–292	$C_8H_7BrN_4S$	35·7	2·65	35·4	2·6
p-BrC_6H_4	$PhCH_2$	D	$CHCl_3$-P.E.	83	155–157	$C_{15}H_{13}BrN_4S$	49·5	3·6	49·9	3·6
m-$F_3C{\cdot}C_6H_4$	H	C	EtOH-P.E.	70	253–254	$C_9H_7F_3N_4S$	41·5	3·0	41·5	2·7
m-$F_3C{\cdot}C_6H_4$	$PhCH_2$	D	$CHCl_3$-P.E.	74	169–171	$C_{16}H_{13}F_3N_4S$	55·3	3·6	54·9	3·7
p-$F_3C{\cdot}C_6H_4$	H	C[g]	EtOH-P.E.	70	263–265	$C_9H_7F_3N_4S$	41·2	3·1	41·5	2·7

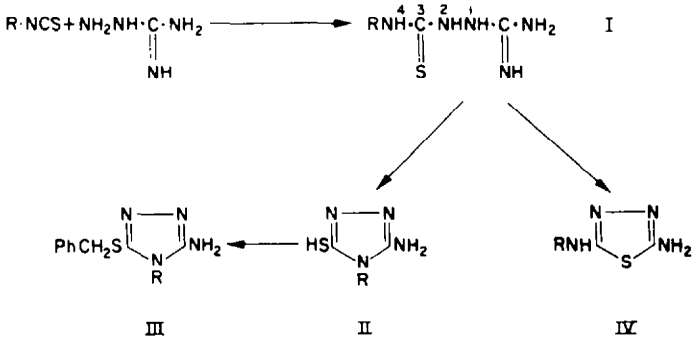
[a] Found: N, 32·9; Calc. N, 32·6%

[b] Large volume of solvent

[c] GEE = Ethylene glycol monoethyl ether

[g] The cyclization was performed by the use of 3 N sodium carbonate (30 min boiling). 3 N Sodium hydroxide appeared to cause gross decomposition.

the comparable *p*-isomer (I, R = *p*-$F_3C{\cdot}C_6H_4$.) underwent ring closure readily in the usual way.



Of the two acidic reagents, viz. phosphoric acid and acetic anhydride, that have been employed[2] in cyclizing amidinothiosemicarbazides (I) to 1,3,4-thiadiazoles (IV) the latter proved more generally applicable: it usually afforded good yields of 2-amino-5-alkyl(or aryl)amino-1,3,4-thiadiazoles as diacetyl-derivatives (cf. Table 3), which were readily converted into the corresponding parent bases (IV) (cf. Table 4) by acid hydrolysis.

TABLE 3. DIACETYL DERIVATIVES OF 2-AMINO-5-SUBSTITUTED-1,3,4-THIADIAZOLES (IV)

R	Solvent	Yield %	m.p.	Formula	Found		Required	
					C	H	C	H
$(CH_3)_2CH.$	EtOH	64	221–222	$C_9H_{14}N_4O_2S$	45·0	5·8	44·6	5·8
$(CH_3)_2CHCH_2$	EtOH	52	220–222	$C_{10}H_{16}N_4O_2S$	47·0	6·1	46·9	6·25
cyclo-C_6H_{11}	EtOH	45	201–203	$C_{12}H_{18}N_4O_2S$	51·3	6·2	51·1	6·4
p-$MeOC_6H_4$	Me_2CO-EtOH[a]	40	272–274	$C_{13}H_{14}N_4O_3S$	51·4	5·0	51·0	4·6
p-ClC_6H_4	EtOH[c]	72	274–275	$C_{12}H_{11}ClN_4O_2S$	46·3	3·9	46·4	3·5
o-$F_3C{\cdot}C_6H_4$[f]	EtOH	38	275–278	$C_{13}H_{11}F_3N_4O_2S$	45·7	3·6	45·35	3·2
m-$F_3C{\cdot}C_6H_4$	Me_2CO-EtOH[a]	64	280–282	$C_{13}H_{11}F_3N_4O_2S$	45·15	3·5	45·35	3·2
p-$F_3C{\cdot}C_6H_4$	EtOH	56	253–254	$C_{13}H_{11}F_3N_4O_2S$	45·1	3·2	45·35	3·2

[a] From a large volume, followed by partial evaporation by distillation.

[f] Prepared by 1 hr heating on a steam-bath, since resinification occurred when the solution was refluxed.

The preparation of *m*-(trifluoromethyl)phenyl isothiocyanate in 50% yields, by the decomposition of the appropriate dithiocarbamate by lead nitrate, has been claimed,[3] but physical constants for the product were not given. Our attempts to prepare this compound, and its *o*-isomer, by this route (Eqs. 1, 2) were unsuccessful: the intermediate ammonium salt was not obtained crystalline and treatment of the whole

[3] F. B. Dains, R. Q. Brewster, and C. P. Olander, *Org. Synth.* Coll. Vol. I., p. 449 (1941).

TABLE 4. 2-AMINO-5-SUBSTITUTED-1,3,4-THIADIAZOLES (IV)

R	Solvent	Yield %	m.p.	Formula	Found		Required	
					C	H	C	H
$(CH_3)_2CH$	EtOH-P.E.	56	186–188	$C_5H_{10}N_4S$	37·8	6·2	38·0	6·3
$(CH_3)_2CHCH_2$	EtOH-P.E.	80	187–189	$C_6H_{12}N_4S$	42·0	7·0	41·9	7·0
cyclo-C_6H_{11}[j]	EtOH-P.E.	70	217–218	$C_8H_{14}N_4S$	48·8	7·6	48·5	7·1
p-MeO·C_6H_4	EtOH	85	196–198	$C_9H_{10}N_4OS$	48·35	4·2	48·65	4·5
p-Cl·C_6H_4	EtOH-P.E.	54	212–214	$C_8H_7ClN_4S$	42·45	3·5	42·4	3·1
o-F_3C·C_6H_4[k]	$CHCl_3$-P.E.	78	204–205	$C_9H_7F_3N_4S$	41·8	3·4	41·5	2·7
m-F_3C·C_6H_4[l]	20% EtOH	80	184–186	$C_9H_7F_3N_4S$	41·3	2·7	41·5	2·7
p-F_3C·C_6H_4[k]	40% EtOH	60	202–204	$C_9H_7F_3N_4S$	42·0	3·4	41·5	2·7

[j] Also prepared directly by the use of phosphoric acid[2] (cf. Experimental).

[k] To ensure completeness of hydrolysis, the diacetyl-derivative was refluxed during 1·5 hr with 4 N hydrochloric acid–ethanol (80 and 40 ml respectively, per 0·01 mole).

[l] To ensure solution, an additional 10 ml ethanol were employed during the refluxing.

reaction mixture with lead nitrate resulted merely in the recovery of some of the amine.

$$RNH_2 + CS_2 + NH_4OH \rightarrow RNHCSSNH_4 + H_2O \quad (1)$$

$$RNHCSSNH_4 + Pb(NO_3)_2 \rightarrow RNCS + NH_4NO_3 + HNO_3 + PbS \quad (2)$$

$$RNH_2 + HCNS \rightarrow RNHCSNH_2 \quad (3)$$

$$RNH_2 + PhCONCS \rightarrow RNHCSNHCOPh \quad (4)$$

$$RNHCSNHCOPh + H_2O \rightarrow RNHCSNH_2 + PhCOOH \quad (5)$$

$$RNHCSNH_2 \rightarrow RNCS + NH_3 \quad (6)$$

$$RNHCSNH_2 \rightarrow RNH_2 + HCNS \quad (7)$$

$$RNH_2 + RNCS \rightarrow RNHCSNHR \quad (8)$$

The three isomeric (trifluoromethyl)phenyl isothiocyanates required in this work were prepared in 50–70% yields by the thermal decomposition of the corresponding thioureas in boiling chlorobenzene, by the method of Cymerman-Craig *et al.*[4,5] (Eq. 6). Small quantities of the corresponding *sym*-diarylthiourea that were formed as a by-product, arose no doubt by the interaction of the aromatic amine and isothiocyanate originating from the two alternative modes of dearrangement of the thiourea (Eq. 6–8).

m-(Trifluoromethyl)phenylthiourea was obtainable by the thermal isomerization of the corresponding amine thiocyanate (Eq. 3).[6] Since this method gave only very small yields of the *o*-isomer, the *o*- and *p*-substituted phenylthioureas were produced by the synthesis of N-benzoyl-N′-arylthioureas from benzoyl isothiocyanate and *o*- and *p*-aminobenzotrifluoride, followed by the hydrolytic removal of the benzoyl group.[7] (Eq. 4 and 5).

[4] J. Cymerman-Craig, M. Moyle, and R. A. White, *Org. Synth.* **36**, 56 (1956).

[5] J. N. Baxter, J. Cymerman-Craig, M. Moyle, and R. A. White, *Chem. & Ind.* 785 (1954).

[6] F. Kurzer, *Org. Synth.* **31**, 21 (1951).

[7] I. B. Douglas and F. B. Dains, *J. Amer. Chem. Soc.* **56**, 1408 (1934); R. L. Frank and P. V. Smith, *Org. Synth.* Coll. Vol. III, p. 735 (1955).

EXPERIMENTAL

Light petroleum had b.p. 60–80°. Dimethylformamide was redistilled and the initial small water-containing fraction rejected.

m-(*Trifluoromethyl*)*phenylthiourea*. A warm solution of *m*-aminobenzotrifluoride (48·3 g; 0·3 mole) in N-hydrochloric acid (330 ml, 0·33 mole), contained in a large evaporation basin, was treated with ammonium thiocyanate (25 g, 0·33 mole) and heated on the steam-bath during 1·5 hr. The liquid was set aside overnight (separation of crystalline solid), then evaporated to dryness on the steambath. The residual solid was powdered, covered with water (300 ml), again evaporated, and the solid residue finally kept at 100° for 4 hr. The residue was ground with cold water (300 ml), the solid collected, washed with water, and air-dried at room-temp. Crystallization from chloroform-light petroleum (3 and 2 ml per g) gave lustrous microplatelets of m-(*trifluoromethyl*)*phenylthiourea* (47·5 g, 72%) m.p. 104–106°. (Found: C, 43·2; H, 3·05; N, 12·5; S, 15·5. $C_8H_7F_3N_2S$ requires: C, 43·6; H, 3·2; N, 12·7; S, 14·5%).

o-(*Trifluoromethyl*)*phenylthiourea*. A solution of dry ammonium thiocyanate (8·4 g, 0·11 mole) in acetone (70 ml) was treated dropwise with benzoyl chloride (14·1 g, 0·1 mole) and the stirred suspension refluxed during 5 min. *o*-Aminobenzotrifluoride (16·1 g, 0·1 mole) was then rapidly added, refluxing continued during 10 min, and the mixture stirred into water (700 ml). The resulting yellow precipitate (of crude N-benzoyl-N′-(*o*-trifluoromethyl)phenylthiourea) was collected after 1 hr, suspended in a solution of sodium hydroxide (14 g, 0·35 mole) in water (150 ml) and boiled during 5 min (loss of some volatile material). The resulting clear liquid was acidified with conc hydrochloric acid, and then just basified with 3 N ammonia. The pale-yellow solid was collected at 0° (m.p. 158–161°, after sintering at 154°; 18·7 g, 85%) and gave, after crystallization from 20% ethanol (15 ml per g, recovery 75%), needles of o-(*trifluoromethyl*)*phenylthiourea*, m.p. 162–164° after sintering from 160°. (Found: C, 43·2; H, 3·3; N, 12·7; S, 14·5. $C_8H_7F_3N_2S$ requires: C, 43·6; H, 3·2; N, 12·7; S, 14·5%).

The direct interaction of the amine with thiocyanic acid (as described for the *m*-isomer, above) gave only 8–12% yields of the desired thiourea, m.p. and mixed m.p. 162–164° (after sintering from 158°).

p-(*Trifluoromethyl*)*phenylthiourea*. The crude *N*-benzoyl-derivative was prepared, by the use of *p*-aminobenzotrifluoride (16·1 g, 0·1 mole), as described for the *o*-isomer. The resulting pale-yellow granular solid was suspended in 3 N sodium hydroxide (150 ml) and carefully heated, with good stirring, on the steam-bath, when solution occurred gradually (5–7 min, max temp 75–85°). The liquid, which began to darken rapidly, was quickly cooled, acidified with conc hydrochloric acid, and basified with 3 N ammonia. The resulting product (20–21 g) gave, on crystallization from chloroform–light petroleum (150 ml each), pale-yellow platelets (14·0 g, 64%) of the *thiourea*, m.p. 140–142°. (Found: C, 44·1, H, 3·8; N, 13·05; S, 14·7. $C_8H_7F_3N_2S$ requires: C, 43·6; H, 3·2; N, 12·7; S, 14·5%). Under more vigorous hydrolytic conditions (see *o*-isomer above), the crude product was a brown granular solid, from which the thiourea was isolated in much diminished yields.

m-(*Trifluoromethyl*)*phenyl isothiocyanate*. A solution of *m*-(trifluoromethyl)phenylthiourea (22·0 g, 0·1 mole) in dry chlorobenzene (200 ml) was refluxed during 18 hr, ammonia being evolved (more rapidly in the beginning). The solvent was removed from the greenish-yellow liquid in a vacuum (steam-bath) and the oily residue dissolved in light petroleum (2 × 75 ml). On storage at 0° overnight, a small amount of crystalline solid had separated. The liquid was decanted therefrom, and the solvent removed under red. press. Fractional distillation of the residue at atm. press gave (after a fore-run, b.p. 175–200°, 1–2 g) the *isothiocyanate* (10·9–13·2 g; 54–65%) as a colourless liquid, b.p. 206–208°. (Found: C, 47·5; H, 1·95. $C_8H_4F_3NS$ requires: C, 47·3; H, 2·0%).

Attempts to prepare *m*-trifluoromethylphenyl isothiocyanate from *m*-aminobenzotrifluoride by the general procedure of Dains *et al.*[8] were unsuccessful, the intermediate ammonium *m*-trifluoromethylphenyl dithiocarbamate being unobtainable under the usual conditions.

o-(*Trifluoromethyl*)*phenyl isothiocyanate*, prepared from recrystallized *o*-(trifluoromethyl)phenylthiourea (22·0 g, 0·1 mole) as described for the *m*-isomer, formed a colourless liquid, (12·2–13·8 g, 60–68%) b.p. 214–216°. (Found: C, 47·8; H, 2·1; N, 7·1; S, 16·0. $C_8H_4F_3NS$ requires: C, 47·3; H, 2·0; N, 6·9; S, 15·8%).

A small light petroleum insoluble fraction (up to 1·1 g, 6%) was NN′-di(*o*-trifluoromethylphenyl)thiourea, m.p. and mixed m.p. (see below) 163–165° (from ethanol–light petroleum).

As in the case of the *m*-isomer, attempts to prepare the isothiocyanate from *o*-aminobenzotrifluoride by the method of Dains *et al.*[3] was unsuccessful.

NN′-*Di*(o-*trifluoromethylphenyl*)*thiourea* was prepared by keeping a solution of *o*-aminobenzotrifluoride and *o*-(trifluoromethyl)phenyl isothiocyanate (0·01 mole each) in anhydrous pyridine (20 ml) at 100° for 1 hr. The liquid was stirred into conc hydrochloric acid (20 ml)–ice, the wax-like product stirred with methanol (5 ml), and the resulting white solid (1·52 g, 42%) crystallized from ethanol–light petroleum, yielding the *thiourea* as minute prisms, m.p. 163–165°. (Found: C, 48·7; H, 3·6; N, 7·7; S, 9·2. $C_{15}H_{10}F_6N_2S$ requires: C, 49·45; H, 2·75; N, 7·7; S, 8·8%).

p-(*Trifluoromethyl*)*phenyl isothiocyanate* was prepared from recrystallized *p*-(trifluoromethyl)-phenylthiourea (22·0 g, 0·1 mole) as described for the *m*-isomer. The residue obtained after removal of the chlorobenzene was extracted with hot light petroleum (4 × 100 ml), and separated from the insoluble residue R by decanting. Removal of the solvent, and distillation of the remaining liquid gave the *isothiocyanate* (10·6 g, 52%) b.p. 205–207°, solidifying to long needles at room temp. (Found: C, 46·9; H, 2·15; N, 6·9; S, 14·7. $C_8H_4F_3NS$ requires: C, 47·3; H, 2·0; N, 6·9; S, 15·8%).

Residue R (m.p. 158–160°; 3·25 g, 18%) consisted, after crystallization from chloroform, (30 ml per g, recovery 75%) of pale yellow needles of NN′-*di*-(p-*trifluoromethylphenyl*)*thiourea*, m.p. 164–165°. (Found: C, 48·7; H, 2·7; N, 7·9; S, 9·25. $C_{15}H_{10}F_6N_2S$ requires: C, 49·45; H, 2·75; N, 7·7; S, 8·8%).

4-Substituted 1-Amidinothiosemicarbazide Toluene-p-sulphonates (cf. Table 1)

Procedure A. A suspension of finely powdered aminoguanidine hydrochloride (11·0 g, 0·1 mole) in dimethylformamide (60 ml) was treated with the isothiocyanate ester (0·1 mole), and heated on the steam-bath during 1 hr, solution occurring generally after 15–30 min. Aliphatic isothiocyanates required 5 hr heating. The liquid was stirred into a solution of toluene-*p*-sulphonic acid monohydrate (23·75 g, 0·125 mole) in water (250 ml); the toluene-*p*-sulphonate was generally precipitated as a crystalline solid, or when oily, solidified presently on stirring; it was collected at 0° and crystallized as shown in Table 1, where individual compounds are listed.

1-Amidino-4-(o-trifluoromethyl)phenylthiosemicarbazide

A solution of the toluene-*p*-sulphonate (1·8 g, 0·004 mole) in 3 N sodium carbonate (16·5 ml, 0·025 mole) was refluxed during 15 min (slight evolution of ammonia), then acidified with 3 N acetic acid. The thick white precipitate, collected at 0°, washed with water, and crystallized from ethanol–light petroleum (12 ml each, per g), formed opaque white prisms (0·93 g, 85%) of 1-*amidino*-4-(o-*trifluoromethyl*)*phenylthiosemicarbazide*, m.p. 239–241° (dec). (Found: C, 39·2; H, 3·55; N, 25·7; S, 11·7. $C_9H_{10}F_3N_5S$ requires: C, 39·0; H, 3·6; N, 25·3; S, 11·55%). The toluene-*p*-sulphonate gave, by procedure C (see below), the same base, m.p. and mixed m.p. 240–242°, but in much reduced yield (20%). The corresponding triazole (II) was not obtained.

4-Substituted 3-Amino-5-mercapto-1,2,4-triazoles (cf. Table 2)

Procedure B. A solution of aminoguanidine hydrochloride (3·32 g, 0·03 mole) in dimethylformamide (8 ml), treated with the isothiocyanate (0·03 mole), was heated on the steambath during 1 hr. To the resulting liquid, 3 N sodium hydroxide (25 ml) was added, and the solution refluxed during 15 min, ammonia being evolved. Acidification with conc hydrochloric acid gave a white granular precipitate, which was collected at 0°, and purified as specified in Table 2.

Procedure C. The 4-substituted 1-amidinothiosemicarbazide toluene-*p*-sulphonate (0·01 mole) dissolved readily in boiling 3 N sodium hydroxide (20–27 ml, 0·06–0·08 mole). The liquid was refluxed during 20 min (evolution of ammonia; usual colour-change: orange → yellow → colourless), allowed to cool somewhat, and acidified with 3 N hydrochloric acid (to Congo-red). The precipitated solid was collected at 0° and purified as above. Individual compounds thus prepared are listed in Table 2.

4-Substituted 3-Amino-5-benzylthiol-1,2,4-triazoles (cf. Table 2)

Procedure D. A warm suspension of the appropriate finely powdered thiol (see procedures B, C) (0·1 mole) in ethanol (20 ml)–benzyl chloride (1·52 g, 0·012 mole) was treated with 3 N sodium

hydroxide (4 ml, 0·012 mole). The resulting clear liquid was refluxed on the steambath during 30 min, (sodium chloride being slowly deposited). The mixture was stirred into water (60 ml), the solidified oil collected at 0°, and crystallized as specified in Table 2.

Diacetyl Derivatives of 2-*Amino*-5-*substituted*-1,3,4-*thiadiazoles* (cf. Table 3)

Procedure E. A solution of the 4-substituted 1-amidinothiosemicarbazide toluene-*p*-sulphonate (0·01 mole) in acetic anhydride (25–30 ml) was refluxed during 3/4 to 1 hr, and the resulting brown liquid stirred into warm water (100–120 ml). The solidified crude product was collected at 0°, and crystallized as specified in Table 3.

2-*Amino*-5-*substituted*-1,3,4-*thiadiazoles* (cf. Table 4)

Procedure F. The crude diacetyl-derivative (0·01 mole) dissolved on being boiled with 3 N hydrochloric acid (30 ml). The liquid was refluxed during 30 min, cooled somewhat, then basified with 3 N ammonia. The precipitated crude product was collected at 0° and purified as specified in Table 4. Small amounts of brown oil separated occasionally during the refluxing, in which case the supernatant liquid was decanted before basification.

2-*Amino*-5-*cyclohexylamino*-1,3,4-*thiadiazole*

1-Amidino-4-cyclohexylthiosemicarbazide toluene-*p*-sulphonate (3·85 g, 0·01 mole) in 100% orthophosphoric acid (12 ml) was kept at 130° during 30 min. The clear dark liquid was stirred into ice (100 g) and basified with conc ammonia. The resulting thick white precipitate was collected after a few min, rinsed with a little water, dried, and exhaustively extracted with acetone–ethanol (1:1, 3 × 40 ml). The filtered extracts, on distillation to small volume (10–15 ml) and storage, deposited clusters of needles (0·90 g, 45%), which gave, on recrystallization from ethanol–light petroleum, needles of the *thiadiazole*, m.p. 217–218°.