Oxidative Cyclisation of Ketone Thiosemicarbazones. Part I. 4-Methyl- and 4-Aryl-thiosemicarbazones

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4-Substituted thiosemicarbazones of ketones undergo oxidative cyclisation, catalysed by chromatographic adsorbents, giving Δ^1-[1,2,4]triazoline-5-thiones, and oxidation on manganese dioxide to 5-imino-Δ^3-[1,3,4]-thiadiazolines. The triazolinethiones may be converted into triazolinones. The reactions are strongly influenced by steric factors.

A RED substance isolated during the chromatographic purification of a derivative of 4-phenylthiosemicarbazide was identified by elemental analysis and spectrometry as acetone 4-phenylthiosemicarbazone (1; Ar = Ph) less two hydrogen atoms. It was formed rapidly when a solution of (1; Ar = Ph) was stirred with basic alumina, and more slowly with neutral or acid alumina or some other chromatographic adsorbents. The n.m.r. spectrum indicated two identical methyl groups, and the alternative structures (2) and (3) were suggested. Since an oxidation was involved, manganese dioxide was tried as the solid reagent; it converted (1) into a yellow compound isomeric with the red compound and having a similar n.m.r. spectrum. Examination of models showed that in the triazolinethione series (2) a bulky *ortho*-substituent on the aryl group should be trapped between the sulphur atom and one of the methyl groups, whereas no such steric hindrance should occur in the thiadiazoline series. The isomeric pairs of cyclic compounds were prepared from (1; Ar = *o*-bromophenyl) and (1; Ar = 1-naphthyl), and in both cases the n.m.r. spectra of the red isomers showed two methyl signals at lower temperatures, whereas those of the yellow isomers showed only one at temperatures down to −60° (Table 1):

TABLE 1

^{1}H N.m.r. spectra of cyclisation products

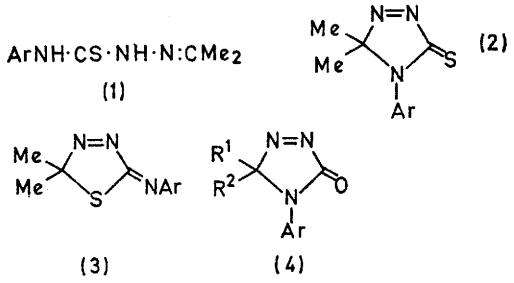
Compound	τ-Aromatic H	τ-Methyl H
(2; Ar = Ph)	2·25—2·85	8·42
(3; Ar = Ph)	2·55—2·8	8·18
(2; Ar = *o*-BrC_6H_4) [a]	2·2—2·9	8·27 8·3
(3; Ar = *o*-BrC_6H_4) [b]	2·3—3·1	8·19
(2; Ar = 1-naphthyl)	1·9—2·85	8·25 8·42
(3; Ar = 1-naphthyl)	1·6—2·8	8·15

[a] At −40°. [b] At −60°.

Further proof of structure was given by the conversion of the triazolinethiones into triazolinones (4) by mercuric acetate.

We have found that oxidative cyclisation to triazolinethiones is a general reaction of the 4-arylthiosemicarbazones of saturated ketones in which there is no great steric hindrance to ring closure. It has not been achieved with thiosemicarbazones of such ketones, or with arylthiosemicarbazones of aldehydes, and αβ-unsaturated ketones, or strongly hindered ketones such as camphor or 17-keto-steroids. A slow cyclisation

was observed with 4-methylthiosemicarbazones, and cyclohexanone 4-phenylsemicarbazone was converted very slowly into the triazolinone (4; Ar = Ph, R^1R^2 = $[CH_2]_5$). The 4-phenylthiosemicarbazone of cyclohexanone cyclised to the triazolinethione with great ease,

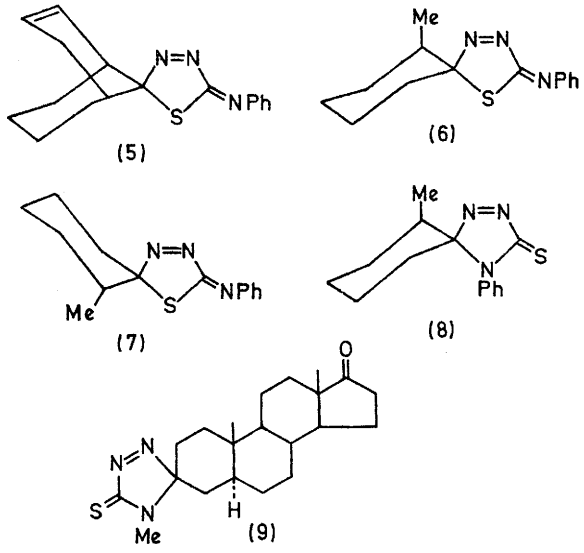


but those from cyclopentanone and cycloheptanone reacted more slowly.

The formation of triazolinethiones probably involves the intermediate, and perhaps reversible, formation of triazolidinethiones by addition of NH to the double bond, and this process may be facilitated if the thiosemicarbazone molecule is held in a suitable configuration on a solid adsorbent. Oxidation by dissolved oxygen would then stabilise the cyclic product. A similar hypothesis would explain the formation of the thiadiazolines, and in one instance (see below) a thiadiazoline was formed over alumina, but the speed and selectivity of thiadiazoline formation over manganese dioxide suggest that with this reagent a different mechanism is involved.

Other products isolated from the reaction on alumina were sulphur and the corresponding 4-phenylsemicarbazone. In some instances appreciable amounts of the triazolinones (4) were produced; these were detected by i.r. absorption at *ca.* 1750 cm.$^{-1}$. The triazolinethiones had a characteristic absorption at *ca.* 1300 cm.$^{-1}$, and the thiadiazolines at *ca.* 1630 cm.$^{-1}$.

The 4-phenylthiosemicarbazones of acetophenone and 1-tetralone cyclised very slowly on alumina, and that of adamantanone to a negligible extent. Steric hindrance to ring-closure would not be expected in the latter case, but perhaps the molecule cannot lie flat enough on the surface of the adsorbent. Bicyclo[3,3,1]-non-2-en-9-one [1] 4-phenylthiosemicarbazone gave the thiadiazolines (5) (two stereoisomers) both with alumina and with manganese dioxide. 2-Methylcyclohexanone 4-phenylthiosemicarbazone gave two stereoisomeric thiadiazolines (6) and (7), but only one triazolinethione, probably (8); there is steric hindrance to ring-closure from one side of the cyclohexane ring. However, both of the possible stereoisomeric triazolinethiones (9) were obtained from the 4-methylthiosemicarbazone of androstane-3,17-dione, (the difference in reactivity of the carbonyl groups in androstane-3,17-dione and in allopregnanedione permitted selective reaction of thiosemicarbazides at position 3 as shown by the i.r. spectra).



Unlike 4-phenyl-1,2,4-triazoline-3,5-dione [2] these triazolines and thiadiazolines are not dienophiles; no evidence of reaction could be found with anthracene, cyclopentadiene, or tetracyclone. They do not appear to generate free radicals on thermal decomposition. The thiadiazolines are unstable and readily liberate isonitriles. No reaction occurred between (2; Ar = Ph) and methyl iodide. The nearest parallel to these ring closures appears to be the oxidation of acetone thiocarbohydrazone with lead tetra-acetate to give 2-isopropylidenehydrazono-5,5-dimethyl-Δ^3-[1,3,4]thiadiazoline.[3]

EXPERIMENTAL

I.r. spectra were determined on a Perkin-Elmer Infracord spectrophotometer, as Nujol mulls, and n.m.r. spectra were determined in deuteriochloroform (internal reference tetramethylsilane) on a Varian A-60 or HA-100 instrument.

4-o-*Bromophenylthiosemicarbazide*.—*o*-Bromoaniline (17·2 g.) and phenyl isothiocyanate (13·5 g.) in ethanol (50 c.c.) were heated under reflux for 1·5 hr. The product that crystallised from the cool solution was separated by chromatography [benzene–ethyl acetate (4 : 1) on alumina] into N^1,N^2-di-*o*-bromophenylthiourea, m.p. 156°, N^1-2-*bromophenyl*-N^2-*phenylthiourea*, m.p. 157—158° (Found: C, 50·8; H, 3·7; N, 9·0. $C_{13}H_{11}BrN_2S$ requires C, 50·8; H, 3·6; N, 9·1%), and N^1,N^2-diphenylthiourea, m.p. 151°. Recrystallisation of the crude product from ethanol gave a constant 3 : 1 mixture of the monobromo-compound and N^1 N^2-diphenylthiourea. N^1-2-Bromophenyl-N^2-phenylthiourea (14·2 g.) and hydrazine hydrate (2·3 g.) in ethanol (150 c.c.) were boiled under reflux for 9 hr., the solvent was evaporated under reduced pressure, and the syrupy residue was triturated with light petroleum (b.p. 40—60°) until it crystallised. Repeated crystallisation from ethanol gave 4-o-*bromophenylthiosemicarbazide*, m.p. 152—153°

[1] S. Brewis and P. R. Hughes, *Chem. Comm.*, 1966, 6.
[2] R. C. Cookson, S. S. H. Giliani, and I. D. R. Stevens, *J. Chem. Soc.* (*C*), 1967, 1905.
[3] P. W. West and J. Warkentin, *J. Org. Chem.*, 1968, **33**, 2089.

(Found: C, 34·7; H, 3·4; N, 17·1. $C_7H_8BrN_3S$ requires C, 34·15; H, 3·25; N, 17·1%).

The same preparative method [4] was satisfactory for 4-(1-naphthyl)thiosemicarbazide, unsatisfactory for 4-*p*-hydroxyphenylthiosemicarbazide, and unsuccessful for 4-*p*-dimethylaminophenylthiosemicarbazide. The latter, m.p. 170°, was prepared from *p*-dimethylaminophenylisothiocyanate (lit.,[5] m.p. 172°; the product of m.p. 192° described by Lieber and Ramachandran [6] had an analysis consistent with it being an isopropylidene derivative).

Thiosemicarbazones were prepared (*a*) by heating the thiosemicarbazide with the ketone in ethanol, or (*b*) by reaction of phenylisothiocyanate with a cold solution of the hydrazone of the ketone in ethanol. New thiosemicarbazones are listed in Table 2.

TABLE 2

Ketone thiosemicarbazones

Thiosemicarbazide	Ketone	Formula	Method	M.p.	Found (%) C	Found (%) H	Found (%) N	Required (%) C	Required (%) H	Required (%) N
4-*o*-Bromophenyl	Acetone	$C_{10}H_{12}BrN_3S$	*a*	144°	42·1	4·2	14·6	42·0	4·2	14·7
4-*p*-Chlorophenyl	,,	$C_{10}H_{12}ClN_3S$	*a*	104	49·6	5·2	17·3	49·7	5·0	17·4
4-*p*-Hydroxyphenyl	,,	$C_{10}H_{13}N_3OS$	*a*	180	54·3	5·7	18·8	53·8	5·8	18·8
4-*p*-Dimethylaminophenyl	,,	$C_{12}H_{18}N_4S$	*a*	202—203	57·1	7·0	22·0	57·6	7·2	22·4
4-Phenyl	Butan-2-one	$C_{11}H_{15}N_3S$	*a*	72	59·3	6·65	19·3	59·7	6·8	19·0
,,	Cyclohex-2-enone	$C_{13}H_{15}N_3S$	*a*	134—135	63·7	5·9	17·1	63·7	6·1	17·1
,,	2-Methylcyclohexanone	$C_{14}H_{19}N_3S$	*a*	106—107	64·4	7·2	16·3	64·4	7·3	16·1
,,	Bicyclo[3,3,1]non-2-en-9-one	$C_{16}H_{19}N_3S$	*a*	144—146	67·3	7·0	14·6	67·4	6·7	14·7
,,	3,5,5-Trimethylcyclohex-2-en-1-one	$C_{16}H_{21}N_3S$	*a*	144—145	66·8	7·4	15·0	66·8	7·3	14·6
,,	1-Diethylaminopentan-4-one	$C_{16}H_{26}N_4S$	*a*	94—95	62·6	8·6	18·1	62·7	8·7	18·3
,,	1-Tetralone	$C_{17}H_{17}N_3S$	*a*	177—178	68·9	5·8	14·2	69·2	5·8	14·2
,,	Adamantanone	$C_{17}H_{21}N_3S$	*a*	136	67·8	6·8	14·1	68·2	7·0	14·05
,,	Camphor	$C_{17}H_{23}N_3S$	*b*	185—187	67·9	7·4	13·6	67·9	7·65	13·9
4-Methyl	5α-Androstane-3,17-dione	$C_{21}H_{33}N_3OS$ [a]	*a*	193—194	67·2	8·9	11·1	67·2	8·8	11·2
4-Phenyl	,,	$C_{26}H_{35}N_3OS$ [b]	*a*	199	71·85	8·2	9·6	71·4	8·0	9·6
,,	17β-Hydroxy-5α-androstan-3-one	$C_{26}H_{37}N_3OS$	*a*, *b*	202—203	71·7	8·7	9·5	71·1	8·4	9·6
,,	3-Hydroxy-5-α-androstan-17-one	$C_{26}H_{37}N_3OS,0{\cdot}5H_2O$	*b*	165—166	69·6	8·4	9·2	69·65	8·5	9·4
,,	5α-Pregnane-3,20-dione	$C_{28}H_{39}N_3OS$ [c]	*a*	222—223	72·0	8·5	8·9	72·25	8·4	9·0
4-*p*-Dimethylaminophenyl	5α-Androstane-3,17-dione	$C_{28}H_{40}N_4OS$ [d]	*a*	211—213	69·8	8·3	11·9	70·0	8·3	11·7

[a] $\nu_{max.}$ 1745s cm.$^{-1}$, 1640m cm.$^{-1}$. [b] $\nu_{max.}$ 1745s cm.$^{-1}$. [c] $\nu_{max.}$ 1690 cm.$^{-1}$ (strong and narrow). [d] $\nu_{max.}$ 1725s cm.$^{-1}$.

TABLE 3

Δ^1-[1,2,4]Triazoline-5-thiones

Name	Formula	M.p.	Found (%) C	Found (%) H	Found (%) N	Found (%) S	Required (%) C	Required (%) H	Required (%) N	Required (%) S
3,3,4-Trimethyl-	$C_5H_9N_3S$	107—108°	41·8	6·3	29·3		42·0	6·3	29·4	
3,3-Dimethyl-4-phenyl-	$C_{10}H_{11}N_3S$	172—174	58·4	5·5	20·4	15·2	58·5	5·4	20·5	15·6
4-*o*-Bromophenyl-3,3-dimethyl-	$C_{10}H_{10}BrN_3S$	190—191	42·6	3·7	14·8		42·3	3·5	14·8	
4-*p*-Chlorophenyl-3,3-dimethyl-	$C_{10}H_{10}ClN_3S$	136	50·3	4·5	17·7		50·1	4·2	17·5	
4-*p*-Hydroxyphenyl-3,3-dimethyl-	$C_{10}H_{11}N_3OS$	172	54·2	5·0	18·6	14·2	54·3	5·0	19·0	14·5
3-Ethyl-3-methyl-4-phenyl-	$C_{11}H_{13}N_3S$	109—110	60·5	5·9	19·3		60·3	5·9	19·2	
3,3-Dimethyl-4-*p*-dimethylaminophenyl-	$C_{13}H_{16}N_4S$	160	58·1	6·3	22·5		58·1	6·45	22·6	
Cyclopentanespiro-3′-(4′-phenyl)-	$C_{12}H_{13}N_3S$	165—167	61·9	6·1	18·2		62·3	5·6	18·2	
Cyclohexanespiro-3′-(4′-phenyl)-	$C_{13}H_{15}N_3S$	188—189	63·5	6·1	16·9		63·6	6·1	17·1	
3,3-Dimethyl-4-(1-naphthyl)-	$C_{14}H_{13}N_3S$	194	65·7	5·2	16·4		65·9	5·1	16·5	
Cycloheptanespiro-3′-(4′-phenyl)-	$C_{14}H_{17}N_3S$	126	64·9	6·6	15·8		64·9	6·6	16·2	
2-Methylcyclohexanespiro-3′-(4′-phenyl)- (8)	$C_{14}H_{17}N_3S$	150—152	64·8	6·6	16·4					
3-Methyl-3,4-diphenyl-	$C_{15}H_{13}N_3S$	138—139	67·4	4·9	15·6		67·5	4·9	15·7	
17-Oxo-5α-androstane-3-spiro-3′-(4′-methyl)- (9)	$C_{21}H_{31}N_3OS$	250—252	67·2	8·2	11·1	8·5	67·6	8·3	11·3	8·6
		229—230	67·4	8·3	11·3					
17-Oxo-5α-androstane-3-spiro-3′-(4′-phenyl)-	$C_{26}H_{33}N_3OS$	229—230	71·7	7·6	9·5	7·1	71·7	7·6	9·6	7·35
17β-Hydroxy-5α-androstane-3-spiro-3′-(4′-phenyl)-	$C_{26}H_{35}N_3OS$	228—229	71·1	8·0	9·4	7·0	71·4	8·0	9·6	7·3
20-Oxo-5α-pregnane-3-spiro-3′-(4′-phenyl)-	$C_{28}H_{37}N_3OS$	242—243	72·15	8·0	8·9		72·6	8·0	9·1	
17-Oxo-5α-androstane-3-spiro-3′-(4′-*p*-dimethylaminophenyl)-	$C_{28}H_{38}N_4OS$	247	70·1	8·0	11·45		70·3	7·95	11·7	

Ring-closures over Alumina.—Acetone 4-phenylthiosemicarbazone (50 g.) in chloroform (1 l.) was stirred at room temperature with basic alumina (Peter Spence grade O) (200 g.) until little or no starting material could be detected by t.l.c. (*ca.* 90 hr.). The alumina was filtered off

[4] M. Busch and Th. Ulmer, *Ber.*, 1902, **35**, 1710.

[5] M. Tišler, *Croat. Chem. Acta*, 1956, **28**, 147 (*Chem. Abs.*, 1957, **51**, 12,016).

[6] E. Lieber and J. Ramachandran, *Canad. J. Chem.*, 1959, **37**, 101.

and washed with chloroform, the filtrates were evaporated, and the product was separated by crystallisation from light petroleum (b.p. 80—100°) and chromatography of the material remaining in the solution on silica gel (chloroform), giving sulphur (0·75 g.), 3,3-*dimethyl*-4-*phenyl*-Δ^1-[1,2,4]*triazoline*-5-*thione* (34·2 g.), m.p. 172—174°, acetone 4-phenylthiosemicarbazone (8·9 g.), and acetone 4-phenylsemicarbazone (2·1 g.).

The triazolinethiones prepared in this way are listed in Table 3.

(*b*) Cyclohexanespiro-3′-(4′-phenyl-$\Delta^{1'}$-[1′,2′,4′]triazoline-5′-thione) (1 g.), mercuric acetate (4 g.), and ethanol (400 c.c.) were boiled under reflux for 40 min., the mixture was evaporated to dryness, and the residue was extracted with chloroform. The product recovered from the chloroform solution was crystallised from ethanol, to give the triazolinone (0·35 g.) m.p. and mixed m.p. 206°.

The following were made by the same desulphurisation procedure: 3,3-*Dimethyl*-4-*phenyl*-Δ^1-[1,2,4]*triazoline*-5-*one*, m.p. 143—144°, $\nu_{max.}$ 1750 cm.$^{-1}$ (Found: C, 63·1; H, 5·6;

TABLE 4

Δ^3-[1,3,4]Thiadiazolines

Name	Formula	M.p.	Found (%) C	H	N	S	Required (%) C	H	N	S
2,2-Dimethyl-5-phenylimino-[a]	$C_{10}H_{11}N_3S$	100—102°	58·4	5·5	20·4		58·5	5·4	20·5	
5-*o*-Bromophenylimino-2,2-dimethyl-	$C_{10}H_{10}BrN_3S$	94—95	42·1	3·7	14·8		42·3	3·5	14·8	
2,2-Dimethyl-5-*p*-dimethylaminophenylimino-	$C_{12}H_{16}N_4S$	119—121	58·5	6·5	22·6		58·1	6·45	22·6	
Cyclohexanespiro-2′-(5′-phenylimino)-	$C_{13}H_{15}N_3S$	80—82	63·7	6·2	17·1		63·6	6·1	17·1	
2,2-Dimethyl-5(1-naphthyl)-imino-	$C_{14}H_{13}N_3S$	94—95	65·6	5·3	16·5		65·9	5·1	16·5	
2-Methylcyclohexane-spiro-2′-(5′-phenylimino)-(6) and (7)	$C_{14}H_{17}N_3S$	104—105 80—81	64·7 64·7	6·75 6·7	16·1 16·1		64·9	6·6	16·2	
Bicyclo[3,3,1]non-2-en-9-spiro-2′(5′-phenylimino)- (5)	$C_{16}H_{17}N_3S$	139 108—109	68·0 67·6	6·3 6·0	14·4 14·65		67·8	6·0	14·8	
17-Oxo-5α-androstane-3-spiro-2′-(5′-methylimino)-[b]	$C_{21}H_{31}N_3OS$	142—143	67·4	8·4	11·1	8·5	67·6	8·3	11·3	8·6
17-Oxo-5α-androstane-3-spiro-2′-(5′-phenylimino)-[b]	$C_{26}H_{33}N_3OS$	162—163 150—151	72·0 71·7	7·5 7·5	10·0 9·4	7·4 7·2	71·7	7·6	9·6	7·35

[a] *M* 206 (cryoscopic, in benzene); required *M* 205. [b] Trace of stereoisomer indicated by Me signal in n.m.r. spectrum.

Ring-closures over Manganese Dioxide.—Acetone 4-phenylthiosemicarbazone (10 g.) in benzene (750 c.c.) was stirred with manganese dioxide (100 g.) for 1 hr.; the manganese dioxide was filtered off and washed with benzene. The filtrates were evaporated and 2,2-*dimethyl*-5-*phenylimino*-Δ^3-[1,3,4]*thiadiazoline* (7·0 g., m.p. 100—102°) was crystallised from light petroleum (b.p. 80—100°). Thiadiazolines made by this method are listed in Table 4.

Preparation of Triazolinones.—(*a*) Cyclohexanone 4-phenylsemicarbazone (1·8 g.), basic alumina (50 g.), and chloroform (100 c.c.) were stirred at room temperature for 7 days. The filtered solution was evaporated and the product was chromatographed ($CHCl_3$–alumina) to give *cyclohexanespiro*-3′-(4′-*phenyl*-$\Delta^{1'}$[1′,2′,4′]*triazoline*-5′-*one*) as white crystals from ethanol, m.p. 208° (decomp.) $\nu_{max.}$ 1755s cm.$^{-1}$ (Found: C, 67·8; H, 6·1; N, 18·2. $C_{13}H_{15}N_3O$ requires C, 68·0; H, 6·55; N, 18·3%).

N, 22·1. $C_{10}H_{11}N_3O$ requires C, 63·5; H, 5·7; N, 22·2%). 5α-*Androstan*-17-*one*-3-*spiro*-3′-(4′-*phenyl*-$\Delta^{1'}$-[1′,2′,4′]*triazoline*-5′-*one*), m.p. 222—224° (Found: C, 73·7; H, 7·6; N, 10·5. $C_{26}H_{33}N_3O_2$ requires C, 73·7; H, 8·1; N, 10·3%).

Cycloheptanone 4-*phenylsemicarbazone* was formed during the treatment of cycloheptanone 4-phenylthiosemicarbazone with alumina and was identical with material made from cycloheptanone and 4-phenylsemicarbazide in boiling ethanol or chloroform; it formed needles (from ethanol), m.p. 189—190° (Found: C, 68·6; H, 7·7; N, 17·6. $C_{14}H_{19}N_3O$ requires C, 68·5; H, 7·75; N, 17·15%).

I am indebted to Dr. J. R. Bedford for the n.m.r. spectra, and to Mr. C. J. Marsden for experimental assistance.

[9/1067 *Received, June 23rd,* 1969]