Heterocyclic Compounds. Part V.[1] Reactions of Phenyl and Benzoyl Isocyanates and Benzoyl Isothiocyanate with Hydrazones

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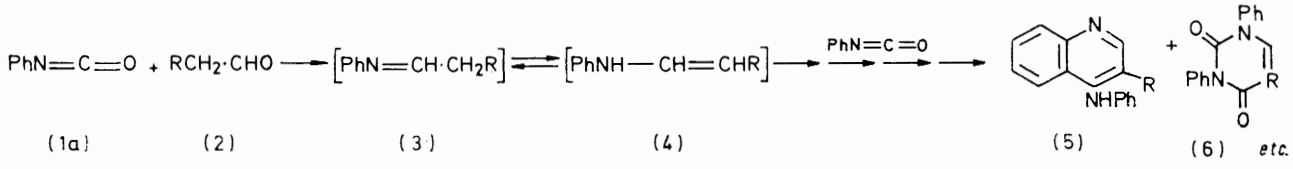
Reactions of phenyl and benzoyl isocyanate with ketone hydrazones gave *s*-triazolidines in good yields, whereas benzaldehyde phenylhydrazone simply gave semicarbazones. With benzoyl isothiocyanate ketone hydrazones and benzaldehyde phenylhydrazone gave oxatriazepinethiones. These reactions are all thought to proceed *via* betaines, and their mechanisms are discussed in the light of semi-empirical INDO calculations.

WE have previously reported a mechanistic study of the thermal reactions between aromatic isocyanates and aliphatic aldehydes.[1] In those reactions, imines (3) and/or enamines (4) were considered as important intermediates in the formation of the heterocycles (5) and (6). We now report a study of reactions of heterocumulenes with nitrogen analogues (hydrazones) of enamines.



RESULTS AND DISCUSSION

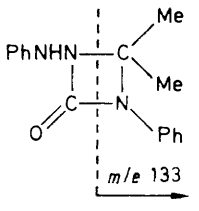
Isocyanates.—The reaction of phenyl isocyanate (1a) with acetone phenylhydrazone (7a) at 100 °C without solvent gave a 1 : 1 adduct (8a) and a 2 : 1 adduct (9). In its mass spectrum the product (8a) showed a molecular ion peak at *m/e* 267 and fragments at *m/e* 253 (M^+ — CH_3), 148 (M^+ — PhNCO), and 133. Three structures, (I)—(III), were considered on the basis of the molecular weight, *viz.* the products from reaction of phenyl isocyanate (1a) with (A) the N=C bond [1,2-cycloaddition, (I)], (B) the NH function [(II)], and (C) both the NH function and the N=C bond [1,3-addition, (III)] of the hydrazone. The peak at *m/e* 133 ($PhN{=}CMe_2$) suggests structures (I) and (III), but not the semicarbazone structure (II). A carbonyl i.r. band at 1 680 cm^{-1} is consistent with the presence of a five- or six-membered ring rather than a four-membered skeleton. Structure (III) for (8a) was thus established. The product (9) was identified from spectral data and elemental analysis; the i.r. spectrum showed NH absorption at 3 300 cm^{-1} and two carbonyl bonds at 1 710 and 1 675 cm^{-1}. Its mass spectrum showed a parent peak at *m/e* 386 and its fragmentation pattern in the mass range below *m/e* 267 was

[1] Part IV, I. Yamamoto, T. Furukawa, H. Nakajima, and H. Gotoh, *J.C.S. Perkin I*, 1976, 1597.

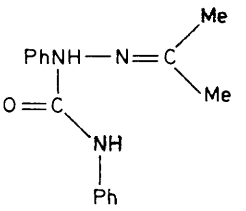
similar to that of (8a). Furthermore, acid-catalysed hydrolysis of (9) in aqueous ethanol gave 1,4-diphenylsemicarbazide (10).

Reactions of phenyl isocyanate with the phenylhydrazones (7b and c) afforded the corresponding *s*-triazolidines (8b and c) in good yields (Table 1).

addition of isocyanates to hydrazones appears to depend on the hydrazone substituents. Ketone hydrazones yielded cyclic products, s-triazolidines, but the aldehyde hydrazone gave acyclic compounds. A suggested mechanism is shown in the Scheme. The betaine (13) is produced by electrophilic attack of the isocyanate



(I)



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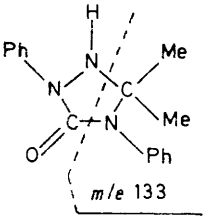

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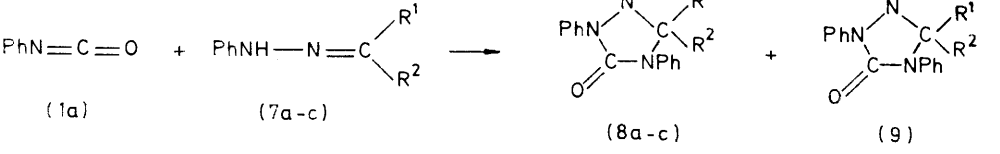
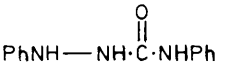


(7a), (8a), (9) $R^1 = R^2 = Me$
(7b), (8b), $R^1 = Me$, $R^2 = Et$
(7c) (8c), $R^1 R^2 = [CH_2]_5$



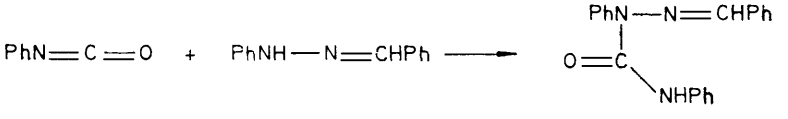
(10)

TABLE 1

Triazolidines (8a—e) and (9)

Products	Yield (%) [a]	M.p. (°C) [b]	$\nu_{max.}$/cm^{-1} NH	$\nu_{max.}$/cm^{-1} C=O	δ [c] CH_3	δ [c] CH_2	δ [c] NH	δ [c] Aromatic
(8a)	32	134.5—135.5	3 160	1 680	1.48		4.13	71.—8.0
(9)	29	202—203	3 300	1 710, 1 675	1.76			7.2—7.9
(8b)	65.5	116—117	3 200	1 695	0.95, 1.43	1.70	3.95	6.85—7.90
(8c)	100	164—164.5	3 190	1 685		0.7—2.1	4.05	6.7—7.95
(8d)	100	139—140	3 200	1 740, 1 650	1 650		4.5	6.8—7.9
(8e)	98.5	160	3 210	1 740, 1 680		1.4—3.0	4.5	6.9—7.95

[a] Based on isocyanates. [b] Nujol mull. [c] In $CHCl_3$.



(1a) (7d) (11a)

Treatment of benzaldehyde phenylhydrazone (7d) with the isocyanate (1a) at 165—170 °C for 1.5 h without solvent gave benzaldehyde 2,4-diphenylsemicarbazone (11a), quantitatively.

Reactions of benzoyl isocyanate (1b) with the hydrazones (7a, c, and d) at room temperature afforded the *s*-triazolidine derivatives (8d and e) and the semicarbazone (11b), respectively, in quantitative yield, as recently reported by Tsuge.[2] Acid-catalysed hydrolysis of these three adducts in each case gave the triazoline (12).

The formation of cyclic or acyclic products from the carbon atom on the hydrazone NH. When both R^1 and R^2 are alkyl, the N=C carbon atom of (13) will be relatively 'hard'; therefore, the carbamoyl nitrogen atom should react to form the triazolidines (8) *via* the intermediate (14). However when $R^2 = H$, the N=C carbon atom will be 'softer', and compounds (11) will result from [1,3] hydrogen migration (path *b*). The results of INDO calculations on the hydrazones (7a and d) (Table 2) support this rationalization. The formal

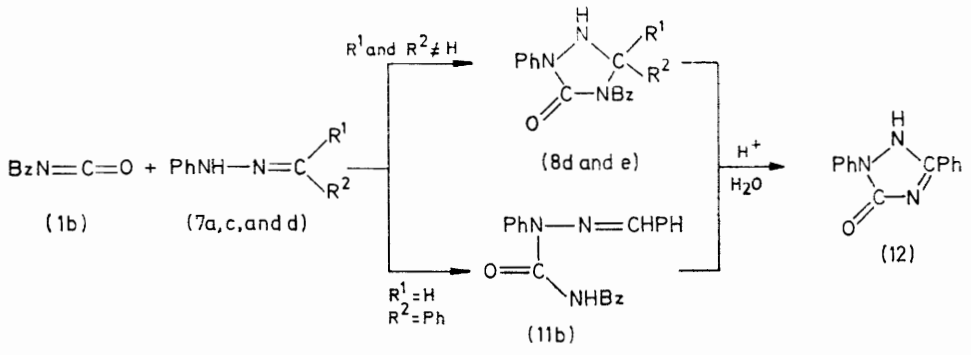
[2] O. Tsuge and S. Kanemasa, *Bull. Chem. Soc. Japan*, 1974, **47**, 2676.

TABLE 2

Electron densities of hydrazones (7a and d) calculated by the INDO method

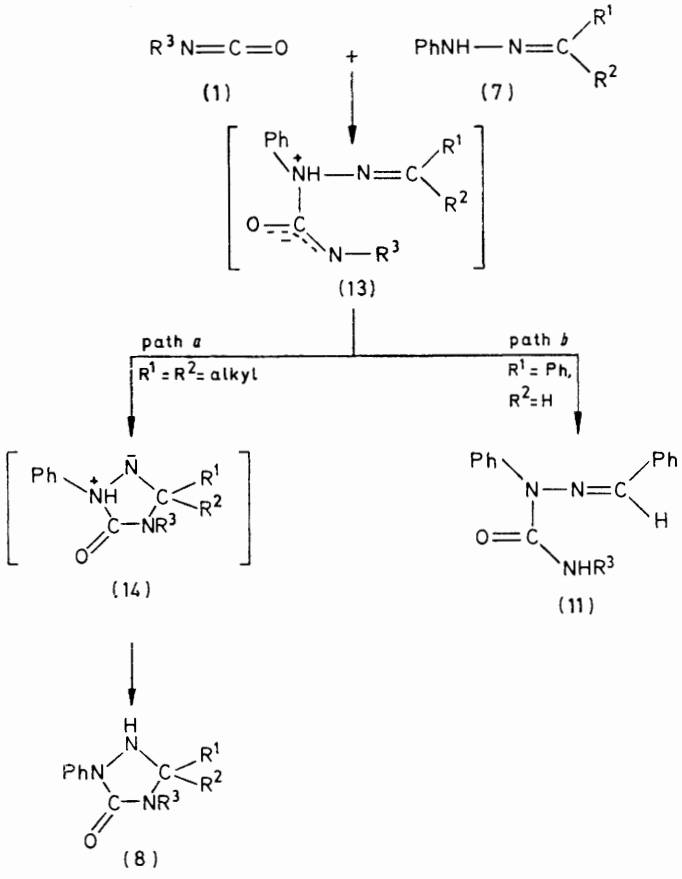
H(4)
PhN(3)–N(2)=C(1)R^1R^2

	R^1	R^2	Electron density (formal charge density) C-1	N-2	N-3	H-4
(7a)	Me	Me	3.7126 (+0.2874)	5.3092 (−0.3092)	5.3351 (−0.3351)	0.7883 (+0.2117)
(7d)	Ph	H	3.9460 (+0.0540)	5.2008 (−0.2008)	5.3325 (−0.3325)	0.7727 (+0.2271)



(8d) $R^1 = R^2 =$ Me
(8e) $R^1R^2 = [CH_2]_5$

charge densities on N-3 of both (7a and d) are larger than on other atoms (*i.e.* N-2 and C-1); therefore initial attack at N-3 to form the betaine (13) would be expected.



SCHEME

Furthermore, the density on C-1 of (7a) is larger than that on C-1 of (7d), favouring cyclization of the betaine (13) to *s*-triazolidines.

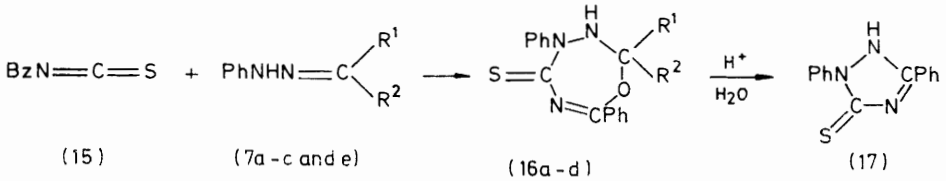
Benzoyl Isothiocyanate.—The reaction of acetone phenylhydrazone (7a) with benzoyl isothiocyanate (15) at room temperature without solvent gave 3,4-dihydro-2,2-dimethyl-4,7-diphenyl-1,3,4,6-oxatriazepine-5(2*H*)-thione (16a) quantitatively. Durant [3] has reported similar cycloadditions of hydrazones to benzoyl isothiocyanate. However he used only acetone and benzaldehyde alkylhydrazones, and we have several criticisms of his reaction mechanisms. We report here independent results on the synthesis and mechanism of formation of the 1,3,4,6-oxatriazepines (16).

The structures of the products (16a—d) from the hydrazones (7a—c and e) were established by spectral data, elemental analyses (Table 3), and chemical properties. Acid-catalysed hydrolysis in aqueous ethanol in each case afforded 1,3-diphenyl-Δ^3-*s*-triazoline-5-thione (17) quantitatively.

On the other hand, the reaction of the isothiocyanate (15) with benzaldehyde phenylhydrazone (7d) in ethyl acetate at room temperature afforded benzaldehyde 4-benzoyl-2-phenyl thiosemicarbazone (18) and 5-benzoylimino-2,4-diphenyl-Δ^2-1,3,4-thiadiazoline (19) in 77 and 14% yields, respectively. The latter was not isolated by Durant.[3] Oxidation of (18) by pyridine–chromic anhydride complex gave the thiadiazoline (19). Compound (19) did not show NH absorptions in its i.r. spectrum, and only aromatic proton resonances in its n.m.r. spectrum. Furthermore, its mass spectrum contained a molecular ion peak at *m/e* 357. Structure (19) was confirmed by *X*-ray analysis.

[3] G. J. Durant, *J. Chem. Soc.* (*C*), 1967, 92, 952.

The formation of the oxatriazepines (16a—d) may be explained as follows. The negative charge on nitrogen in the initially formed betaine (20) will be delocalized over the sulphur atom. Therefore, the nitrogen will become 'softer', resulting in preferential attack by the oxygen on the N=C carbon atom. In the case of benzaldehyde hydrazone (7d), the reaction proceeds similarly to that with the isocyanates, giving the thiosemicarbazone (18) as a major product. The minor product (19) presumably arises from cyclization of the corresponding betaine (21).



(15) (7a-c and e) (16a-d) (17)

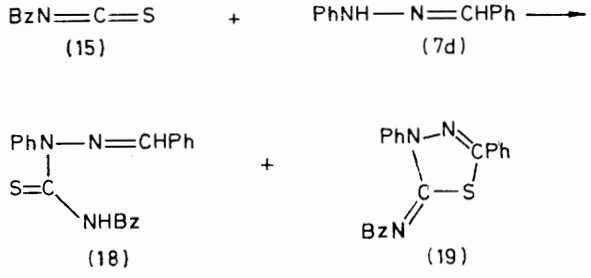
(7a), (16a) $R^1 = R^2 = Me$ (7b), (16b) $R^1 = Me$, $R^2 = Et$
(7c), (16c) $R^1 R^2 = [CH_2]_5$ (7e), (16d) $R^1 R^2 = [CH_2]_4$

TABLE 3

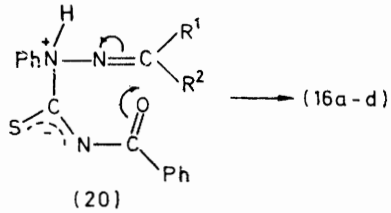
1,3,4,6-Oxatriazepine-5-thiones (16a—d)

Product	Yield (%) [a]	M.p. (°C)	δ [b] CH_3	δ [b] CH_2	δ [b] NH	δ [b] Aromatic	Found (%) (Reqd) C	H	N
(16a)	99.6	131	1.65		5.05	7.18—8.35	70.95 (70.85)	4.65 (4.85)	17.75 (17.7)
(16b)	100	121.5—122	1.05 1.60	1.93	5.05	7.10—8.40	66.45 (66.45)	5.7 (5.9)	12.9 (12.9)
(16c)	99.7	163		1.15—2.1	4.90	7.00—8.40	68.55 (68.35)	6.05 (6.0)	12.1 (11.95)
(16d)	63.3	148.5—149		1.60—2.4	4.15	7.00—8.38	67.4 (67.65)	5.7 (5.7)	12.25 (12.45)

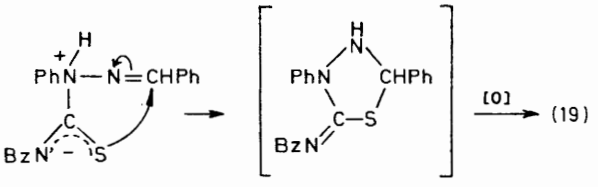
[a] Based on isothiocyanate (15). [b] In $CHCl_3$.



(15) (7d) (18) (19)



(20)



Saxena *et al.*[4] have reported the reaction of benzaldehyde phenylhydrazone with dimethylacetylenedicarboxylate to give pyrazole derivatives *via* autoxidation of a pyrazoline intermediate. Durant[3] reported that oxatriazepines were produced *via* thiosemicarbazones. If his hypothesis is right, the thiosemicarbazone (18) should be convertible into the oxatriazepine (16) or the thiadiazoline (19) on heating. However, the thiosemicarbazone (18) was unchanged after refluxing for 10 h in benzene, suggesting that it was not the precursor of the oxatriazepine (16) or the thiadiazoline (19). This supports the intermediacy of betaines [(13) or (20)] in these reactions.

The thiadiazoline (19) is remarkably stable towards acid- and base-catalysed hydrolysis, reductive acetylation, reduction by Raney nickel (W-2 type), and photolysis by a low pressure mercury lamp.

EXPERIMENTAL

M.p.s were taken with a Mitamura capillary microapparatus. I.r. spectra (Nujol mulls) were recorded with a JASCO IR-A spectrometer. A JEOL JNM-C-60HL spectrometer was used for ^1H n.m.r. measurement, and mass spectra (75 eV) were obtained with a JEOL JMS-01SG-2 spectrometer on line to JEOL JEC-6 spectrum computer. The INDO calculations were carried out on the HITAC 8700/8800 computers of the Computation Center of the University of Tokyo.

Reactions of Phenyl Isocyanate (1a).—*With acetone phenylhydrazone* (7a). A mixture of compounds (1a) (2.40 g, 21 mmol) and (7a) (2.96 g, 20 mmol) was heated at 100 °C for 2 h without solvent, chilled with ether and filtered to afford *5,5-dimethyl-2,4-diphenyl-1-phenylcarbamoyl-s-tri-*

[4] M. K. Saxena, M. N. Gudi, and M. V. George, *Tetrahedron*, 1973, **29**, 101.

azolidin-3-one (9) (1.1 g, 29%), m.p. 202—203° (from benzene–hexane); *m/e* 386 (M^+), 267, 252, 148, and 133 (Found: C, 71.35; H, 5.85; N, 14.6. $C_{23}H_{22}N_4O_2$ requires C, 71.5; H, 5.75; N, 14.5%). Removal of ether from the filtrate left a reddish oil which was chromatographed on alumina to give 5,5-*dimethyl*-2,4-*diphenyl*-s-*triazolidin*-3-*one* (8a) (1.7 g, 32%), m.p. 134—135.5° (from benzene–hexane); *m/e* 267 (M^+), 252, 148, and 133 (Found: C, 71.65; H, 6.65; N, 15.6. $C_{16}H_{17}N_3O$ requires C, 71.9; H, 6.4; N, 15.7%).

With ethyl methyl ketone phenylhydrazone (7b). A mixture of compounds (1a) (1.8 g, 15 mmol) and (7b) (2.43 g, 15 mmol) was heated at 100 °C for 6 h without solvent. After cooling, the mixture was chromatographed on alumina to give 5-*ethyl*-5-*methyl*-2,4-*diphenyl*-s-*triazolidin*-3-*one* (8b) (2.8 g, 65.5%), m.p. 116—117° (from benzene–hexane); *m/e* 281 (M^+), 266, 251, 162, and 147 (Found: M^+, 281.1504. $C_{17}H_{19}N_3O$ requires M, 281.1528).

With cyclohexanone phenylhydrazone (7c). A similar reaction of compounds (1a) (3.0 g, 25 mmol) and (7c) (4.7 g, 25 mmol) gave 1′,4′-*diphenylcyclohexanespiro*-3′-s-*triazolidin*-5′-*one* (8c) (7.5 g, 100%), m.p. 164—164.5° (from ethanol); *m/e* 307 (M^+), 264, 251, and 188 (Found: M^+ 307.1680. $C_{19}H_{21}N_3O$ requires M, 307.1685).

With benzaldehyde phenylhydrazone (7d). A similar reaction at 165—170 °C for 1.5 h with (1a) (1.2 g, 10 mmol) and (7d) (1.96 g, 10 mmol) gave *benzaldehyde* 2,4-*diphenylsemicarbazone* (11a) (2.9 g, 92%), m.p. 151—152°; $\nu_{max.}$ 3 395 (NH), 1 695 (C=O), and 1 650 cm^{-1} (C=O); *m/e* 315 (M^+), 212, 196, 180, 168, 167, and 119 (Found: C, 76.1; H, 5.5; N, 13.5. $C_{20}H_{17}N_3O$ requires C, 76.15; H, 5.45; N, 13.35%).

Acid-catalysed Hydrolysis of the Triazolidinone (9).—A solution of compound (9) (1.5 g, 3.9 mmol) in aqueous ethanol (20 ml) was refluxed for 2 h in the presence of concentrated hydrochloric acid (1.0 ml). Cooling gave a white powder, 1,4-*diphenylsemicarbazide* (10), quantitatively; m.p. 203.5—204.5°; *m/e* 227 (M^+), 108, and 91 (Found: C, 68.8; H, 5.75; N, 18.7. $C_{13}N_{13}N_3O$ requires C, 68.7; H, 5.75; N, 18.5%).

Reactions of Benzoyl Isocyanate (Ib).—*With acetone phenylhydrazone* (7a). Benzoyl isocyanate (1b) (1.47 g, 10 mmol) was added dropwise to compound (7a) (1.48 g, 10 mmol) without solvent at room temperature. An exothermic reaction afforded 4-benzoyl-5,5-dimethyl-2-phenyl-*s*-triazolidin-3-one (8d) (2.95 g, 100%), m.p. 139—140° (lit.,[2] 140.5—141°).

With cyclohexanone phenylhydrazone (7c). To a solution of compound (7c) (1.88 g, 10 mmol) in benzene, the isocyanate (1b) (1.47 g, 10 mmol) was added, and the mixture was refluxed for 50 min. Removal of solvent afforded 4′-*benzoyl*-1′-*phenylcyclohexanespiro*-3′-s-*triazolidin*-5′-*one* (8e) (3.3 g, 99%), m.p. 160° (from ethanol); *m/e* 335 (M^+), 188, and 165 (Found: C, 72.45; H, 6.3; N, 12.65. $C_{20}H_{21}N_3O_2$ requires C, 72.6; H, 6.3; N, 12.55%).

With benzaldehyde phenylhydrazone (7d). A similar reaction in chloroform with (1b) (2.2 g, 15 mmol) and (7d) (2.94 g, 15 mmol) gave benzaldehyde 4-benzoyl-2-phenylsemicarbazone (11c) (5.1 g, 89%), m.p. 163° (lit.,[2] 164°).

Acid-catalysed Hydrolysis of the Triazolidine (8d).—A solution of compound (8d) (1.1 g, 3.72 mmol) in 95% ethanol was refluxed for 5 h in the presence of concentrated hydrochloric acid (1.5 ml). On cooling, a white powder precipitated; this was collected and recrystallized from ethanol to afford 1,3-diphenyl-Δ^3-*s*-triazolin-5-one (12) (0.52 g, 59%), m.p. 229—229.5° (lit.,[2] 230—231°).

Acid-catalysed Hydrolysis of Benzaldehyde 4-*Benzoyl*-2-*phenylsemicarbazone* (11c).—A solution of compound (11c) (1.0 g, 2.9 mmol) containing concentrated hydrochloric acid (1.5 ml) in 95% ethanol was refluxed for 5 h. Similar work-up gave the triazoline (12) (0.4 g, 59%).

Reactions of Benzoyl Isothiocyanate (15).—*With acetone phenylhydrazone* (7a). Benzoyl isothiocyanate (15) (3.26 g, 20 mmol) was added dropwise to compound (7a) (2.96 g, 20 mmol) without solvent at room temperature. After a few minutes, the mixture solidified to afford 3,4-*dihydro*-2,2-*dimethyl*-4,7-*diphenyl*-1,3,4,6-*oxatriazepine*-5(2H)-*thione* (16) (6.20 g, 99.6%); m.p. 131° (from benzene–hexane); $\nu_{max.}$ 3 160, 1 600, and 1 560 cm^{-1} (Found: M^+, 311.1074. $C_{17}H_{17}N_3OS$ requires M, 311.1093) (see Table 3).

With ethyl methyl ketone phenylhydrazone (7b). A similar reaction with compounds (15) (1.63 g, 10 mmol) and (7b) (1.62 g, 10 mmol) gave 2-*ethyl*-3,4-*dihydro*-2-*methyl*-4,7-*diphenyl*-1,3,4,6-*oxatriazepine*-5(2H)-*thione* (16b) (3.25 g, quantitative) m.p. 121.5—122° (from benzene–hexane); *m/e* 325 (M^+), 310, and 296 (Table 3).

With cyclohexanone phenylhydrazone (7c). To a solution of compound (7c) (3.76 g, 20 mmol) in benzene was added dropwise the isothiocyanate (15) (3.26 g, 20 mmol). After a few minutes, removal of solvent *in vacuo* gave of 3,4-*dihydro*-4,7-*diphenyl*-1,3,4,6-*oxatriazepine*-2-*spirocyclohexane*-5(2H)-*thione* (16c) (7.0 g, quantitative), m.p. 163° (from benzene–hexane); *m/e* 351 (M^+), 308, 211, and 188 (Table 3).

With cyclopentanone phenylhydrazone (7e). A similar reaction with compounds (15) (1.63 g, 10 mmol) and (7e) (1.74 g, 10 mmol) in benzene gave 3,4-*dihydro*-4,7-*diphenyl*-1,3,4,6-*oxatriazepine*-2-*spirocyclopentane*-5(2H)-*thione* (16e) (2.2 g, 63.3%), m.p. 148—149° (from benzene–hexane); *m/e* 337 (M^+), 308, and 174 (Table 3).

With benzaldehyde phenylhydrazone (7d). A similar reaction with compounds (15) (3.26 g, 20 mmol) and (7d) (3.92 g, 20 mmol) in ethyl acetate after 4 days (monitored by i.r.) afforded a yellow precipitate of 5-*benzoylimino*-2,4-*diphenyl*-Δ^2-1,3,4-*thiadiazoline* (19) (0.9 g, 14%), m.p. 163° (from ethanol); $\nu_{max.}$ 1 610 cm^{-1}; *m/e* 357 (M^+) and 280 (Found: C, 70.65; H, 4.15; N, 11.7. $C_{21}H_{15}N_3OS$ requires C, 70.6; H, 4.25; N, 11.95%). The filtrate was evaporated *in vacuo* to afford *benzaldehyde* 4-*benzoyl*-2-*phenylthiosemicarbazone* (18) (5.52 g, 77%), m.p. 136—136.5° (from benzene–hexane); $\nu_{max.}$ 3 340 (NH) and 1 720 cm^{-1} (C=O); *m/e* 359 (M^+) (Found: C, 70.45; H, 4.55; N, 11.4. $C_{21}H_{17}N_3OS$ requires C, 70.2; H, 4.75; N, 11.7%).

Acid-catalysed Hydrolysis of the Oxatriazepines (16a—d); *General Procedure.*—The hydrolysis of (16a) is described as an example. A solution of (16a) (1.5 g, 4.8 mmol) in ethanol was refluxed for 2.5 h in the presence of concentrated hydrochloric acid (1.5 ml). Cooling gave a white powder, 1,3-*diphenyl*-Δ^3-s-*triazoline*-5-*thione* (17) (1.19 g, 98%), m.p. 239—240° (from ethanol); $\nu_{max.}$ 1 600, 1 520, and 1 260 cm^{-1}; *m/e* 253 (M^+), 221, 194, and 149 (Found: C, 66.65; H, 4.4; N, 16.55. $C_{14}H_{11}N_3OS$ requires C, 66.4; H, 4.4; N, 16.6%).

Acid-catalysed Hydrolysis of the *Thiosemicarbazone* (18).—A solution of compound (18) (1.5 g, 4.17 mmol) in ethanol was refluxed for 7 h in the presence of concentrated hydrochloric acid (1.0 ml). The solvent was then removed and the residue was extracted with benzene; the extract was washed with water, dried (Na_2SO_4), and evaporated to give the triazoline (17) (1.0 g, 95%).

Oxidation of the Thiosemicarbazone (18).—To a mixture of

chromic anhydride (8.5 g) and pyridine (60 ml) was added a solution of compound (18) (1.8 g, 5 mmol) in pyridine at room temperature with stirring. After 30 h, the mixture was poured into ice–water (500 ml) and the yellow precipitate of the thiadiazoline (19) (1.6 g, 88%) was collected.

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