The Reaction of Benzoyl Isothiocyanate with Hydrazine Derivatives. Part II.[1] Reaction with Some Alkyl Hydrazones

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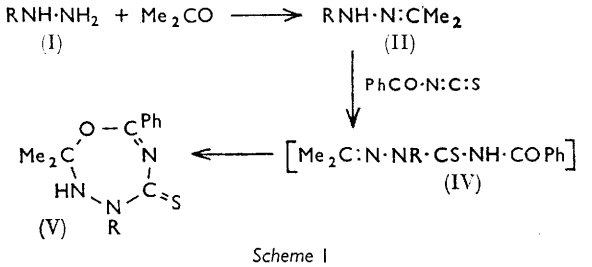
The reaction of benzoyl isothiocyanate with 1-alkyl-2-isopropylidenehydrazines leads to the formation of 1,3,4,6-oxatriazepine-5-thione derivatives rather than the open-chain benzoyl thiosemicarbazones PhCO·NH·CS·NR·N:CMe_2. The related benzylidenehydrazines gave non-cyclic products under comparable conditions. Structural assignments have been made largely on the basis of spectral data. Acid hydrolysis of the oxatriazepinethiones to 1,2,4-triazoline-5-thiones has also been studied.

In Part I [1] we described some reactions of benzoyl isothiocyanate (III) with alkylhydrazines, in which both addition to the thiocyanate function and substitution at the carbonyl was observed. The reaction of the same reagent with some related hydrazones has now been studied.

The hydrazones (IIa, b) were obtained from the alkylhydrazines (I) and acetone, and were distilled before use. Condensation with benzoyl isothiocyanate occurred readily, affording well defined crystalline products. The seven-membered cyclic structure (V) rather than the open-chain thiosemicarbazone structure (IV) is assigned to these products on the basis of spectroscopic data (see Table). Certain of these cyclic derivatives could be obtained directly from the hydrazine by reaction with

[1] Part I, G. J. Durant, *J. Chem. Soc.* (*C*), 1967, 92.

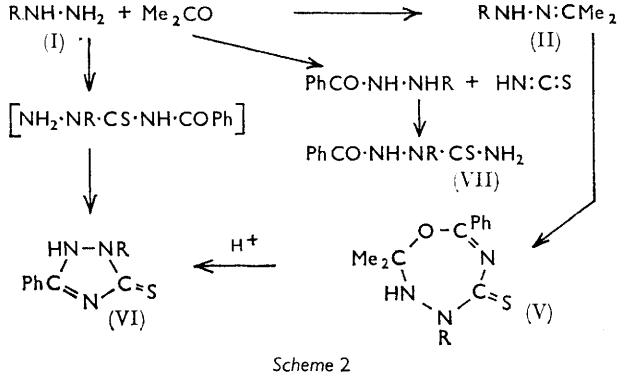
benzoyl isothiocyanate prepared *in situ* from benzoyl chloride and ammonium thiocyanate in the presence of



Scheme 1

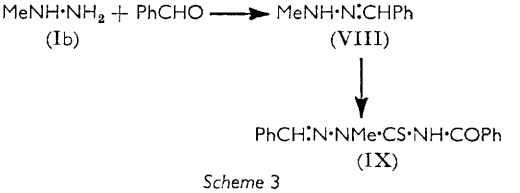
R = (a) 2,6-$Me_2C_6H_3$·O·$[CH_2]_2$; (b) Me; (c) Ph·$[CH_2]_2$; (d) $PhCH_2$

acetone. Compound (Vc) was prepared from 2-phenylethylhydrazine (Ic) in 60% yield by this means. 2-(2,6-Xylyloxy)ethylhydrazine (Ia) yielded compound



Scheme 2

(Va) in 29% yield under similar conditions, but the triazolinethione (VIa) [1] was also formed. The product (Va) obviously arises from the hydrazone (IIa) formed *in situ*, whilst (VIa) is presumably formed either from the free hydrazine or by subsequent cleavage of (Va). No cyclic derivatives were isolated from similar reactions with benzylhydrazine (Id) and methylhydrazine (Ib). The former yielded only the triazolinethione (VId), whilst the latter gave a mixture of (VIb) and 1-benzoyl-2-methylthiosemicarbazide (VIIb) when an excess of methylhydrazine was used. Rapid reaction with the hydrazine prior to hydrazone formation is indicated in these cases. The formation of (VIIb) is in accord with the greater nucleophilicity of methylhydrazine, which leads to competition between benzoylation with benzoyl isothiocyanate and the addition reaction which was discussed previously.[1] The equilibria involved in these reactions are of such complexity that minor changes in conditions can affect the yields of the products, and repetition of a reaction under similar conditions can result in a different ratio of products.



Scheme 3

However, when precautions were taken to ensure complete formation of the hydrazone by boiling an acetone solution of methylhydrazine for 1 hr. and subsequently dehydrating with potassium carbonate, the cyclic derivative (Vb) was obtained (55%) by subsequent reaction with benzoyl isothiocyanate in the presence of sodium hydrogen carbonate. In a similar experiment without added sodium hydrogen carbonate, the triazolinethione (VIb) was formed in 68% yield, presumably owing to the cleavage of (Vb) under the mildly acidic reaction conditions. This synthesis of 1-alkyl-3-phenyl-Δ^3-1,2,4-triazoline-5-thiones is an improvement over the procedure of condensation of the alkylhydrazine with benzoyl isothiocyanate in benzene.[1]

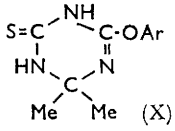
The reaction of benzoyl isothiocyanate with the benzylidene derivative (VIII) of methylhydrazine yielded a crystalline product which has the open-chain thiosemicarbazone structure (IX); its infrared spectrum (Nujol) has strong absorption in the carbonyl region ($\nu_{max.}$ 1718 cm.$^{-1}$). The analogous product (Vb) from

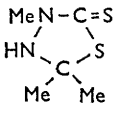
4-Substituted 2,3,4,5-tetrahydro-2,2-dimethyl-7-phenyl-1,3,4,6-oxatriazepine-5-thiones (V)

	R	M. p.	λ_{max} (mμ) (log ε) [a]	ν_{max} (cm.$^{-1}$) [b]	τ [c]	Found (%) C	H	N	Formula	Required (%) C	H	N
(Va)	2,6-$Me_2C_6H_3$·O·$[CH_2]_2$	115—117°	243—245 (4·07) 274—280 (4·12) 297·5 (4·11)	3200 1600 1475 1460 1200 720	8·37 (6H)s 7·74 (6H)s 5·6—5·8 (4H)m	65·6	6·6	10·8	$C_{21}H_{25}N_3O_2S$ [d]	65·8	6·6	11·0
(Vb)	Me	128—130	242 (4·09) 275—280 (4·08) 296 (4·07)	3190 1600 1450—1470 720	8·41 (6H)s 6·47 (3H)s	58·0	6·2	16·8	$C_{12}H_{15}N_3OS$ [e]	57·8	6·1	16·8
(Vc)	$PhCH_2$·CH_2	154—156	242 (4·06) 274—281 (4·10) 298 (4·07)	3180 1600 1460—1475 720	8·51 (6H)s 6·91 (2H)t 5·79 (2H)t	67·5	6·2	12·6	$C_{19}H_{21}N_3OS$	67·5	6·2	12·4

[a] In ethanol. [b] As Nujol mulls. [c] In $CDCl_3$. s = Singlet; t = triplet; m = multiplet. Complex signals to aromatic protons not included. [d] Found: S, 8·8%; *M*, 381 (Rast). $C_{21}H_{25}N_3O_2S$ requires S, 8·35%; *M*, 383. [e] Found: *M*, 249 (mass spectrometry). $C_{12}H_{15}N_3OS$ requires *M*, 249.

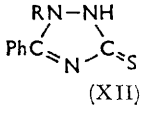
the isopropylidene derivative of methylhydrazine completely lacked absorption in the carbonyl region (no peaks between 1600 and 2900 cm.$^{-1}$ in Nujol or chloroform). The products (Va) and (Vc) were also transparent in the carbonyl region. Microanalytical data for (Vb) suggested the empirical formula $C_{12}H_{15}N_3OS$, the mass number (249) obtained by mass spectrometry agreeing with this formulation. Structure (Vb) is in accord with these data, and n.m.r. spectra for this and related compounds conform with this structure (see Table).

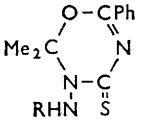

(X)


(XI)

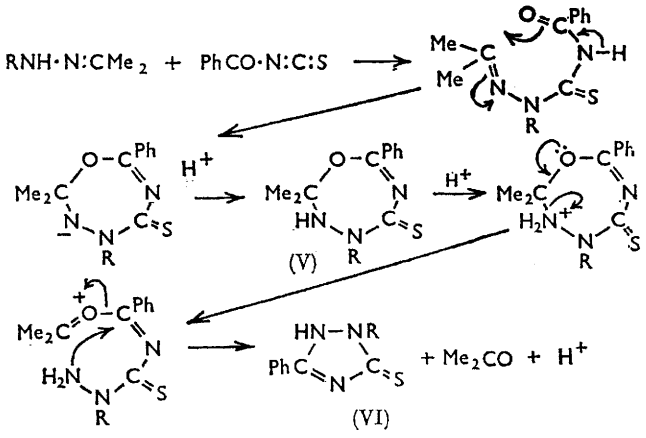
The chemical shift for the methyl groups of (V) is reasonably consistent with the value published [2] for the methyl protons in the related structure (X) (singlet τ 8·72), and the values we find for the methyl groups in the 1,3,4-thiadiazolidine-2-thione (XI) (τ 8·36). The singlet shown by (V) indicates rapid conformational changes which are consistent with the proposed seven-membered ring structure.[3]

The oxatriazepinethiones (V) are very acid sensitive, and rapidly break down to yield the triazolinethiones (VI) with concomitant liberation of acetone. The progress of this acid hydrolysis is followed readily by ultraviolet and n.m.r. spectroscopy (see Experimental section). The rate of acid hydrolysis is much faster than that expected for an acetone thiosemicarbazone derivative but is in accord with the presence of the cyclic aminoacetal structure (cf. the rapid acid hydrolysis of oxazolidines [4] and imidazolidines [5]). The formation of the triazolinethiones (VI) rather than the isomeric structure (XII) rules out structure (XIII) as a possible alternative to (V) for the cyclic addition products.


(XII)


(XIII)

The formation of (V) from the hydrazones (II) and benzoyl isothiocyanate (III) is envisaged as taking place by the mechanism shown in Scheme 4. A cycloaddition from compounds (II) and (III) yielding (V) by a concerted process is considered less likely, although it is known that benzoyl isothiocyanate and related compounds may undergo 1,4- and 1,2-cycloadditions with suitably polar multiple bond systems.[6] The nucleophilicity of the nitrogen carrying the proton in the hydrazones (II) must be of sufficient magnitude to make an attack at this centre, leading to the intermediate (IV), the initial step in the reaction. The facile acid hydrolysis of (IV) is accommodated by the mechanism depicted (Scheme 4).


Scheme 4

EXPERIMENTAL

Nuclear magnetic resonance spectra were determined using a Varian A60 instrument with tetramethylsilane as internal standard.

1-Isopropylidene-2-(2,6-xylyloxyethyl)hydrazine (IIa) was obtained by boiling a mixture of 2-(2,6-xylyloxy)ethylhydrazine [7] (18·0 g.) and acetone (50 ml.) under reflux for 1 hr. Concentration, followed by fractional distillation, yielded the *hydrazone*, b. p. 106—108°/0·1—0·2 mm., n_D^{24} 1·5174 (22 g., 87%) (Found: C, 71·0; H, 9·0; N, 12·6. $C_{13}H_{20}N_2O$ requires C, 70·9; H, 9·15; N, 12·7%).

1-Isopropylidene-2-methylhydrazine (IIb) * was obtained by the above method in 50% yield, b. p. 118—120°, n_D^{25} 1·4479.

Reaction of Benzoyl Isothiocyanate with Alkyl Hydrazones.—*2,3,4,5-Tetrahydro-2,2-dimethyl-7-phenyl-4-[2-(2,6-xylyloxy)ethyl]-1,3,4,6-oxatriazepine-5-thione* (Va). 1-Isopropylidene-2-(2,6-xylyloxy)ethylhydrazine (IIa) (5·0 g., 0·023 mole) was added dropwise to a solution of benzoyl isothiocyanate (3·7 g., 0·023 mole) in benzene, with stirring, and the mixture was boiled under reflux for 15 min., and then concentrated *in vacuo* to an oil. An ethanolic solution of the oil deposited the crystalline *thione* (Va) (7·5 g.), m. p. 115—117°, which recrystallised unchanged from ethanol.

2,3,4,5-Tetrahydro-2,2,4-trimethyl-7-phenyl-1,3,4,6-oxatriazepine-5-thione (Vb). (i) 1-Isopropylidene-2-methylhydrazine (4·3 g., 0·05 mole) reacted with benzoyl isothiocyanate (8·15 g., 0·05 mole) in benzene, in a similar manner to that described in the previous example, and yielded the *thione* (Vb) (7·6 g., 69%), m. p. 129—130°. (ii) The previous reaction was repeated using tetrahydrofuran as solvent below —10° during the addition and subsequent reaction period (3½ hr.). The addition of light petroleum afforded the pure thione (Vb) (75%), m. p. 130—130·5°, identical with the material obtained in (i).

4-Benzoyl-1-benzylidene-2-methylthiosemicarbazide (IX).—1-Benzylidene-2-methylhydrazine [8] (3·1 g., 0·023 mole)

* Microanalysis could not be carried out because the compound explodes when combustion is attempted.

[2] E. Grigat and R. Putter, *Chem. Ber.*, 1966, **199**, 958.
[3] J. E. Anderson, *Quart. Rev.*, 1965, **19**, 426.
[4] E. D. Bergmann, *Chem. Rev.*, 1953, **53**, 309.
[5] R. J. Ferm and J. L. Riebsomer, *Chem. Rev.*, 1954, **54**, 593.
[6] J. Goerdeler, *Angew. Chem. Internat. Edn.*, 1964, **3**, 594.
[7] G. J. Durant, G. M. Smith, R. G. W. Spickett, and S. H. B. Wright, *J. Medicin. Chem.*, 1966, **9**, 22.
[8] D. Todd, *J. Amer. Chem. Soc.*, 1949, **71**, 1353.

reacted with benzoyl isothiocyanate (3·7 g., 0·023 mole) in benzene (15 ml.) and afforded the *product* (IX) (4·5 g., 65%) as yellow needles, m. p. 134—135·5° (Found: C, 64·5; H, 5·3; N, 14·2; S, 11·0. $C_{16}H_{15}N_3OS$ requires C, 64·6; H, 5·1; N, 14·1; S, 10·8%), $\nu_{max.}$ (Nujol) 1718, 3320 cm.$^{-1}$, $\lambda_{max.}$ (log ε) (in EtOH) 235 (4·24), 275 (4·13), 335 mμ (4·38), n.m.r. τ 6·07 (3H, singlet) in addition to complex aromatic signals).

The Reaction of Benzoyl Isothiocyanate with Alkyl Hydrazines in an Acetone Medium.—Reaction with 2-phenylethylhydrazine. Benzoyl isothiocyanate reagent was prepared by reaction of benzoyl chloride (4·58 g., 0·037 mole) and ammonium thiocyanate (2·8 g., 0·037 mole) in boiling acetone (50 ml.) for 5 min.[9] Inorganic material was filtered off, and 2-phenylethylhydrazine (Ic) (5·0 g., 0·037 mole) was added dropwise with stirring, maintaining a gentle reflux, and the mixture was then boiled under reflux for 15 min., cooled, and added to water. The yellow oil which precipitated gradually crystallised and was recrystallised from ethanol yielding 2,3,4,5-*tetrahydro*-2,2-*dimethyl*-7-*phenyl*-4-(2-*phenylethyl*)-1,3,4,6-*oxatriazepine*-5-*thione* (Vc) (8·2 g., 60%), m. p. 151—155°. Further recrystallisation from ethanol afforded 7·5 g., m. p. 154—156°.

Reaction with benzylhydrazine. The hydrazine (9·15 g., 0·075 mole) was added to benzoyl isothiocyanate (12·2 g., 0·075 mole) in acetone (50 ml.). Working up in the usual way afforded the pure thione [1] (VId) (6·0 g.), m. p. 235—238°, and slightly less pure material (5·0 g.), m. p. 230—235°.

Reaction with 2-(2,6-*xylyloxy*)*ethylhydrazine.* (i) Benzoyl isothiocyanate, from benzoyl chloride (14·1 g., 0·10 mole) and ammonium thiocyanate (8·5 g., 0·11 mole) in acetone, reacted with 2-(2,6-xylyloxy)ethylhydrazine (Ia) (18·0 g., 0·10 mole) and gave a product which was recrystallised from ethanol, yielding material (24·0 g.) of m. p. 114—125°. Three recrystallisations from ethanol gave the thione (Va) (11·0 g., 29%), m. p. 115—117°. From the ethanolic mother-liquors, by repeated recrystallisation from ethanol, there was obtained the thione (VIa) [1] (2·6 g., 8%), m. p. 185—186°.

(ii) In a repeat experiment, the hydrazine (Ia) (9·0 g., 0·050 mole) reacted with benzoyl isothiocyanate (9·0 g., 0·055 mole) in acetone, under otherwise identical conditions. The product was recrystallised twice from ethanol, yielding the thione (VIa) (5·9 g., 37%), m. p. 186—187°. From the mother-liquors, there was obtained the thione (Va) (1·7 g., 9%), m. p. 112—114°.

(iii) Experiment (i) was repeated on the same scale, but the crude product was agitated directly with 5N-hydrochloric acid (200 ml.) for 1 hr. Filtration, followed by recrystallisation from ethanol, yielded the thione (VIa) (15·7 g., 55%), m. p. 186—187°, and slightly less pure material (2·2 g.), m. p. 180—186°.

Reaction with methylhydrazine. (i) Benzoyl isothiocyanate, prepared from benzoyl chloride (14·1 g., 0·10 mole) and ammonium thiocyanate (8·5 g., 0·11 mole), reacted with methylhydrazine (4·6 g., 0·10 mole). The product obtained was recrystallised twice from ethanol, yielding the thione [1] (VIb) (3·58 g.), m. p. 261—264°. From the mother-liquors further quantities of the same product (2·6 g.; m. p. 265—267°) were obtained, giving a total yield of 6·27 g. (33%).

(ii) In a repeat experiment, benzoyl isothiocyanate reagent, from benzoyl chloride (14·1 g., 0·10 mole) and ammonium thiocyante (8·5 g., 0·11 mole) in acetone, was added to an excess of methylhydrazine (Ib) (13·8 g., 0·30 mole) in ethanol (100 ml.) during 30 min. After boiling under reflux for 50 min., the mixture was set aside at room temperature overnight and then evaporated to dryness under reduced pressure. The residual solid (13·0 g.; m. p. 181—184°) was triturated with water and recrystallised from ethanol, yielding 1-benzoyl-2-methylthiosemicarbazide [1] (VIIb) (5·5 g., 26%), m. p. 208—210°, and less pure material (3·8 g.), m. p. 192—210°. Acidification of the previous aqueous filtrate yielded slightly impure thione (VIb) (0·6 g.), m. p. 252—256°. Repetition of this reaction under apparently similar conditions gave a crude product (19·7 g.) which, following recrystallisation from ethanol, yielded the thione (VIb) (7·03 g., 37%), m. p. 260—264°, and the benzoylthiosemicarbazide (VIIb) (2·29 g.), m. p. 206—208°.

(iii) Methylhydrazine (4·6 g., 0·10 mole) was added slowly to acetone (50 ml.), and the resultant solution was boiled under reflux for 1 hr., cooled, and dried over potassium carbonate for 15 min. Following filtration, this solution reacted with benzoyl isothiocyanate, prepared from benzoyl chloride (15·5 g., 0·11 mole) and ammonium thiocyanate (9·9 g., 0·13 mole) in acetone (100 ml.), by boiling under reflux for 1 hr., filtering, and cooling. Prior to addition of the hydrazone solution, sodium hydrogen carbonate (10 g.) was added to the benzoyl isothiocyanate reagent, and the mixture was cooled and stirred during the addition. The resultant mixture was gradually heated to reflux temperature during 30 min., and then filtered and concentrated to low bulk. Dilution with a little ether, and chilling, afforded the thione (Vb) (13·86 g., 56%) as needles, m. p. 130—131·5°, identical with that obtained previously.

(iv) When (iii) was repeated, but without addition of sodium hydrogen carbonate, the crude product following recrystallisation from aqueous ethanol yielded the thione (VIb) (81%) as yellow needles, m. p. 258—260° (slight shrinking). Further recrystallisation from ethanol gave the pure product (VIb) (68%), m. p. 264—267°.

(v) The procedure in experiment (i) was repeated on the same scale but the crude product was agitated directly with 5N-hydrochloric acid (200 ml.) for 5 hr. Filtration followed by recrystallisation from ethanol yielded the thione (VIb) (10·0 g., 52%), m. p. 255—260°, and in addition less pure material (2·0 g.), m. p. *ca.* 240°.

Acid Hydrolysis of Oxatriazepinethiones (V).—(*a*) Compound (Va) (0·51 g.) in methanol (3 ml.) was treated with a solution of hydrogen chloride in isopropyl alcohol (0·6 ml.), and the mixture was heated under reflux for 30 min. Cooling and filtration yielded the pure thione (VIa) (0·44 g.), m. p. 184—186°. Under similar conditions, compound (Vb) yielded the thione (VIb), m. p. 260—262°.

(*b*) Compound (Va) (0·19 g.) and 2,4-dinitrophenylhydrazine (0·098 g.) in ethanol (5 ml.) containg hydrochloric acid (0·1 ml.) was boiled under reflux for 15 min. On cooling, acetone 2,4-dinitrophenylhydrazone (0·06 g.) was deposited as crystals, m. p. and mixed m. p. 127—127·5° (from ethanol). Chilling of the original mother-liquor afforded the thione (VIb) (0·091 g.), m. p. 184—185·5° (from ethanol).

Spectral Observations.—(a) *Ultraviolet spectra.* The u.v. spectrum of a 0·002% solution of compound (Va) in 0·01N ethanolic hydrochloric acid, measured immediately, was the same as that in ethanol. After 24 hr. at room temperature, the spectrum was mainly that of the triazolinethione (VIa), $\lambda_{max.}$ (log ε) 259·5 mμ (4·24).[1] Similarly, of

[9] I. B. Douglass and F. B. Dains, *J. Amer. Chem. Soc.*, 1934, **56**, 1408.

compound (Vb) after 24 hr. in acidic ethanol it was 259 mμ (4·23).

(b) *Nuclear magnetic resonance spectra.* (1) A deuteriochloroform solution of compound (Va) had the expected peaks due to CMe_2 at τ 8·37 and Ar-Me at 7·74. However, peaks of low intensity at 7·67 and 8·28 could not be assigned to the structure (Va) and could be due to the presence of a small proportion of the open-chain structure (IVa). The intensities of the anomalous peaks increased after 24 hr. at room temperature, and the infrared spectrum now showed a weak carbonyl band at 1670 $cm.^{-1}$ in accord with the presence of some (IVa). Further standing at room temperature for 5 days did not result in any increase in intensity of the bands at τ 7·67 and 8·28 but new peaks appeared at 7·82 and 7·92. The peak at 7·82 was assigned to the presence of the triazolinethione (VIa) (Ar-Me band), and the peak at 7·92 was due to a volatile component, *viz.*, acetone (peak disappeared on boiling the solution). An infrared spectrum now showed a band at 1720 $cm.^{-1}$ as expected for the carbonyl group of acetone. The addition of trifluoroacetic acid to a deutriochloroform solution of (Va) resulted in complete transformation into the triazolinethione (VIa), and the n.m.r. spectrum of the solution after 3 days was identical with that of the latter compound.

(2) The n.m.r. spectrum of acetone thiosemicarbazone in deuteriochloroform showed 2 peaks approximately 7 c./sec. apart near τ 8 corresponding to the two different methyl groups. Trifluoroacetic acid was added, and subsequently the spectrum showed only one broad peak near τ 8 when measured after 15 min. No significant change occurred on standing apart from a peak of very weak intensity at approximately 7·8 which could have been due to a low concentration of acetone (spectrum measured after 6 days).

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