Thiadiazoles and Dihydrothiadiazoles. Part 5.[1] Synthesis of 2,3-Dihydro-1,3,4-thiadiazoles by Reaction of Aldehydes or Ketones with Thioaroylhydrazines

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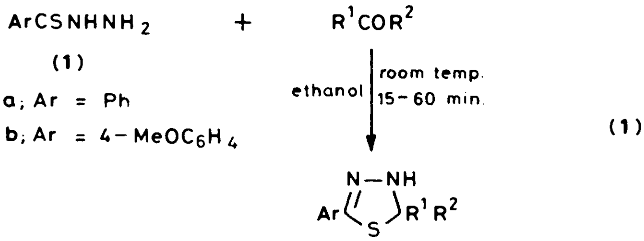
A general method for the synthesis of 2,5- and 2,2,5-substituted 2,3-dihydro-1,3,4-thiadiazoles is described, involving the condensation of aldehydes or ketones with thioaroylhydrazines. Evidence for the cyclic nature of the products is discussed. The reaction of 4-methoxythiobenzoylhydrazine with β-chloropropiophenone gives 1-(4-methoxythiobenzoyl)-3-phenyl-4,5-dihydro-1*H*-pyrazole, whereas the corresponding reaction with α-chloroacetophenone gives the known compound 2-(4-methoxyphenyl)-5-phenyl-6*H*-1,3,4-thiadiazine. 4-Methoxybenzoylhydrazine also reacts with pentane-2,4-dione to give a mixture of 5-hydroxy-1-(4-methoxythiobenzoyl)-3,5-dimethyl-4,5-dihydro-1*H*-pyrazole and 2-acetonyl-5-(4-methoxyphenyl)-2-methyl-2,3-dihydro-1,3,4-thiadiazole, and with 4-oxo- and 5-oxo-alkanoic acids to give 2-(2-carboxyethyl)- and 2-(3-carboxypropyl)-5-(4-methoxyphenyl)-2-methyl-2,3-dihydro-1,3,4-thiadiazoles which are readily cyclized to 3-(4-methoxyphenyl)-5-methyl-4-thia-1,2-diazabicyclo[3.3.0]oct-2-en-8-one and 8-(4-methoxyphenyl)-6-methyl-7-thia-1,9-diazabicyclo[4.3.0]non-8-en-2-one.

In a preliminary communication[2] we reported the unexpected formation of 2,3-dihydro-1,3,4-thiadiazoles (**2**) when thioaroylhydrazines (**1**) are treated with aldehydes or ketones. We now report the details of our investigation into this general reaction [equation (1)], which includes a study of the use of aliphatic aldehydes and of ketones containing additional functionality.



(**2**)

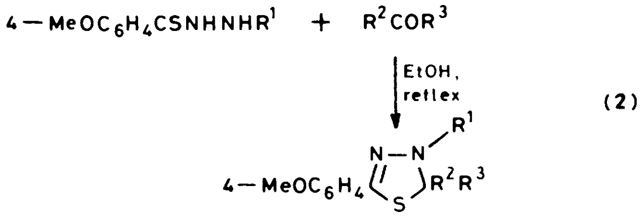
a; Ar = Ph, R^1 = H, R^2 = Ph
b; Ar = Ph, R^1 = H, R^2 = 4-MeC_6H_4
c; Ar = Ph, R^1 = H, R^2 = 4-$MeOC_6H_4$
d; Ar = Ph, R^1 = H, R^2 = 4-ClC_6H_4
e; Ar = Ph, R^1 = H, R^2 = 2-HOC_6H_4
f; Ar = 4-$MeOC_6H_4$, R^1 = H, R^2 = Ph
g; Ar = R^2 = $MeOC_6H_4$, R^1 = H
h; Ar = 4-$MeOC_6H_4$, R^1 = H, R^2 = 4-ClC_6H_4
i; Ar = Ph, R^1 = R^2 = H
j; Ar = 4-$MeOC_6H_4$, R^1 = R^2 = H
k; Ar = Ph, R^1 = R^2 = Me
l; Ar = Ph, R^1R^2 = $-[CH_2]_5-$
m; Ar = 4-$MeOC_6H_4$, R^1 = R^2 = Me
n; Ar = 4-$MeOC_6H_4$, R^1R^2 = $-[CH_2]_5-$
o; Ar = 4-$MeOC_6H_4$, R^1 = Ph, R^2 = Me
p; Ar = 4-$MeOC_6H_4$, R^1R^2 = $-[CH_2]_2NMe[CH_2]_2-$
q; Ar = 4-$MeOC_6H_4$, R^1 = Me, R^2 = $AcCH_2$
r; Ar = 4-$MeOC_6H_4$, R^1 = Me, R^2 = $HO_2C[CH_2]_2$
s; Ar = 4-$MeOC_6H_4$, R^1 = Me, R^2 = $HO_2C[CH_2]_3$

At the outset of this work it was assumed, on the evidence of a number of earlier studies,[3-5] that a thioaroylhydrazine (**1**), unsubstituted at N^2, would react with an aldehyde or ketone in the same manner as a thiosemicarbazide or dinitrophenylhydrazine, *i.e.*, to give an acyclic thioaroylhydrazone (**3**) by a

$ArCSNHN{=}CR^1R^2$

(**3**)

straightforward addition–elimination pathway. Only when such a pathway was blocked by N^2-substitution in the aroylhydrazine was cyclization expected to lead to 3-substituted 2,3-dihydro-1,3,4-thiadiazoles (**4**), a reaction [equation (2)]



(**4**)

a; R^1 = Ph, R^2 = 4-$MeOC_6H_4$, R^3 = H
b; R^1 = Pr^i, R^2 = R^3 = Me
c; R^1 = Pr^i, R^2 = 4-$MeOC_6H_4$, R^3 = H
d; R^1 = $PhCH_2$, R^2 = 4-$MeOC_6H_4$, R^3 = H

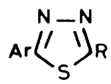
extensively investigated by Wuyts and co-workers[6] and by others.[7,8]

Indeed, Sandstrom[9] had specifically rejected a cyclic structure such as (**2**) for the product he obtained by treating phenylthioacetylhydrazine with benzaldehyde, on the basis of a comparison of its u.v. spectrum with those of known 2,3-dihydro-1,3,4-thiadiazoles (**4**), and in spite of its ready oxidation to the corresponding 1,3,4-thiadiazole (**5**). Accordingly, our objective was to prepare acyclic thioaroylhydrazones (**3**) and to

Table 1. N.m.r. data for aldehyde-derived 3-dihydro-1,3,4-thiadiazoles (**2a**—**h**) and (**11a**—**b**)

	δ_H [a]				δ_C [b]				
Cmpd.	ArH	2-H	NH	Other	*C*OR	C=N	Ar	C-2	Other
(**2a**)	7.2—7.7	6.3	6.25	—	—	146.3	126.4—141.6	74.7	—
(**2b**)	7.1—7.7	6.3	6.0	2.3 (Me)	—	146.1	124.6—138.7	74.5	20.9 (Me)
(**2c**)	6.7—7.8	6.3	6.45	3.7 (OMe)	159.0	145.7	126.6—132.3	74.4	54.7 (OMe)
(**2d**)	7.2—7.8	6.3	6.0	—	—	146.3	125.9—139.0	73.7	—
(**2e**) [c]	6.8—7.8	6.6	*d*	2.9 (OH)	152.4	144.4	116.7—132.2	67.6	—
(**2f**)	6.9—7.7	6.3	6.3	3.8 (OMe)	160.7	146.3	113.8—140.6	74.4	55.0 (OMe)
(**2g**)	6.7—7.6 [e]	6.3	5.9	3.8 (OMe), 3.7 (OMe)	160.2, 160.8	146.6	113.8—132.7	74.6	55.2 (2 × OMe)
(**2h**) [f]	6.9—7.6 [e]	6.3	*d*	3.8 (OMe)	160.6	146.2	113.7—138.9	73.6	55.0 (OMe)
(**11a**)	7.1—7.8	4.8(2)	—	4.9 (NCH_2N)	—	146.1	126.8—131.3	59.2	72.6 (NCN)
(**11b**)	6.9—7.6 [g]	4.8(2)	—	4.9 (NCH_2N), 3.8 (OMe)	160.8	146.1	113.9—128.3	59.2	72.9 (NCN), 55.2 (OMe)

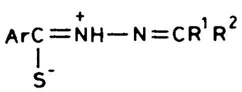
[a] 90 MHz; $CDCl_3$ unless otherwise indicated. [b] 20.1 MHz; $CDCl_3$. [c] In [$^2H_6$]acetone. [d] Masked by aromatic signals. [e] Two AA'BB' systems, J_{AB} 9 Hz. [f] At 220 MHz. [g] One AA'BB' system, J_{AB} 9 Hz.



(**5**)

ArCCl=NN=CHR

(**6**)



(**7**)

study their reactions in the presence of strong, non-nucleophilic, bases.

Reaction of Thioaroylhydrazines with Aromatic Aldehydes.— Treatment of thiobenzoylhydrazine (**1a**) with benzaldehyde in ethanol gave, after 15 min at room temperature, the single product (**2a**) in 88% yield; no acidic catalyst was required and no evidence for the formation of any intermediate was obtained (*e.g.*, by t.l.c. analysis). The outcome of such reactions seems to be independent of both solvent [dichloromethane, methanol, toluene, diethyl ether (hereafter called ether), and aqueous ethanol may all replace ethanol] and temperature (in the range 20—100 °C), except that the formation of a by-product identified as the corresponding 2,5-disubstituted 1,3,4-thiadiazole (**5**) is slightly faster at reflux in ethanol.

The generality of the reaction was established by the use of four other aromatic aldehydes (4-methyl-, 4-methoxy-, 4-chloro-, and 2-hydroxy-benzaldehyde), and by treating 4-methoxythiobenzoylhydrazine (**1b**) with three of these aromatic aldehydes, giving in all instances the corresponding 2,5-disubstituted 2,3-dihydro-1,3,4-thiadiazoles (**2a**—**h**) in good yield (64—97%, not optimized) [equation (1)].

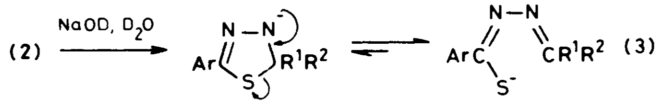
In three cases (**2a,c,e**) these compounds had been reported previously[3,4] but with the alternative acyclic structure (**3**) assigned. We are convinced that the cyclic structure (**2**) is correct on the basis of the following evidence (n.m.r. data shown in Table 1).

(1) The ^{13}C n.m.r. shift of the C-2 usually in the range 73—75, is incompatible with sp^2-hybridization, which would be required for the acyclic structure (**3**), but supports sp^3-hybridization with a deshielding environment.

(2) The ^1H n.m.r. signal of the methine proton at C-2 is normally situated at 6—7, *i.e.* upfield of the aromatic region, which is incompatible with the imino-proton of a hydrazone.

(3) The key n.m.r. shifts discussed above are very similar to those shown by known 3-substituted 2,3-dihydro-1,3,4-thiadiazoles (**4**), such as those we have prepared by repeating the experiments of Wuyts and co-workers[6] or by treating chlorodiazabutadienes (**6**) with thioureas.[10]

We have also tested for the occurrence of solvent-dependent tautomeric equilibria between dihydrothiadiazoles (**2**) and various alternative structures such as (**3**) and (**7**). Such equilibria have been proposed by other investigators of these compounds,[11,12] who have claimed that acyclic forms arise in polar solvents such as dimethyl sulphoxide (DMSO) and in the solid state. ^1H and ^{13}C n.m.r. analysis of a [$^2H_6$]DMSO solution of compound (**2g**) was hindered by rapid oxidation to the thiadiazole, and no n.m.r. evidence for acyclic isomers was obtained in $CDCl_3$, C_6D_6, or [$^2H_6$]acetone. The i.r. spectra of solid samples of (**2**) revealed no bands attributable to $H–N^+$ vibrations [*cf.* PhCH=$\overset{+}{N}$H–N=C(S^-)CH_2Ph, $\nu_{max.}$ 2 480 cm^{-1} [12]], although rapid ^1H n.m.r. analysis of a freshly prepared [$^2H_6$]DMSO solution of compound (**2g**) revealed a diminution in the intensity of the 2-CH signal (δ_H 6.5), accompanied by the appearance of a low-intensity singlet at δ_H 13.2, possibly compatible with the existence of some of the zwitterionic form (**7**). However, when compound (**2g**) was dissolved in [$^2H_6$]acetone and the solution was shaken vigorously with NaOD–D_2O immediately prior to n.m.r. analysis, a ^{13}C n.m.r. signal at δ_C 153.8 replaced that of C-2 (normally at δ_C 74.9 in this solvent), suggesting that deprotonation is accompanied by ring-opening [equation (3)].



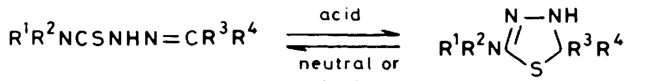
The behaviour of these dihydrothiadiazoles is thus similar to, but not the same as, thiosemicarbazones (**8**), which have been shown[11] to cyclize to 2-aminodihydrothiadiazoles (**9**) in acidic solution, but which apparently exist predominantly or exclusively in the open-chain form in neutral and basic solution.

Reaction of Thioaroylhydrazines with Aliphatic Aldehydes.— When the thioaroylhydrazine (**1a**) was treated with an excess of formaldehyde in ethanol, a single product was obtained. Although the absence of NH stretching in the i.r. spectrum of this product is compatible with the structure (**10**) proposed for it by Holmberg,[3] and the m.p. of our product (89—90 °C) suggests that it is the same as that isolated by Holmberg, the correct structure appears to be (**11a**), since its ^1H n.m.r. and broad-band ^{13}C n.m.r. spectra do not reveal any $=CH_2$ group, only two

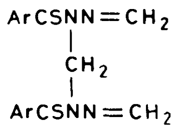
Table 2. N.m.r. data for ketone-derived 2,3-dihydro-1,3,4-thiadiazoles (**2k**—**p**)

	δ_H[a]			δ_C[b]				
Cmpd.	ArH	NH	Other	COMe	C=N	Ar	C-2	Other
(**2k**)	7.2—8.1	4.2—5.8[c]	1.7 (2 × Me)	—	146.5	126.3—131.7	79.9	29.0 (2 × Me)
(**2l**)	7.2—7.8	5.6—6.2[c]	1.2—2.4 (5 × CH_2)	—	145.3	126.5—132.0	85.8	39.1(2), 24.7(1), 24.4(2)
(**2m**)	6.8—7.6	5.7	3.8 (OMe), 1.7 (2 × Me)	160.4	146.9	113.6—129.1	79.9	54.9 (OMe), 29.2 (2 × Me)
(**2n**)[d]	6.9—7.5[e]	5.6	3.9 (OMe), 1.2—2.4 (5 × CH_2)	160.4	147.0	113.6—129.1	85.6	55.0 (OMe), 38.4(2), 24.7(1), 24.5(2)
(**2o**)	6.9—7.8	5.5—6.5[c]	3.8 (OMe), 2.1 (Me)	160.5	144.2	112.5—132.4	83.9	55.0 (OMe), 29.2 (Me)
(**2p**)	6.9—7.6	5.8	3.8 (OMe), 1.8—2.8 (4 × CH_2), 2.3 (NMe)	160.5	146.1	113.6—128.0	82.9	55.0 (NCH_2), 53.9 (OMe), 45.4 (CCH_2), 38.4 (NMe)

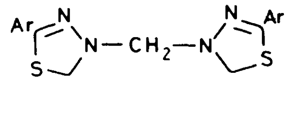
[a] At 90 MHz in $CDCl_3$ unless otherwise indicated. [b] 20.1 MHz. [c] Broad signal. [d] At 220 MHz. [e] AA'BB' system, J_{AB} 9 Hz.



(8) (9)



(10)



(11)
a; Ar = Ph
b; Ar = 4-MeOC$_6$H$_4$

different types of deshielded CH_2 groups (ratio 2:1). An analogous product (**11b**) was readily obtained from the corresponding reaction of compound (**1b**) (74%).

We were unable to detect any intermediate products such as (**2i,j**) by t.l.c. analysis of aliquots withdrawn during the reactions leading to compounds (**11a,b**) and attempts to extend this synthesis to higher aliphatic aldehydes, or to aromatic aldehydes used in large excess, were unsuccessful in that pure products could not be isolated. Since the preliminary report of our work appeared[2] Zelenin and co-workers have reported similar reactions between thiobenzoylhydrazine (**1a**) and acetaldehyde and propionaldehyde; they isolated 2-alkyl-2,3-dihydrothiadiazoles from such reactions, albeit in low yield.[13]

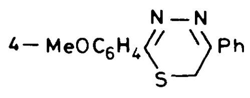
Reaction of Thioaroylhydrazines with Ketones.—Both of the thioaroylhydrazines studied react readily with simple ketones such as acetone and cyclohexanone to give, in 51—98% yield, 2,2-disubstituted 2,3-dihydro-1,3,4-thiadiazoles (**2k**—**n**) [equation (1)], and comparable reactions of the hydrazine (**1b**) with acetophenone (79%), and 1-methyl-4-piperidone (71%), gave dihydrothiadiazoles (**2o,p**) respectively. These reactions proceed to completion within 1 h at room temperature.

Holmberg[3] had previously assigned an acyclic structure (**3**) to one of these products (**2k**), but although the ^1H n.m.r. data are less conclusive than in the case of aldehyde-derived dihydrothiadiazoles, owing to the higher substitution at C-2, the ^{13}C n.m.r. spectra of these ketone-derived dihydrothiadiazioles all show signals corresponding to the sp^3-hybridized C-2 of compounds (**2**), and no evidence of even small amounts of an acyclic isomer such as (**3**) (no signal at δ_C *ca.* 158) (Table 2).

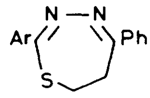
These products are less stable, especially those from cyclic ketones, and less easily crystallized, than those derived from aldehydes.

During the course of our investigation, Zelenin and co-workers[14] reported a similar study with aliphatic ketones, using the equivalence of the 2-Me ^1H n.m.r. signals as proof of the structure of compound (**2k**).

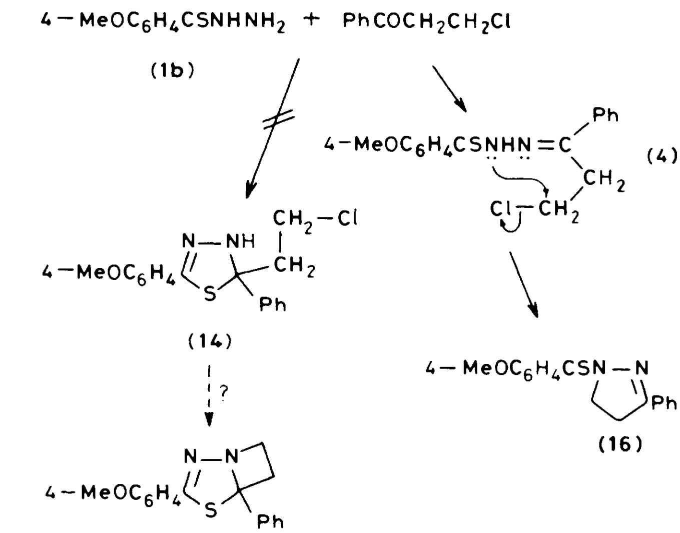
Treatment of the hydrazine (**1b**) with chloroacetone gave unstable products which were not identified. However, the same hydrazine (**1b**) when treated with α-chloroacetophenone in the presence of acid gave a single product. This proved to be the thiadiazine (**12**), previously reported[15] to result from the corresponding reaction of this hydrazine with α-bromoacetophenone, and not the hoped-for dihydrothiadiazole. Reasoning that closure to a seven-membered thiadiazepine ring (**13**) would



(12)



(13)



(1b) (4) (14) (15) (16)

Table 3. Mass spectrometric data for 2,3-dihydro-1,3,4-thiadiazoles

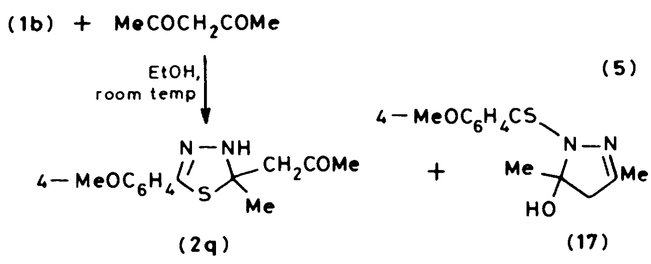
Cmpd.	Intensity of ions relative to base peak (%)[a] $M - R^2$	ArCS	ArCNS	ArCHN	ArCN	R^1R^2CN	Base (100%)
(**2a**)	27	37	(100)	32	55	32	$PhNCS^+$
(**2b**)	84	43	62	25	43	63	M^+
(**2c**)	5	13	34	15	(100)	23	$PhCN^+$
(**2d**)	73	48	53	56	(100)	48	PhCN
(**2e**)	5	62	20	39	69	18	Ph^+
(**2f**)	16	27	24	31	79	38	$PhCN^+$
(**2g**)	13	53	20	(100)	54	(100)	$ArCHN^+$
(**2h**)	30	28	15	49	40	18	*m/z* 227
(**2k**)	(100)	15	5	11	10	29	$(M - Me)^+$
(**2l**)	—	18	5	23	5	5	$(M - Pr)^+$
(**2m**)	(100)	5	5	14	25	71	$(M - Me)^+$
(**2n**)	—	17	5	27	27	5	$(M - Pr)^+$
(**2o**)	(100)	22	5	9	23	22	$(M - Me)^+$
(**2p**)	—	25	5	16	15	12	$(M - C_4H_9N)^+$
(**2r**)	68	70	29	37	96	5	$(M - CH_4O)^+$
(**4a**)	5	40	5	(100)	54	(100)	$ArCHN^+$
(**4b**)	63	17	11	13	8	6	$(M - C_4H_9)^+$
(**4c**)	5	13	5	17	23	17	$(M - CH_2N)^+$
(**4d**)	5	58	24	12	36	12	$C_7H_7^+$
(**11a**)	—	27	52	59	49	—	$C_8H_6N_2S^+$
(**11b**)	—	18	7	28	(100)	—	$ArCN^+$

[a] Base peaks shown as (100).

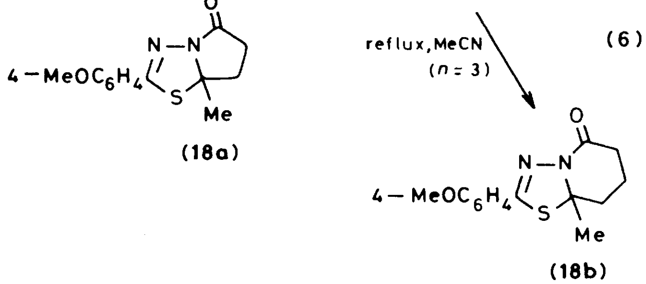
be less likely to compete with dihydrothiadiazole formation than would closure to a six-membered thiadiazine ring, we treated the hydrazine (**1b**) with β-chloropropiophenone, intending to attempt the conversion of the expected (chloroethyl)dihydrothiadiazole (**14**) into the bicyclic derivative (**15**). The product contained no halogen atom, and was shown spectroscopically to be the thioaroyldihydropyrazole (**16**), possibly formed as shown in equation (4).

We next attempted to obtain dihydrothiadiazoles with carboxyl substitution at C-2. Reactions of hydrazines (**1**) with pyruvic acid afforded no identifiable products. The thioaroylhydrazine (**1b**) was next treated with pentane-2,4-dione in the hope of obtaining the 2-acetonyl-2,3-dihydrothiadiazole (**2q**), from which a haloform reaction might lead to the same end-product as would be obtained using acetoacetic acid. The reaction proceeded readily and the product analysed correctly for (**2q**). However, n.m.r. analysis indicated that a mixture of two isomers was present, the major product being the 3,5-dimethyl-5-hydroxydihydropyrazole (**17**) [equation (5)]. In $CDCl_3$ the isomer ratio is estimated to be 5:2 [(**17**):(**2q**)], but all attempts to isolate the two substances by chromatography failed. We suspect that the two isomers are in equilibrium while in contact with silica gel. A similar observation has been made by Zelenin and co-workers using thiobenzoylhydrazine (**1a**) and pentane-2,4-dione.[16]

In contrast to pyruvic acid, levulinic acid (4-oxopentanoic acid) and compound (**1b**) reacted cleanly to give, in 76% yield, the 2-(2-carboxyethyl)dihydrothiadiazole (**2r**). Good structural

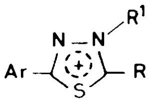


evidence was provided for this compound by its i.r. (CO_2H at 2 950 cm^{-1}, NH at 3 280 cm^{-1}) and n.m.r. spectra (C-2 δ_C 82.9). It proved possible to cyclize this γ-amino acid quite readily, by intramolecular amide-bond formation using dicyclohexylcarbodi-imide (DCC) [equation (6)]. A single product was obtained, with the expected molecular ion (*m/z* 262). Its n.m.r. spectra were entirely in accord with the thiadiazabicyclo-[3.3.0]octenone structure (**18a**), and its i.r. spectrum showed neither the NH nor the OH stretching bands of its precursor.



To test the generality of this diazathiabicycloalkenone synthesis, the next higher homologue of levulinic acid, 5-oxohexanoic acid, was treated with the thioaroylhydrazine (**1b**) under similar conditions. Unexpectedly, the product obtained after recrystallization of an initially formed oil displayed neither NH nor OH i.r. stretching bands, and inspection of its n.m.r. spectra, in comparison with those of product (**18a**), revealed that cyclization had occurred spontaneously during recrystallization to provide the analogous 7-thia-1,9-diazabicyclo-[4.3.0]nonenone (**18b**) in 80% yield.

Mass Spectrometric Fragmentations of 2,3-Dihydro-1,3,4-thiadiazoles (**2**).—When the mass spectra of *N*-substituted dihydrothiadiazoles were reported by Wolkoff and Hammerum,[17] they noted that thiadiazolium ions (**19**), formed by loss of a radical from C-2, are important intermediates in the fragmentation of such structures. As can be seen from Table 3 of the 3-substituted dihydrothiadiazoles (**4a—d**) investigated only (**4b**) behaves as predicted. The 3-H analogues (**2**) do not usually show significant abundances of such ions unless they are derived from acyclic ketones. This may be due to the intervention of alternative pathways, or to more rapid fragmentation of the thiadiazolium ions (**19**) when R^2 = H. The other principal



(**19**)

$Ar\overset{+}{C}=NN=CR^1R^2$

(**20**)

pathway noted by the previous workers, namely S–C-2 fission followed by loss of HS˙ to give diazabutadienyl cations (**20**), is also not obvious in the mass spectra of 2,3-dihydrothiadiazoles (**2**), unless it accounts for the high abundance of ions such as $ArCHN^+$, $R^1R^2CN^+$, and $ArCN^+$.

Experimental

General techniques and spectroscopic apparatus were as described previously,[10] except that in addition a Perkin-Elmer R34 220 MHz n.m.r. spectrometer was available. Light petroleum refers to the fraction boiling in the range 60—80 °C except where stated otherwise.

Thiobenzoylhydrazine (**1a**), m.p. 68—70 °C [light petroleum (40—60)–ether (1 : 1)] (lit.,[3] 70 °C), and 4-methoxythiobenzoylhydrazine (**7b**), m.p. 125—127 °C (from water) (lit.,[4] 126—128 °C), were prepared by hydrazinolysis of the corresponding sodium thiobenzoylthioglycolates at 0 °C, followed by acidification to pH 4 (conc. HCl) and recrystallization. 4-Methoxythiobenzoylthioglycolic acid was prepared by addition of carbon disulphide to a chilled solution of the corresponding phenylmagnesium bromide in anhydrous ether, followed by reaction of the liberated dithioacid with sodium chloroacetate.[4] Thiobenzoylthioglycolic acid was prepared by the reaction of potassium hydrogensulphide with benzotrichloride (α,α,α-trichlorotoluene), followed by treatment of the dithio acid with sodium chloroacetate.[18]

Reactions of Thioaroylhydrazines with Aromatic Aldehydes.—The following general procedure was used. Benzaldehyde (2.71 g, 25.6 mmol) was added in a single portion to a stirred solution of thiobenzoylhydrazine (**1a**) (3.77 g, 24.8 mmol) in ethanol (100 cm^3). After 15 min at room temperature the solvent was removed under reduced pressure and the residue was recrystallized from aqueous ethanol to yield white crystals, identified spectroscopically (n.m.r. data in Table 1) as *2,5-diphenyl-2,3-dihydro-1,3,4-thiadiazole* (**2a**) (5.2 g, 88%), m.p. 78—80 °C (lit.,[3] 81—82 °C)* (Found: C, 70.0; H, 4.7; N, 11.7; S, 12.9%; M^+, 240. $C_{14}H_{12}N_2S$ requires C, 70.0; H, 5.0; N, 11.7; S, 13.3%; *M*, 240).

The following compounds (n.m.r. data in Table 1) were prepared in this way, with minor variations of solvent, reaction time, and recrystallization solvent.

*5-Phenyl-2-(*p*-tolyl)-2,3-dihydro-1,3,4-thiadiazole* (**2b**) (69%), m.p. 52—54 °C (from EtOAc–light petroleum) (Found: C, 71.0; H, 5.4; N, 11.0; S, 12.5%; M^+, 254. $C_{15}H_{14}N_2S$ requires C, 70.8; H, 5.6; N, 11.0; S, 12.6%; *M*, 254).

2-(4-Methoxyphenyl)-5-phenyl-2,3-dihydro-1,3,4-thiadiazole (**2c**) (71%), m.p. 82—84 °C (from light petroleum) (lit.,[4] 84 °C)* (Found: C, 66.7; H, 5.1; N, 10.2; S, 11.4%; M^+, 270. $C_{15}H_{14}N_2OS$ requires C, 66.7; H, 5.2; N, 10.4; S, 11.9%, *M*, 270).

2-(4-Chlorophenyl)-5-phenyl-2,3-dihydro-1,3,4-thiadiazole (**2d**) (64%), m.p. 106—108 °C (from light petroleum) (Found: C, 61.5; H, 4.2; Cl, 12.9; N, 10.1; S, 11.5%; M^+, 274, 276. $C_{14}H_{11}{}^{35}ClN_2S$ requires C, 61.2; H, 4.0; Cl, 12.9; N, 10.2; S, 11.7%; *M*, 274).

2-(2-Hydroxyphenyl)-5-phenyl-2,3-dihydro-1,3,4-thiadiazole (**2e**) (72%), m.p. 152—154 °C (from EtOH) (lit.,[3] 155 °C)* (Found: C, 65.7; H, 4.5; N, 10.9; S, 12.3%; M^+, 256. $C_{14}H_{12}N_2OS$ requires C, 65.6; H, 4.7; N, 10.9; S, 12.5%, *M*, 256).

5-(4-Methoxyphenyl)-2-phenyl-2,3-dihydro-1,3,4-thiadiazole (**2f**) (82%), m.p. 97—99 °C (from EtOH) (Found: C, 66.4; H, 5.0; N, 10.4; S, 11.9%; M^+, 270. $C_{15}H_{14}N_2OS$ requires C, 66.6; H, 5.2; N, 10.4; S, 11.9%; *M*, 270).

2,5-Bis-(4-methoxyphenyl)-2,3-dihydro-1,3,4-thiadiazole (**2g**) (97%), m.p. 120—122 °C (from EtOH) (Found: C, 63.7; H, 5.2; N, 9.2; S, 10.7%; M^+, 300. $C_{16}H_{16}N_2O_2S$ requires C, 64.0; H, 5.3; N, 9.3; S, 10.7%; *M*, 300).

2-(4-Chlorophenyl)-5-(4-methoxyphenyl)-2,3-dihydro-1,3,4-thiadiazole (**2h**) (64%), m.p. 116—118 °C (from EtOH) (Found: C, 59.1; H, 4.1; N, 9.0; S, 10.5%; M^+, 304, 306. $C_{15}H_{13}{}^{35}ClNOS$ requires C, 59.1; H, 4.3; N, 9.2; S, 10.5%; *M*, 304).

Reactions of Thioaroylhydrazines with Formaldehyde.—Formaldehyde (40% aqueous solution; 1.5 cm^3, 20 mmol) was added in a single portion to a solution of thiobenzoylhydrazine (**1a**) (2.70 g, 18 mmol) in ethanol (50 cm^3). After 30 min at room temperature the solution was concentrated to *ca.* 5 cm^3 under reduced pressure and cooled in ice. A white precipitate was recrystallized from ethanol and identified spectroscopically (n.m.r. data in Table 1) as bis-(5-phenyl-2,3-dihydro-1,3,4-thiadiazol-3-yl)methane (**11a**) (2.11 g, 69%), m.p. 89—90 °C (lit.,[3] 90—91 °C) (Found: C, 59.8; H, 4.6; N, 16.2%; M^+, 340. Calc. for $C_{17}H_{16}N_4S_2$: C, 60.0; H, 4.7; N, 16.5%; *M*, 340).

Also prepared by this procedure was *bis-[5-(4-methoxyphenyl)-2,3-dihydro-1,3,4-thiadiazol-3-yl]methane* (**11b**) (74%), m.p. 128—130 °C (from aqueous EtOH) (Found: C, 56.7; H, 5.3; N, 14.3; S, 15.8%; M^+, 400. $C_{19}H_{20}N_4O_2S_2$ requires C, 57.0; H, 5.0; N, 14.0; S, 16.0%; *M*, 400); n.m.r. data are in Table 1.

Reactions of Thioaroylhydrazines with Ketones.—Acetone (520 mg, 9 mmol) was added in a single portion to a solution of thiobenzoylhydrazine (**1a**) (7.5 mmol) in ethanol (50 cm^3), and after about 30 min at room temperature the solvent was removed under reduced pressure. The residue was recrystallized from aqueous ethanol to give a pale-yellow solid identified spectroscopically (n.m.r. data in Table 2) as a 2,2-dimethyl-5-phenyl-2,3-dihydro-1,3,4-thiadiazole (**2k**) (64%), m.p. 49—51 °C (lit.,[3] 52 °C) (Found: M^+, 192. Calc. for $C_{10}H_{12}N_2S$: *M*, 192).

The following compounds (n.m.r. data in Table 2) were prepared by minor modification of the above procedure.

From (**1a**) and cyclohexanone, *2-phenyl-1-thia-3,4-diaza-spiro[4.5]dec-2-ene* (**2l**) (52%) m.p. 52—54 °C (from EtOAc–light petroleum) (Found: C, 67.3; H, 6.7; N, 11.8; S, 13.7%; M^+, 232. $C_{13}H_{16}N_2S$ requires C, 67.2; H, 6.9; N, 12.1; S, 13.8%; *M*, 232).

From (**1b**) and acetone, *5-(4-methoxyphenyl)-2,2-dimethyl-2,3-dihydro-1,3,4-thiadiazole* (**2m**) (98%), m.p. 51—53 °C (from

* Compounds have previously been prepared, but were assigned incorrect structures (**3**) in the literature cited; they are therefore designated as being 'new'.

Table 4. N.m.r. data for *N*-substituted 2,3-dihydro-1,3,4-thiadiazoles (**4a**—**d**)

	δ_H [a]				δ_C [b]					
Cmpd.	ArH	2-H	MeO	Other	*C*OMe	C=N	Ar	C-2	OCH_3	Other
(**4a**)	6.7—7.7	[c]	3.8	—	159.6, 160.6	142.1	114.0—144.3	73.0	56.0, 55.1	—
(**4b**)	6.9—7.5	—	3.8	3.4 (C*H*Me), 1.6 (2 × Me, s) 1.3 (d, *J* 7 Hz, CHMe_2)	159.6	137.6	113.6—127.2	82.8	55.2	47.9 (CH), 27.8 (CMe_2), 23.7 (CHMe_2)
(**4c**)	6.8—7.6	6.1	3.8	3.1 (C*H*Me_2), 1.3 (d, Me_a)[e] 1.1 (d. Me_b)[e]	160.0(2)	142.4	113.8—130.6	75.6	55.2(2)	51.5 (*C*HMe_2), 22.3 (Me), 17.4 (Me)
(**4d**)[d]	6.8—7.7	5.9	3.8	4.5 (d, CH_a) 3.95 (d, CH_b, *J* 16 Hz)	161.5(2)	143.6	113.3—136.6	78.2	55.2(2)	55.8 (CH_2)

[a] At 90 MHz in $CDCl_3$ unless otherwise indicated. [b] At 20.1 MHz. [c] Masked by aromatic signal. [d] At 220 MHz. [e] J_d 7.5 Hz; collapses to a singlet when irradiated at frequency of 3.1 signal

aqueous EtOH) (Found: C, 59.4; H, 6.3; N, 12.4; S, 13.9%; M^+, 222. $C_{11}H_{14}N_2OS$ requires C, 59.4; H, 6.3; N, 12.6; S, 14.4%; *M*, 222).

From (**1b**) and cyclohexanone, 2-(4-*methoxyphenyl*)-1-*thia*-3,4-*diazaspiro*[4.5]*dec*-2-*ene* (**2n**) (51%), m.p. 65—67 °C (from aqueous EtOH) (Found: C, 64.0; H, 6.6; N, 10.4; S, 12.3%; M^+, 262. $C_{14}H_{18}N_2OS$ requires C, 64.1; H, 6.9; N, 10.7; S, 12.2%; *M*, 232).

From (**1b**) and acetophenone, 5-(4-*methoxyphenyl*)-2-*methyl*-2-*phenyl*-2,3-*dihydro*-1,3,4-*thiadiazole* (**2p**) (79%), m.p. 86—87 °C (from aqueous EtOH) (Found: C, 67.7; H, 6.0; N, 9.8; S, 11.2%; M^+, 284. $C_{16}H_{16}N_2OS$ requires C, 67.6; H, 5.6; N, 9.9; S, 11.3%; *M*, 284).

From (**1b**) and *N*-methyl-4-piperidone, 2-(4-*methoxyphenyl*)-8-*methyl*-1-*thia*-3,4,8-*triazaspiro*[4.5]*dec*-2-*ene* (**2o**) (71%), m.p. 132—134 °C (from EtOH) (Found: C, 60.2; H, 7.1; N, 15.0%; M^+, 277. $C_{14}H_{19}N_3OS$ requires C, 60.6; H, 6.9; N, 15.1%; *M*, 277), and, after treatment of compound (**2p**) with anhydrous hydrogen chloride in ether, the corresponding *dihydrochloride* (69%), m.p. 206—208 °C (from EtOH–ether) (Found: C, 48.3; H, 6.1; N, 11.8%; M^+, 277. $C_{14}H_{21}Cl_2N_3OS$ requires C, 48.0; H, 6.0; N, 12.0%; *M*, 349).

Reaction of Thioaroylhydrazine (**1b**) *with Pentane*-2,4-*dione*.—Pentane-2,4-dione (250 mg, 2.5 mmol) was added in a single portion to a solution of compound (**1b**) (440 mg, 2.4 mmol) in ethanol (25 cm^3). After 2 h at room temperature a single product was detected by t.l.c. [light petroleum–EtOAc (1:1)], which was isolated by evaporation under reduced pressure and trituration of the residual red oil with light petroleum (40—60). Recrystallization (EtOH) gave off-white crystals (430 mg, 68%), m.p. 82—84 °C (Found: C, 59.1; H, 6.2; N, 10.3; S, 12.2%; M^+, 264. Calc. for $C_{13}H_{16}N_2O_2S$: C, 59.1; H, 6.1; N, 10.6; S, 12.1%; *M*, 264) believed to be a mixture (2:5 in $CDCl_3$) of 2-acetonyl-5-(4-methoxyphenyl)-2-methyl-2,3-dihydro-1,3,4-thiadiazole (**2q**) and its tautomer 5-hydroxy-1-(4-methoxythiobenzoyl)-3,5-dimethyl-4,5-dihydro-1*H*-pyrazole (**17**) on the basis of the following data: $\nu_{max.}$(KBr) 3 300—3 150br [OH str. of (**17**)], 1 638w, [C=O str. of (**2q**)], and 1 250s cm^{-1} [C–O str. of (**17**)]; δ_H (90 MHz) 7.6 and 6.8 (dd, *J* 9 Hz, 2 × Ar), 6.95 [s, NH of (**2q**) and OH of (**17**)], 3.83 (2 × OMe), 3.20 and 2.85 [ABdd, J_{AB} 20 Hz, CH_2 of (**17**)], 3.18 [weak s, CH_2 of (**2q**)], 2.10 and 2.0 [2 × s, 2 × Me of (**17**)], and 2.17 and 1.76 [2 × s, 2 × Me of (**2q**)]; δ_C (20.1 MHz) 193.24 (C=S), 161.24 (*C*OMe), 158.81 (C=N), 135—112.5 (Ar), 96.37 (*C*MeOH), 55.2 (OMe), 52.04 (CH_2), and 25.08 and 16.25 (Me) [all attributable to (**17**); no signals assignable firmly to (**2q**)].

Reaction of 4-*Methoxythiobenzoylhydrazine* (**1b**) *with Keto Acids*.—(a) *Levulinic acid*. A solution of aroylhydrazine (**1b**) (546 mg, 3.0 mmol) in ethanol (40 cm^3) was treated with 4-oxopentanoic acid (levulinic acid) (350 mg, 3.0 mmol) for 12 h at room temperature. The single product (t.l.c.; EtOAc; R_F 0.34) was isolated by evaporation and was recrystallized (from aqueous EtOH) to give 3-[5-(4-*methoxyphenyl*)-2-*methyl*-2,3-*dihydro*-1,3,4-*thiadiazol*-2-*yl*]*propanoic acid* (**2r**) (641 mg, 76%), m.p. 105—107 °C (Found: C, 56.0; H, 5.8; N, 9.7; S, 11.4%; M^+, 280. $C_{13}H_{16}N_2O_3S$ requires C, 55.7; H, 5.7; N, 10.0; S, 11.4%; *M*, 280); δ_H ($CDCl_3$; 90 MHz) 7.5 and 6.8 (dd, *J* 9 Hz, ArH), 6.55 (2 H, br exchangeable, OH and NH), 3.8 (s, OMe), 2.65 and 2.2 (m, 2 × CH_2), and 1.7 (s, Me); δ_C 177.59 (CO_2H), 160.70 (*C*OMe), 147.23 (C=N), 128.75 (2 C) 123.96 (1 C), and 113.87 (2 C) (all Ar), 82.86 (C-2), 55.20 (OMe), 35.68 (*C*H_2CO_2H), 30.33 (*C*H_2CMe), and 29.15 (Me).

(b) 5-*Oxohexanoic acid*. The acid (0.44 g, 3.38 mmol) was added to a solution of the aroylhydrazine (**1b**) (0.56 g, 3.08 mmol) in ethanol (25 cm^3) and the mixture was stirred at ambient temperature for 24 h. T.l.c. [EtOAc–light petroleum (1:1)] indicated total consumption of starting material, and evaporation under reduced pressure gave an oil believed to be the dihydrothiadiazole (**2s**) [$\nu_{max.}$ 3 280br (NH str.) and 2 950 cm^{-1} (H-bonded OH str.)]. After having been kept for 10 days, the oil slowly solidified. The solid was recrystallized (aqueous MeCN) and identified as 8-(4-*methoxyphenyl*)-6-*methyl*-7-*thia*-1,9-*diazabicyclo*[4.3.0]*non*-8-*en*-2-*one* (**18b**) (0.67 g, 79%), m.p. 156—158 °C (Found: C, 60.8; H, 5.9; N, 9.9; S, 11.6%; M^+, 276. $C_{14}H_{16}N_2O_2S$ requires C, 60.8; H, 5.8; N, 10.1; S, 11.6%; *M*, 276); δ_H ($CDCl_3$; 90 MHz) 7.73 and 6.94 (dd, *J* 9 Hz, ArH), 3.82 (s, OMe), 1.9—2.7 (br m, 3 × CH_2), and 1.71 (s, Me); δ_C 163.85 (C=O), 161.28 (*C*OMe), 153.56 (C=N), 128.87 (2 C), 121.95 (1 C), and 113.15 (2 C) (all Ar), 76.90 (C-6), 54.58 (OMe), 33.07 (*C*H_2C=O), 29.44 (*C*H_2CMe), 28.63 (CH_2), and 17.04 (Me).

Treatment of compound (**1b**) with pyruvic acid under similar conditions yielded no identifiable product.

Reaction of Thioaroylhydrazine (**1b**) *with Chloroalkyl Ketones*.—Glacial acetic acid (2 drops) was added to a solution of compound (**1b**) (300 mg, 1.6 mmol) and α-chloroacetophenone (290 mg, 1.9 mmol) in ethanol (25 cm^3), and after 3 h the mixture was cooled; the precipitate was collected and recrystallized (EtOH) to give 2-(4-methoxyphenyl)-5-phenyl-6*H*-1,3,4-thiadiazine (**12**) (290 mg, 64%), m.p. 142—144 °C (lit.,[14] 142 °C) (Found: C, 68.2; H, 5.1; N, 9.9; S, 11.1%; M^+, 282. Calc. for $C_{16}H_{14}N_2OS$: C, 68.1; H, 5.0; N, 9.9; S, 11.4%; *M*, 282); δ_H (60 MHz) 7.0—8.25 (ArH), 3.85 (s, OMe), and 3.45 (s, CH_2).

In a similar reaction to that described above, compound (**1b**) (510 mg, 2.8 mmol) and β-chloropropiophenone (490 mg, 2.9 mmol) gave, after 18 h, 1-(4-*methoxythiobenzoyl*)-3-*phenyl*-4,5-*dihydro*-1H-*pyrazole* (**16**) (600 mg, 72%), m.p. 138—140 °C (Found: C, 68.7; H, 5.4; N, 9.5; S, 10.6%; M^+, 296. $C_{17}H_{16}N_2OS$ requires C, 68.9; H, 5.4; N, 9.5; 10.8%; *M*, 296); δ_H (90 MHz) 6.82—8.0 (ArH), 4.6 (t, *J* 10 Hz, CH_2N), 3.8 (s, OMe), and 3.3 (=CCH_2); δ_C (20 MHz) 191.43 (C=S), 160.67 (C=N), 112.16—161.27 (all Ar), 55.05 (OMe), 51.30 (NCH_2), and 31.06 (=CCH_2).

Treatment of compound (**1b**) with chloroacetone under similar conditions yielded an unstable product which could not be characterized.

Reactions of N[2]-*substituted Thioaroylhydrazines with Aldehydes and Ketones*.—(a) N[1]-(4-*Methoxythiobenzoyl*)-N[2]-*phenylhydrazine*. Treatment of N^1-(4-methoxythiobenzoyl)-N^2-phenylhydrazine[19] (600 mg, 2.3 mmol) with 4-methoxybenzaldehyde (400 mg, 2.9 mmol) and AcOH (3 drops) in ethanol (25 cm^3) at reflux for 26 h gave, on cooling the partially evaporated solution, 2,5-*bis*-(4-*methoxyphenyl*)-3-*phenyl*-2,3-*dihydro*-1,3,4-*thiadiazole* (**4a**) (608 mg, 70%), m.p. 120—122 °C (from EtOH) (Found: C, 70.3; H, 5.1; N, 7.7; S, 8.5%; M^+, 376. $C_{22}H_{20}N_2O_2S$ requires C, 70.2; H, 5.4; N, 7.4; S, 8.5%; *M*, 376); n.m.r. data are in Table 4.

(b) N[2]-*Isopropyl*-N[1]-(4-*methoxythiobenzoyl*)*hydrazine*. Similarly (reflux for 48 h) was obtained, from acetone (in excess), 3-*isopropyl*-5-(4-*methoxyphenyl*)-2,2-*dimethyl*-2,3-*dihydro*-1,3,4-*thiadiazole* (**4b**) (226 mg, 86%), m.p. 84—85 °C (from light petroleum) (Found: C, 63.8; H, 7.5; N, 10.6; S, 12.0%; M^+, 264. $C_{14}H_{20}N_2OS$ requires C, 63.6; H, 7.6; N, 10.6; S, 12.1%; *M*, 264); n.m.r. data are in Table 4.

By the same method was obtained, from 4-anisaldehyde, 3-*isopropyl*-2,5-*bis*-(4-*methoxyphenyl*)-2,3-*dihydro*-1,3,4-*thiadiazole* (**4c**) (81%), m.p. 89—90 °C (EtOH) (Found: C, 66.8; H, 6.5; N, 8.0; S, 9.4%; M^+, 342. $C_{19}H_{22}N_2O_2S$ requires C, 66.6; H, 6.5; N, 8.2; S, 9.4%; *M*, 342); n.m.r. data are in Table 4.

(c) N[2]-*Benzyl*-N[1]-4-*methoxythiobenzoyl*)*hydrazine*. Similarly (reflux for 12 h) was obtained, from 4-anisaldehyde (1 mmol), 3-*benzyl*-2,5-*bis*-(4-*methoxyphenyl*)-2,3-*dihydro*-1,3,4-*thiadiazole* (**4d**) (86%), m.p. 84—86 °C (from aqueous EtOH) (Found: C, 70.6; H, 5.6; N, 7.0; S, 8.1%; M^+, 390. $C_{23}H_{22}N_2O_2S$ requires C, 70.7; H, 5.7; N, 7.2; S, 8.2%; *M*, 390); n.m.r. data are in Table 4.

Reaction of Dihydrothiadiazole (**2q**) *with Dicyclohexylcarbodi-imide*.—A solution of DCC (387 mg, 1.9 mmol) in dichloromethane (25 cm^3) was added dropwise at 0 °C to a solution of the dihydrothiadiazole (**2q**) (513 mg, 1.8 mmol) in CH_2Cl_2 (100 cm^3). After 15 min a white precipitate of dicyclohexylurea was observed, and the mixture was allowed to attain room temperature while being stirred for 12 h. T.l.c. (EtOAc) indicated a single soluble product; the solution was filtered to remove dicyclohexylurea (304 mg) and the filtrate was evaporated. The white residue was taken up in a little chloroform, and the solution was filtered to remove additional dicyclohexylurea (total 348 mg, 83%) and further purified by column chromatography (silica; EtOAc) to give 3-(4-*methoxyphenyl*)-5-*methyl*-4-*thia*-1,2-*diazabicyclo*[3.3.0]*oct*-2-*en*-8-*one* (**18a**) (369 mg, 77%), m.p. 124—126 °C (Found: C, 59.6; H, 4.6; N, 10.7; S, 12.3%; M^+, 262. $C_{13}H_{14}N_2O_2S$ requires C, 59.5; H, 5.4; N, 10.7; S, 12.2%; *M*, 262); δ_H ($CDCl_3$; 220 MHz) 7.8 and 6.4 (dd, J_{AB} 9 Hz), 3.83 (s, MeO), 3.0—2.45 (complex m, CH_2CH_2), and 1.71 (Me); δ_C ($CDCl_3$; 20.1 MHz) 168.28 (NC=O), 161.70 (*C*OMe), 159.99 (C=N), 129.07 (2 C), 122.20 (1 C), and 113.47 (2 C) (all Ar), 80.19 (C-5), 54.81 (OMe), 33.66 (CH_2C=O), 31.65 (CH_2CMe), and 29.57 (Me).

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