vic-Iodothiocyanates and Iodoisothiocyanates. Part 4.† The Synthesis of 2-Substituted-2-thiazolines

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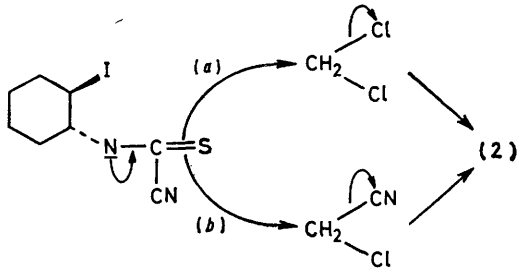
The reactions of *trans*-1-iodo-2-isothiocyanatocyclohexane with a number of carbon nucleophiles to form 2-substituted-2-thiazolines are described. Reactions of several *vic*-iodoisothiocyanates with butyl-lithium give products which are dependent on the solvent and/or temperature.

In preceding papers we have reported methods for the conversion of *vic*-iodoisothiocyanates into thiazolidin-2-ones,[1] 2-amino-2-thiazolines,[1] and 2-alkoxy-2-thiazolines.[2] We report here reactions of a representative *vic*-iodoisothiocyanate (1), with a series of carbon nucleophiles to form 2-cyano-, 2-alkyl-, and 2-aryl-2-thiazolines. The latter compounds are of synthetic value since protons on carbon atoms attached to C-2 of the thiazoline nucleus are acidic; use has been made of this property by Meyers and his co-workers [3] in the synthesis of protected carbonyl compounds. For example, the labile β-hydroxyaldehyde (4) is formed when the lithio-thiazoline (5) is treated with cyclohexanone and the thiazolinyl moiety is removed subsequently by reduction and mercury(II)-catalysed hydrolysis. Hackler and Balko [4] recently reported the preparation of two 2-alkyl-2-thiazolines from the reaction of carbon nucleophiles with *vic*-chloro- and *vic*-bromo-isothiocyanates but their products were obtained in only moderate yields (35% and 42%).

RESULTS AND DISCUSSION

Reactions of *trans*-1-iodo-2-isothiocyanatocyclohexane (1) with carbon nucleophiles are summarized in Table 1. Treatment of the iodoisothiocyanate with cyanide ion in the dipolar aprotic solvent dimethyl sulphoxide [5] did not give the desired heterocycle (6) but afforded the intermediate adduct *N*-(*trans*-2-iodocyclohexyl)cyanothioformamide (15) (67%), m.p. 91—92.5 °C (*cf.* ref. 6). However, cyclization was effected in 77% yield by heating the adduct (15) under reflux in tetrachloroethylene for 5 h. In contrast, the 2-cyano-2-thiazoline (6) was formed directly in yields of 58% and 48% respectively, when the reactions of (1) with cyanide ion were carried out in water–dichloromethane in the presence of the liquid–liquid phase-transfer catalysts TEBACl (benzyltriethylammonium chloride) and Adogen 464 [methyltrialkyl(C_8—C_{10})ammonium chloride]. From these latter reactions a low yield (8%) of a compound identified from its spectral data (see Experimental section) as (chloromethylthio)cyano-*N*-(*trans*-2-iodocyclohexyl)methanimine (2) was also obtained. Presumably (2) arises from attack of the cyanothioformamide anion on the solvent (Scheme 1, path *a*) (*cf.* ref. 7) rather than by attack on chloroacetonitrile (which could arise from reaction of cyanide ion with the solvent) (Scheme 1, path *b*) since chloride has been shown to be a better leaving group than cyanide.[8] The alternative structure (3) for the minor product was ruled

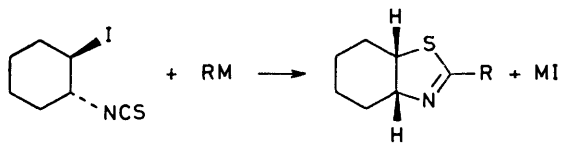


Scheme 1

out by examination of the mass spectrum, which showed fragmentation peaks corresponding to the loss of Cl, CH_2Cl, and SCH_2Cl from the molecular ion, but not to the loss of CN, CH_2CN, or SCH_2CN. Moreover, the use of ^{13}C n.m.r. substituent chemical-shift values [9] allows differentiation between the structures (2) and (3); the combined α-effect of a carbon bearing a sulphur and chlorine atom would afford a chemical shift of *ca.* δ_C 51 (Cl = +31, SR = +20) (observed δ_C 42.5) compared with a chemical shift of *ca.* δ_C 24 (SR = +20, CN = +4) for a carbon bearing a sulphur atom and a nitrile group.

Table 1

Reactions of *trans*-1-iodo-2-isothiocyanatocyclohexane



RM	Product	Yield (%) [a]
KCN	(6)	100
p-$OMeC_6H_4C{\equiv}CLi$	(7)	73
$PhC{\equiv}CLi$	(8)	68 [b]
$Me_3SiC{\equiv}CLi$	(9)	41 [c]
MeMgI	(10)	70 [c]
EtMgI	(11)	72 [b] (88 crude)
BuMgBr	(12)	83 [b]
PhLi	(13)	80 [b]

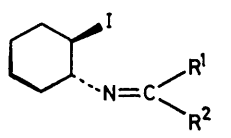
[a] Some products were prepared by several modifications; the yield quoted is the highest obtained. [b] Isolated by p.l.c. [c] After distillation.

† Part 3 is the preceding paper.

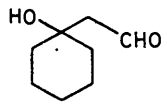
In a series of experiments in which the iodoisothiocyanate (1) was treated for increasing times with an excess of potassium cyanide in dichloromethane in the presence of the solid–liquid phase-transfer catalyst 18-crown-6 (1,4,7,10,13,16-hexaoxacyclo-octadecane),[10] it was shown that the iodocyanothioformamide (15) was formed rapidly (≤5 min) and quantitatively as the only product in the early stages of the reaction. Thereafter, a gradual decrease in the amount of this compound occurred as it was converted in a slower step (*ca.* 3 h) into the solvent-incorporated product (2). The yield of compound (2) reached a maximum (51%) after *ca.* 5 h whereupon it was converted either directly, or *via* reversion to (15) which is transformed, slowly and irreversibly, into the 2-cyano-2-thiazoline (6). Hine *et al.*[11] have shown that in an S_N2 reaction the ease of displacement of a halogen atom from an alkyl halide is decreased by replacement of an α-hydrogen atom by an additional halogen atom and that, in the absence of catalysis by base, the reaction of thiophenoxide (a strong nucleophile but weak base) with chloroform is negligibly slow.[12] It was anticipated, therefore, that changing the solvent from dichloromethane to chloroform in the above reaction would effectively prevent formation of any solvent-incorporated product. In the event, treatment of the iodoisothiocyanate (1) with potassium cyanide–18-crown-6 in refluxing chloroform–water for 2.5 h afforded only the iodocyanothioformamide (15) while reaction for 92 h gave a quantitative yield of the 2-cyano-2-thiazoline (6). Similar treatment of the iodoisothiocyanate using TEBACl in place of the 18-crown-6 for 111 h gave mainly the heterocycle (6) and a trace of starting material.

Initial attempts to form the 2-alkynyl-2-thiazoline (7) by treatment of the iodoisothiocyanate (1) with (4-methoxyphenyl)ethynyl-lithium in tetrahydrofuran–HMPT (hexamethylphosphoric triamide) at −78 °C for 10 min gave a 64% yield of the unstable yellow adduct *N*-(*trans*-2-iodocyclohexyl)-(4-methoxyphenyl)ethynyl-thioformamide (16). Use of HMPT as a co-solvent enhanced the rate of reaction since in tetrahydrofuran alone a longer time and a higher temperature (20 °C) were required in order to achieve a 54% yield. Attempted thermal cyclization of the thioformamide (16) in refluxing carbon tetrachloride resulted in its decomposition. However, stirring the compound (16) with potassium carbonate in acetone[13] afforded a quantitative yield of 1-(4-methoxyphenyl)-2-(*cis*-3α,4,5,6,7,7a-hexahydrobenzothiazol-2-yl)acetylene (7). Cyclization was also achieved in 94% yield by treatment of the thioformamide (16) with triethylamine in tetrahydrofuran for 94 h. Treatment of the iodoisothiocyanate (1) with (4-methoxyphenyl)acetylene and butyl-lithium in benzene (*cf.* ref. 14)–TMEDA (*NNN'N'*-tetramethyl-1,2-diaminoethane) at 0 °C for 40 min gave the thioformamide (16) in 71% yield.

In a series of reactions of the iodoisothiocyanate (1) with (4-methoxyphenyl)ethynyl-lithium in tetrahydrofuran–HMPT it was found that a 1 : 1 : 1 molar ratio of (1) : alkyne : butyl-lithium at 0—20 °C also gave a moderate (38%) yield of the arylethynyl-2-thiazoline (7) but that a 1 : 2 : 2 molar ratio at −78 °C consistently gave the intermediate (16) as the predominant product. Further reactions indicated that the temperature and the molar excess of butyl-lithium were not affecting the product distribution. However, use of a further excess



(1) R^1, R^2 = S
(2) R^1 = CN, R^2 = SCH_2Cl
(3) R^1 = Cl, R^2 = SCH_2CN



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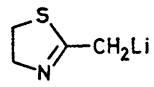

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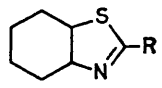
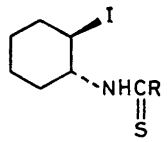
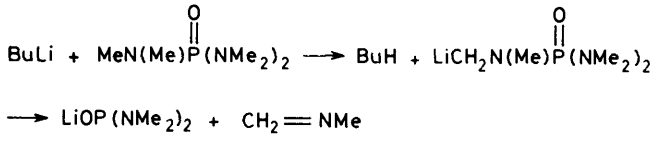


(6) R = CN
(7) R = C≡C—C_6H_4OMe-*p*
(8) R = C≡C—Ph
(9) R = C≡CH
(10) R = Me
(11) R = Et
(12) R = Bu
(13) R = Ph
(14) R = CH=C(Cl)—C_6H_4OMe-*p*



(15) R = CN
(16) R = C≡C—C_6H_4OMe-*p*
(18) R = C≡CPh
(19) R = C≡CH
(20) R = C≡CSiMe
(21) R = Ph

of butyl-lithium (2.5 mol equiv.) gave many products including two [(17) and (22)] resulting from reaction with the solvent. Compound (17) arises by attack of the tetramethylphosphoric diamide anion on the iodoisothiocyanate (1) (Scheme 2); Abatjoglou and Eliel [15] have



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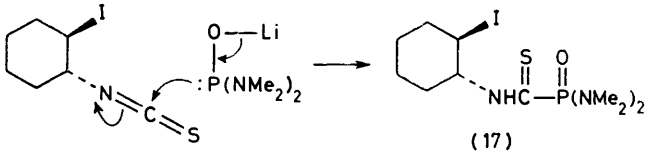
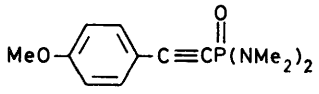


(17)

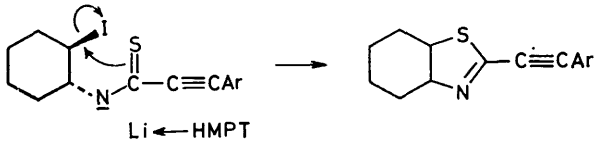
SCHEME 2

recently shown that butyl-lithium reacts with HMPT to give the lithio-derivative (23). However, production of the compound (22) was unexpected since its formation must involve displacement by the alkynide at phosphorus of the HMPT, a solvent which is relatively inert to nucleophilic attack.[16] Presumably, in the case where a



(22)

1 : 1 : 1 molar ratio of reactants was used, solvation of the lithium cation allows the uncomplexed anion to displace iodide (Scheme 3). However, in the absence of HMPT only the compound (16) was formed and in this case cyclization is prevented by intimate binding of the anion with a lithium cation. Where the 1 : 2 : 2 molar ratio of reactants was used it is possible that the excess of alkynide forms a complex with the intermediate anionic species, thereby preventing cyclization. Support for



SCHEME 3

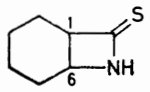
this proposal comes from the observation that the yellow colour of the intermediate (16) appeared only when these reactions were quenched with water. It is unlikely that complexing between the iodothioformamide anion and the excess of reagent is simply a metal exchange, since an excess of HMPT was used and thus all the lithium ions should have been solvated.

For comparison, the iodoisothiocyanate (1) was also treated at room temperature for 2 h with (4-methoxyphenyl)ethynylmagnesium bromide, prepared by refluxing ethylmagnesium bromide and 4-methoxyphenylacetylene for 30 min. This afforded a 73% yield of the heterocycle (7) when a four-fold molar excess of the Grignard reagent was used but this reaction was slower and less convenient than that using the organolithium species. The alkynylmagnesium halide formed slowly [17] and this was reflected in the isolation of only the 2-ethyl-2-thiazoline (11) if the ethylmagnesium bromide and the (4-methoxyphenyl)acetylene were stirred at 20 °C for 5 min prior to the addition of (1). Attempted hydrolysis of the (arylethynyl)-2-thiazoline (7) with dilute hydrochloric acid failed to give a propiolic acid (*cf.* hydrolysis of 2-arylethenyloxazolines [18]) but afforded the product of addition of hydrogen chloride to the triple bond, *i.e.* 1-chloro-1-(4-methoxyphenyl)-2-(*cis*-3a,4,5,6,7,7a-hexahydrobenzothiazol-2-yl)ethylene (14) in 91% yield. Although the ^{1}H n.m.r. spectrum of the product was similar to that of the starting material, an additional singlet at δ 7.03 was assigned to the C-2 proton. The high-resolution mass spectrum did not show a molecular ion but by metastable re-focusing a metastable ion was detected for the transition *m/e* 307.05 ± 0.2→306.07, *i.e.* for $M^{+\cdot}\rightarrow M^{+\cdot}-H\cdot$. Assignment of structure (14) was confirmed by a characteristic 3 : 1 isotope distribution expected for a single chlorine atom in the $M^{+\cdot}-H\cdot$ ion and other fragment peaks in the mass spectrum. The regiochemistry of the product (14) was assigned by analogy with that from the addition of aqueous hybrobromic acid to 3-phenylpropynoic acid, which affords *E*-3-bromo-3-phenylpropenoic acid.[19] However, no check on the stereochemistry could be made since an attempt to transform the product into the thermodynamically more stable *Z*-isomer by treatment with dry hydrogen chloride in ether [19] resulted in precipitation of the *E*-diastereoisomer as its thiazolinium hydrochloride. Treatment of the compound (7) with aqueous sulphuric acid under reflux afforded 4-methoxyacetophenone (32%) by hydration of the alkyne, ketonisation, and decarboxylation of the resulting β-keto-acid.

Unlike the reaction with (4-methoxyphenyl)ethynyllithium, treatment of the iodoisothiocyanate (1) with phenylethynyl-lithium in benzene–TMEDA did not give a heterocycle but afforded the adduct *N*-(*trans*-2-iodocyclohexyl)(phenylethynyl)thioformamide (18) as an unstable yellow oil. However, as before, cyclization was effected by treatment of the iodothioformamide with potassium carbonate in acetone, which afforded 1-(*cis*-3a,4,5,6,7,7a-hexahydrobenzothiazol-2-yl)-2-phenylacetylene (8) in 68% overall yield. No product could be isolated when the iodoisothiocyanate (1) was treated with ethynyl-lithium, prepared from acetylene and butyl-lithium in tetrahydrofuran [20] or benzene–TMEDA in the absence of oxygen, although formation of the unstable *N*-(*trans*-2-iodocyclohexyl)(ethynyl)-thioformamide (19) was indicated by t.l.c. analysis. In order to stabilize the product (19) the ethynyl group was introduced in a protected [21] form as trimethylsilyl-ethynyl-lithium.[22] Reaction of the latter with the iodo-

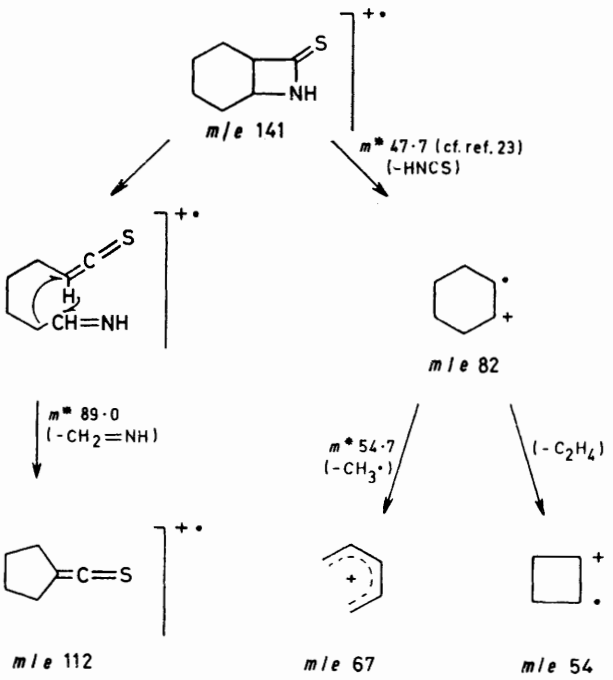
isothiocyanate (1) gave the adduct (20) which was isolable but still very unstable and which when treated immediately with potassium carbonate in acetone underwent both cyclization and cleavage of the trimethylsilyl group to give 2-ethynyl-*cis*-3a,4,5,6,7,7a-hexahydrobenzothiazole (9) as an unstable solid, in 41% yield.

In addition to its use as a strong base as in the preceding reactions, the reaction of butyl-lithium as a nucleophile was also examined. Treatment of the iodoisothiocyanate (1) with butyl-lithium in ether at −78 °C for 5 min afforded *cis*-7-azabicyclo[4.2.0]-octane-8-thione (24) rather than the anticipated product (12). The thione (24) was characterized from its ^{1}H



(24)

n.m.r., i.r., and mass spectra, and by elemental analysis. In the ^{1}H n.m.r. spectrum, multiplets centred at δ 2.73 ($W_{\frac{1}{2}}$ 18.5 Hz) and 3.69 ($W_{\frac{1}{2}}$ 17 Hz) were assigned to methine protons on C-1 and C-6, respectively. The proton attached to nitrogen resonated at δ 7.90 and exchanged with deuterium oxide, while in the i.r. spectrum the NH stretching vibration occurred at 3 390

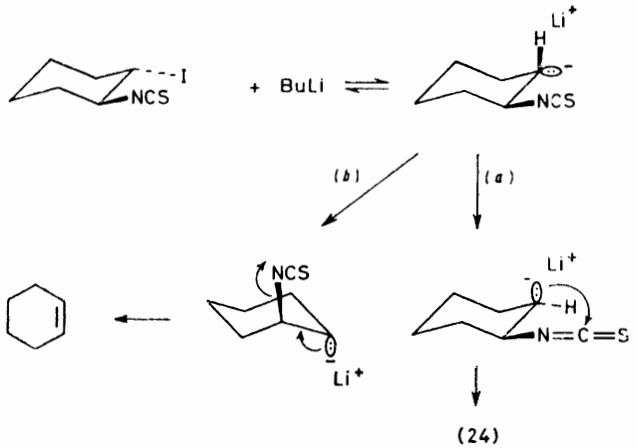


Scheme 4

cm^{-1}. The mass spectrum showed the molecular ion at *m/e* 141 and fragment peaks corresponding to those in Scheme 4.

The reaction of butyl-lithium with the iodoisothiocyanate (1) is a novel, although not general (see later), method for the synthesis of thioxo-β-lactams.[24]

The first step in the formation of the thioxo-β-lactam (24) involves the well-known but generally unfavourable equilibrium reaction between an alkyl halide and a simple alkyl-lithium.[25] The present reaction is a special case since the contiguous relationship of the substituents of the *vic*-iodoisothiocyanate (1) results in displacement of the equilibrium by irreversible attack of the carbanionic centre on the electropositive carbon atom of the isothiocyanate group. The fate of the anion generated in the present reaction was dependent on the solvent and/or temperature. For example, when the reaction was carried out in tetrahydrofuran at −78 °C the product was cyclohexene, which was trapped as *trans*-1,2-dibromocyclohexane by the subsequent addition of bromine. The ^{1}H n.m.r. spectrum of the iodoisothiocyanate (1) [26] indicates that the iodide and isothiocyanate groups occupy equatorial positions in a chair conformer.

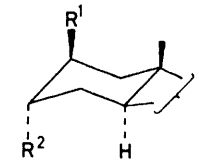


Scheme 5

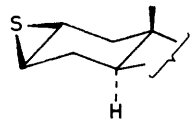
It is envisaged that reaction of the compound (1) with butyl-lithium in ether gives a carbanion which undergoes inversion at the anionic centre but maintains the isothiocyanate group in an equatorial position [Scheme 5, path (*a*)]. This conformation would favour intramolecular nucleophilic attack to yield the thioxo-β-lactam (24) rather than displacement of the isothiocyanate group. In the more basic solvent tetrahydrofuran, it is suggested that elimination occurs [Scheme 5, path (*b*)] through conformational inversion of the initial carbanion so that the isothiocyanate group occupies an axial position *anti*-periplanar to the carbanionic lone pair. When the reaction with butyl-lithium was carried out in ether at 0 °C rather than −78 °C, only a 30—50% yield of the thioxo-β-lactam (24) was obtained, since at the higher temperature elimination began to compete favourably with cyclization.

Evidence supporting the conformational requirements in the above reactions was obtained from the reaction of butyl-lithium with the regioisomeric mixture of the more rigid *vic*-iodoisothiocyanates (25) and (26) derived from 5α-androst-2-ene,[26] where the substituent groups occupy axial positions. No reaction was observed at −78 °C but on warming the mixture to ambient temperature elimination resulted in the formation of 5α-

androst-2-ene. In contrast, the elimination occurred at −78 °C when the mixture of regioisomeric iodoisothiocyanates derived from the conformationally biased 4-t-butylcyclohexene was treated with butyl-lithium. Treatment of the mixture of iodoisothiocyanates (25) and (26) with butylmagnesium bromide also afforded



(25) R^1 = NCS, R^2 = I
(26) R^1 = I, R^2 = NCS
(27) R^1 = SCN, R^2 = I

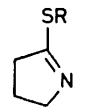


(28)

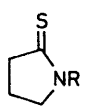
5α-androst-2-ene only. Although it is possible that attack of the Grignard reagent at the isothiocyanato-carbon atom of the 2β-steroid derivative (25) may be hindered as a result of the 1,3-diaxial relationship of the isothiocyanate and C-19 methyl groups, such a steric effect could not operate in the 3α-regioisomer (26).

3α-Iodo-2β-thiocyanato-5α-androstane (27) also underwent metal–halogen exchange with butyl-lithium to give eventually 5α-androst-2-ene together with a small amount of the 2β,3β-thiiran (28). This elimination reaction was much faster than that of the mixture of iodoisothiocyanates (25) and (26), in agreement with the fact that the sulphur-bonded thiocyanate anion is a better leaving group than the nitrogen-bonded isothiocyanate anion.

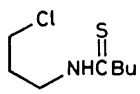
Thus, relatively rigid substrates with *trans*-diaxial substituents favour elimination: conformationally mobile isothiocyanates might therefore favour preferential thioxo-lactam formation. In support of this postulate, treatment of 1-iodo-3-isothiocyanatopropane with butyl-lithium afforded a 73% yield of a tautomeric



(29) R = H
(30) R = Me



(31) R = H
(32) R = Me



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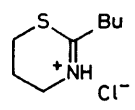

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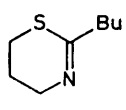

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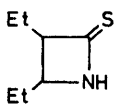


(36)

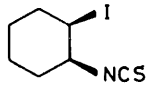
(7 : 3) mixture of 4,5-dihydro-2-mercapto-1-pyrroline (29) and 2-thioxopyrrolidine (31) which decomposed shortly after work-up. However, addition of iodomethane to the freshly prepared product gave 2-methylthio-1-pyrroline (30) [27] in 92% yield with no trace of the *N*-methylated isomer (32).[28] Thus, the ^{1}H n.m.r. spectrum of the crude product showed a singlet at δ 2.44, characteristic of a methyl group bound to sulphur, but no peak at δ 3.27 which has been reported for the methyl group of the *N*-methyl isomer (32).[28]

The infrequency of metal–halogen exchange reactions between organo-lithium reagents and alkyl chlorides was illustrated by the reaction of 1-chloro-3-isothiocyanatopropane with butyl-lithium. In this case the butyl carbanion attacked the isothiocyanato-carbon atom to give *N*-(3-chloropropyl)thiopentanamide (33) (93%) which on heating gave 2-butyl-5,6-dihydro-4*H*-1,3-thiazinium chloride (34) as a dark red water-soluble solid. Treatment of the salt with sodium hydrogencarbonate gave 2-butyl-5,6-dihydro-4*H*-1,3-thiazine (35) in 71% overall yield. T.l.c. analysis of the reaction mixture from treatment of *erythro*-3-iodo-4-isothiocyanatohexane [2] with butyl-lithium at −78 °C for 2 min showed the formation of a single product with an R_F value similar to that of the thioxo-β-lactam (24). However, after work-up 8 min later, a volatile oil containing 1-iodobutane and a complex mixture of unidentified products was isolated, and no confirmatory evidence that either stereoisomer of 3,4-diethyl-2-thioxoazetidine (36) had been formed was obtained.

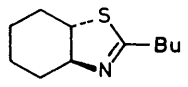
Unlike most of the carbon nucleophiles used above, the reactions of simple alkyl Grignard reagents with the iodoisothiocyanate (1) afforded the corresponding 2-substituted-2-thiazoline in one step. Although the products have the potential to react further with carbanionic reagents to form a 2,2-dialkyl-1,3-thiazolidine,[29] use of an excess of Grignard reagent did not result in further alkylation of the 2-thiazolines. The reaction of the iodoisothiocyanate (1) with butylmagnesium bromide was faster than that with butylmagnesium iodide but both reagents underwent some metal–halogen exchange as shown by the detection (^{1}H n.m.r.) of traces of 1-iodobutane in the crude products. The ^{1}H n.m.r. spectra of the 2-methyl- and 2-ethyl-2-thiazolines (10) and (11) each showed five-bond coupling between the protons geminal to nitrogen and either the methyl group of (10) or the methylene protons of the ethyl group of (11). Such coupling is characteristic of 2-alkyl-2-thiazolines.[30] The 2-thiazolines (10) and (11) have been synthesized previously [31] in low yields (30% and 20% respectively) by cyclization of an intermediate halogenothioxoamide formed in a Ritter-type reaction.

During the course of reactions of the iodoisothiocyanate (1) with butylmagnesium iodide or bromide, but with neither methyl- nor ethyl-magnesium iodide, the formation of a further product was detected by t.l.c. This compound was transformed along with starting material into the 2-thiazoline (12) as the reaction progressed, but by quenching a reaction before completion it was isolated and identified as *cis*-1-iodo-2-isothiocyanatocyclohexane (37). The *cis*-stereochemistry of the substituent groups was indicated by the ^{1}H n.m.r. spectrum, which exhibited a multiplet at δ 4.36 ($W_{\frac{1}{2}}$ 15 Hz) for the proton geminal to iodine, in contrast to the symmetrical six-line pattern for the analogous proton in the

trans-isomer (1). A slightly narrower multiplet ($W_{\frac{1}{2}}$ 11 Hz) due to the proton geminal to the isothiocyanato-group appeared at δ 3.75, while a strong band characteristic of the isothiocyanato-group appeared at 2 065 cm^{-1} in the



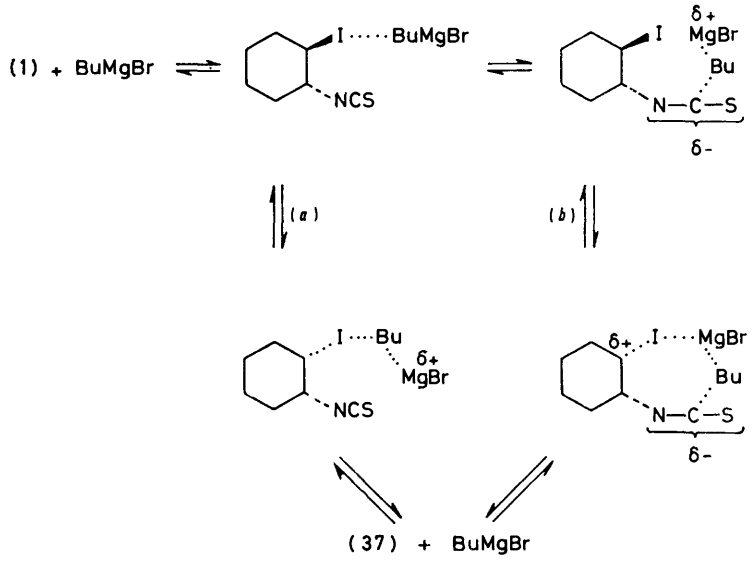
(37)



(38)

i.r. spectrum. Microanalytical and mass-spectral data were also in accord with the structure (37). The compound appears to arise by rapid and reversible isomerization of the *trans*-isomer (1) since no *trans*-thiazoline (38) was isolated from the reaction. The isomerization is not simply due to nucleophilic displacement at either of the secondary carbon atoms, since t.l.c. monitoring of A point in favour of path (*a*) is the detection of traces of 1-iodobutane concomitant with isomerization.

Reaction of exogenous phenyl-lithium [35] with the iodoisothiocyanate (1) at −78 °C for 25 min afforded a quantitative yield of *N*-(*trans*-2-iodocyclohexyl)thiobenzamide (21) but, as before, treatment of the product with potassium carbonate–acetone at 20 °C for 15 h effected cyclization to give 2-phenyl-*cis*-3a,4,5,6,7,7a-hexahydrobenzothiazole (13). Although dialkylthioketens [36] and diaryl- [37] and dialkyl-thioketones [38] have been shown to react with phenyl-lithium *via* thiophilic addition, no product resulting from attack of the phenyl anion on the sulphur atom of the isothiocyanate group of the iodoisothiocyanate (1) was isolated. Moreover, no metal–halogen exchange between the substrate and phenyl-lithium was observed. Treatment of the iodoisothiocyanate (1) with phenyl-lithium, generated *in situ*



SCHEME 6

the reaction of the iodoisothiocyanate (1) with lithium iodide in ether for 19 h or with potassium thiocyanate–18-crown-6 for 1 h, showed no formation of the *cis*-isomer (37). Moreover, in an independent reaction it was found that magnesium bromide, a compound likely to be formed from butylmagnesium bromide in the Schlenk equilibrium,[32] did not effect isomerization. The possibility (since protons geminal to an isothiocyanate group are acidic [33]) of any mechanism involving the intervention of a fully developed kinetically-free carbanionic centre was also eliminated since neither compound (1) nor compound (37) showed any detectable (^{1}H n.m.r.) incorporation of deuterium when a reaction between the iodoisothiocyanate (1) and butylmagnesium bromide was quenched after 30 min with deuterium oxide. The *cis*-isomer (37) may arise by isoracemization [34] in which an intimate ion-pair involving the Grignard reagent is formed (Scheme 6) and inversion occurs either at a potential carbanionic site [path (*a*)] or a potential carbocationic site [path (*b*)]. from iodobenzene and butyl-lithium[35] afforded the acyclic phenyl adduct (21) (43%), the phenyl-2-thiazoline (13) (15%), recovered starting material (28%), and several unidentified products. In this case, the phenyl-2-thiazoline (13) was shown in an independent experiment to arise by cyclization of the intermediate (21) during chromatography of the crude product on silica gel. The compound (21) was the only iodothioformamide isolated during the present study which would cyclize on this medium. Treatment of the iodoisothiocyanate (1) with phenylmagnesium bromide at 20 °C for 90 min also afforded the intermediate (21) which after multiple p.l.c. gave the heterocycle (13) in 31% yield.

EXPERIMENTAL

General experimental details are given in ref. 26. The molarity of butyl-lithium and phenyl-lithium solutions was determined by either the method of Watson and Eastham [39] or of Kofron and Baclawski.[40] All reactions involving air-

and moisture-sensitive reagents, and metallated anions, were carried out in an oven-dried argon-flushed three-neck flask equipped with a magnetic stirring bar and a septum-capped inlet. Solvents and solutions were added by syringe. Unless otherwise stated, all reactions were quenched in water or aqueous ammonium chloride. Work-up involved extraction with ether, washing with water, and (if necessary) with saturated aqueous sodium hydrogensulphite and/or sodium hydrogencarbonate, followed by drying over magnesium sulphate (desiccated) and removal of solvent under reduced pressure.

Reaction of trans-1-*Iodo*-2-*isothiocyanatocyclohexane with Potassium Cyanide.*—(a) *In dimethyl sulphoxide.* A mixture of *trans*-1-iodo-2-isothiocyanatocyclohexane (1) (0.20 g, 0.75 mmol) and potassium cyanide (0.12 g, 1.84 mmol, dried at 85—90 °C at 25 mmHg) was stirred in dimethyl sulphoxide (5 ml) at 20 °C for 5 min. The mixture was quenched in saturated brine solution and extracted with ether. The ether layer was washed with brine, dried, and the solvent was removed to give an oil (0.16 g). P.l.c. (chloroform) gave *N*-(trans-2-*iodocyclohexyl*)*cyanothioformamide* (15) (0.15 g, 67%) which crystallized from pentane–ether as yellow needles, m.p. 91—92.5 °C (Found: C, 32.7; H, 3.7; I, 43.2; N, 9.7; S, 11.3. $C_8H_{11}IN_2S$ requires C, 32.7; H, 3.8; I, 42.9; N, 9.5; S, 10.9%); $\nu_{max.}$ 3 260 (NH), and 2 240 cm^{-1} (C≡N); δ 0.74—2.73 (m, CH_2), 4.10 (ddd, *J* 10, 10, and 4.5 Hz, CHI), 4.67 ($W_{\frac{1}{2}}$ 20 Hz, CHN), and 9.0 (m, NH, exchanged with D_2O); *m/e* 294 ($M^{+\cdot}$), 267 ($M^{+\cdot}$ − HCN), 208 [$M^{+\cdot}$ − $H_2NC(:S)CN$], and 167 ($M^{+\cdot}$ − I·).

Reaction for a longer time (3 h) gave a mixture of decomposition products.

The compound (15) in tetrachloroethylene was heated under reflux for 5 h. P.l.c. of the product gave the 2-cyano-2-thiazoline (6) (see below). Attempts to effect the cyclization of (15) by stirring with silver(I) sulphate (1.5 mol equiv.) or silver(I) perchlorate in ether at 20 °C for 20 h, or with silver(I) cyanide (1.1 mol equiv.) in ether–dimethyl sulphoxide (4 : 1) at ambient temperature for 20 h, were unsuccessful.

(b) *In dichloromethane–water–TEBACl.* A solution of TEBACl (20 mg, 0.08 mmol) in dichloromethane (4 ml) was added to a solution of potassium cyanide (60 mg, 0.92 mmol) in water (3 drops). *trans*-1-Iodo-2-isothiocyanatocyclohexane (1) (0.10 g, 0.37 mmol) was added and the mixture was stirred vigorously at 20 °C for 66 h, diluted with dichloromethane, and passed through a short column of magnesium sulphate to yield an oil (91 mg). P.l.c. [hexane–chloroform (1 : 1)] gave: (*i*) (chloromethylthio)cyano-*N*-(*trans*-2-iodocyclohexyl)methanimine (2) (10 mg, 8%) which crystallised from pentane–ether as irregular plates, m.p. 53.5—55 °C (Found: * I, 37.0; N, 8.2. $C_9H_{12}ClINS$ requires I, 37.0; N, 8.2%); $\nu_{max.}$ 2 230 (C≡N), and 1 600 cm^{-1} (C=N); δ 0.66—2.88 (m, CH_2), 3.95 (m, CHN), 4.24 (ddd, *J* 9, 9, and 4 Hz, CHI), and 5.30 (m, SCH_2Cl); *m/e* 342 ($M^{+\cdot}$), 307 ($M^{+\cdot}$ − Cl·), 293 ($M^{+\cdot}$ − CH_2Cl), 261 ($M^{+\cdot}$ − SCH_2Cl), 215.042 3 ($M^{+\cdot}$ − I·), 163.033 8 [$M^{+\cdot}$ − (I + NCCN)], and 77 (*m**, 342→163); δ_C 23.8 (C-4′), 27.7 (C-5′), 34.0 (C-3′), 35.2 (C-6′), 38.2 (C-2′), 42.5 (SCH_2Cl), 74.4 (C-1′), 107.0 (C≡N), and 134.9 (C=N): and (*ii*) 2-*cyano*-cis-3a,4,5,6,7,7a-*hexahydrobenzothiazole* (6) (35 mg, 58%), b.p. 90 °C at 1.5 mmHg (Found: C, 58.1; H, 6.2; N, 16.8; S, 19.1. $C_8H_{10}N_2S$ requires C, 57.8; H, 6.1; N, 16.9; S, 19.3%); $\nu_{max.}$ no 2 200 peak (*cf.* ref. 41), 1 562 cm^{-1} (C=N); δ 0.66—2.56 (m, CH_2), and 4.0 ($W_{\frac{1}{2}}$ 21 Hz, CHS and CHN); *m/e* 166.056 2 ($M^{+\cdot}$); δ_C 21.4 (C-6), 22.5 (C-5), 27.5 (C-7), 29.1 (C-4), 53.3 (C-7a), 75.4 (C-3a), 112.3 (C≡N), and 143.1 (C-2).

* The compound contained a trace of a persistent impurity which precluded the obtaining of correct C and H values.

The experiment was repeated in a mixture of dichloromethane–deuteriodichloromethane (2 : 1). The mass spectrum of the solvent-incorporated products (2) indicated the presence of 24% (theory 33%) of the dideuteriated derivatives.

(c) *In dichloromethane–water–Adogen* 464. A mixture of *trans*-1-iodo-2-isothiocyanatocyclohexane (1) (0.10 g, 0.37 mmol), potassium cyanide (60 mg, 0.92 mmol), water (4 drops), and Adogen 464 (36 mg, 0.07 mmol) in dichloromethane (4 ml) was stirred at 20 °C for 128 h. Work-up gave an oil (0.12 g) which after p.l.c., gave the methanimine (2) (10 mg, 8%) and the 2-cyanothiazoline (6) (30 mg, 48%).

(d) *In dichloromethane–*18-*crown*-6. *trans*-1-Iodo-2-isothiocyanatocyclohexane (1) (50 mg, 0.19 mmol) was added to potassium cyanide (36 mg, 0.55 mmol) and 18-crown-6 (60 mg, 0.22 mmol) in dichloromethane (5 ml) and the mixture was stirred at 20 °C for the time recorded. Products were isolated by p.l.c. without other work-up and are shown in Table 2.

TABLE 2

Time/h	Products	Yield (%)
0.5	(15)	67
3.5	(2)	41
5	(2)	51
16	(2)	25
23	(2)	16
	(6)	32

With a 1 : 1 : 1.2 molar ratio of reactants and a time of 3.25 h the products were (15) (37%) and (2) (24%).

(e) *In chloroform–water–*18-*crown*-6. A mixture of *trans*-1-iodo-2-isothiocyanatocyclohexane (1) (0.10 g, 0.37 mmol), potassium cyanide (60 mg, 0.92 mmol), and 18-crown-6 (20 mg, 0.75 mmol) was heated under reflux in chloroform–water (4 : 1, 5 ml) for 92 h. Work-up and p.l.c. gave the 2-cyano-2-thiazoline (6) in 100% yield.

(f) *In chloroform–water–TEBACl.* A mixture of *trans*-1-iodo-2-isothiocyanatocyclohexane (1) (0.10 g, 0.37 mmol), potassium cyanide (60 mg, 0.92 mmol), and TEBACl (20 mg, 0.08 mmol) in chloroform–water (1 : 1, 6 ml) was heated under reflux for 111 h. Work-up and ^1H n.m.r. and t.l.c. analysis of the crude product (59 mg) showed the presence of mainly the 2-cyano-2-thiazoline (6), and starting material (trace).

Conversion of the Chloromethyl Derivative (2) *into the Cyano*-2-*thiazoline* (6).—The chloromethyl derivative (2) (1 mol equiv.) was stirred with a mixture of 18-crown-6–potassium cyanide–potassium chloride (1.2 : 2 : 1 mol equiv.) in dichloromethane at 20 °C. No change occurred after 3 h, but after 21 h t.l.c. showed the presence of the 2-cyano-2-thiazoline (6) and a trace of the iodocyanothioformamide (15), starting material, and a minor unidentified product.

Reaction of trans-1-*Iodo*-2-*isothiocyanatocyclohexane with* 4-*Methoxyphenylethynyl-lithium.*—(a) *In benzene–TMEDA.* Butyl-lithium (0.6 ml, 0.89 mmol) was added dropwise to a cold (0 °C) solution of (4-methoxyphenyl)acetylene (99 mg, 0.75 mmol) and TMEDA (0.5 ml) in benzene (5 ml). The solution was stirred for 2 min, *trans*-1-iodo-2-isothiocyanatocyclohexane (1) (0.20 g, 0.75 mmol) was added, and

the mixture was stirred at 0 °C for 40 min. Work-up afforded a yellow oil (0.32 g) which, after p.l.c. [hexane–dichloromethane (1 : 1)], gave *N*-(*trans*-2-iodocyclohexyl)-(4-methoxyphenylethynyl)thioformamide (16) (0.21 g, 71%) as an unstable yellow oil; $\nu_{max.}$ 3 400 (NH), 2 207 (C≡C), 1 610 (C=C), and 1 250 cm^{-1} (OMe); δ 1.00—2.66 (m, CH_2), 3.76 (m, CHN), 3.82 (s, OMe), 4.23 (ddd, *J* 10, 10, and 4.5 Hz, CHI), 7.22 (m, ArH), and 8.28 (m, NH, exchanged with D_2O).

(b) *In tetrahydrofuran–HMPT.* In a typical experiment, butyl-lithium (1 ml, 1.49 mmol) was added to a solution of (4-methoxyphenyl)acetylene (0.20 g, 1.49 mmol) in tetrahydrofuran (6 ml) cooled to 0 °C, and the mixture was stirred for 5 min. After addition of HMPT (0.5 ml), the solution was cooled to −78 °C and *trans*-1-iodo-2-isothiocyanatocyclohexane (1) (0.20 g, 0.75 mmol) in tetrahydrofuran (2 ml) was added. The mixture was stirred at −78 °C for 10 min and worked up to yield an oil (0.41 g) which gave the iodothioformamide (16) (0.19 g, 64%) after purification by p.l.c. Other results are given in Table 3.

TABLE 3

Molar ratio (1)	*p*-$MeOC_6H_4C{\equiv}CH$	BuLi	Temp. (°C)	Time/h	Product	Yield (%)
1	1	1	0—20	0.5	(7)	38 [a]
1	1	1.5	−78	1.0	(7)	36 [a]
1	2	2	−78	0.5	(16)	54
1	3	3 [b]	20	0.5	(16)	56
1	1	2.5	−78	0.5	(17)	11
					(22)	5 [c]

[a] Plus starting material. [b] No HMPT. [c] Plus two further unidentified products, $C_{13}H_{24}N_2S$, in 7% and 10% yields.

Cyclization of N-(trans-2-*Iodocyclohexyl*)-(4-*methoxyphenylethynyl*)*thioformamide.*—Compound (16) (0.11 g, 0.28 mmol) was treated with potassium carbonate (46 mg, 0.33 mmol) in acetone (5 ml) for 21 h. Work-up gave 1-(4-*methoxyphenyl*)-2-(cis-3a,4,5,6,7,7a-*hexahydrobenzothiazol*-2-*yl*)*acetylene* (7) (81 mg, 100%), b.p. 164 °C at 0.4 mmHg (Found: C, 70.7; H, 6.3; N, 5.0; S, 11.3; $C_{16}H_{17}NOS$ requires C, 70.8; H, 6.3; N, 5.2; S, 11.8%); $\nu_{max.}$ 2 218 (C≡C), 1 605 (C=C), 1 545 (C=N), and 1 250 cm^{-1} (OMe); δ 0.67—2.42 (m, CH_2), 3.75 (m, CHS and CHN), 3.80 (s, OMe), 6.76 and 7.43 (2d, *J* 9 and 9 Hz, ArH); *m/e* 271 ($M^{+\cdot}$), 157 ($M^{+\cdot}$ − $C_6H_{10}S$), and 114 ($C_6H_{10}S^{+\cdot}$); δ_C 21.4 (C-6′), 23.1 (C-5′), 28.3 (C-7′), 29.9 (C-4′), 52.1 (C-7a′), 55.2 (OCH_3), 74.6 (C-3a′), 82.1 (C-1), 93.8 (C-2), 112.8 (*ipso*-C), 114.1 (*o*-C), 133.8 (*m*-C), 151.1 (C-2′), and 160.7 (*p*-C).

Compound (16) (0.10 g, 0.92 mmol) was also cyclized to the thiazoline (7) (65 mg, 94%) by stirring it with triethylamine (0.5 ml) in tetrahydrofuran (5 ml) at 20 °C for 94 h.

Reaction of trans-1-*Iodo*-2-*isothiocyanatocyclohexane with* 4-*Methoxyphenylethynylmagnesium Bromide.*—Ethylmagnesium bromide [from bromoethane (0.39 g, 3.7 mmol) and magnesium (91 mg, 3.75 mmol)] in ether (4 ml) was added to (4-methoxyphenyl)acetylene (0.49 g, 3.7 mmol) dissolved in tetrahydrofuran (7 ml) and the mixture was heated under reflux for 30 min, and then cooled to 20 °C. A solution of *trans*-1-iodo-2-isothiocyanatocyclohexane (1) (0.20 g, 0.75 mmol) in ether (1 ml) was added, and the mixture was stirred at ambient temperature for 2 h. Work-up, followed immediately by p.l.c., gave the iodothioformamide (16) (0.22 g, 73%).

Other results are given in Table 4.

Reaction of 1-(4-*Methoxyphenyl*)-2-(cis-3a,4,5,6,7,7a-*hexahydrobenzothiazol*-2-*yl*)*acetylene with Hydrochloric Acid.*—A mixture of 1-(4-methoxyphenyl)-2-(*cis*-3a,4,5,6,7,7a-hexahydrobenzothiazol-2-yl)acetylene (7) (0.14 g, 0.52 mmol) and hydrochloric acid (5 ml of a 2 mol l^{-1} solution) was heated under reflux for 40 min. Work-up gave 1-*chloro*-1-(4-*methoxyphenyl*)-2-(cis-3a,4,5,6,7,7a-*hexahydrobenzothiazol*-2-*yl*)*acetylene* (14) (0.14 g, 91%) which after

TABLE 4

Molar ratio (1)	*p*-$MeOC_6H_4C{\equiv}CMgBr$	Time/h	Product	Yield (%)
1	1.5 [a]	21	(16)	29
1	2 [a]	2	(16)	32

[a] Pre-formed by refluxing for 30 min.

p.l.c. [hexane–chloroform (3 : 7)] and crystallization from pentane yielded pale yellow needles, m.p. 64—66 °C (Found: C, 62.7; H, 6.0; Cl, 11.5; N, 4.7; S, 10.3. $C_{16}H_{18}ClNOS$ requires C, 62.4; H, 6.0; Cl, 11.5; N, 4.6; S, 10.4%); $\nu_{max.}$ ($CHCl_3$) 1 600 cm^{-1} (C=N); δ 1.00—2.50 (m, CH_2), 3.89 (m, CHS and CHN), 3.85 (s, OMe), 6.88 and 7.64 (2 d, *J* 9 and 9 Hz, ArH), and 7.03 (s, 2-H); *m/e* 306.072 5 ($M^{+\cdot}$ − H·, requires 306.072 0), (metastable refocusing with a very narrow β-slit showed a metastable for 307.05 ± 0.2→306.07) 306 and 308 (3 : 1, $M^{+\cdot}$ − H·), and 226 and 228 (3 : 1, $M^{+\cdot}$ − C_6H_9·).

Reaction of 1-(4-*Methoxyphenyl*)-2-(cis-3a,4,5,6,7,7a-*hexahydrobenzothiazol*-2-*yl*(*acetylene with Sulphuric Acid.*—A mixture of 1-(4-methoxyphenyl)-2-(*cis*-3a,4,5,6,7,7a-hexahydrobenzothiazol-2-yl)acetylene (7) (56 mg, 0.2 mmol) and aqueous sulphuric acid (6 ml of a 1.5 mol l^{-1} solution 9 mmol) was heated under reflux for 40 min. Work-up afforded a solid (42 mg) which after p.l.c. (chloroform, extracted with 1% methanolic chloroform) yielded 4-methoxyacetophenone (10 mg, 32%); $\nu_{max.}$ ($CHCl_3$) 1 700 cm^{-1} (CO); δ 2.51 (s, COMe), 3.85 (s, OMe), 6.90 and 7.93 (2 d, *J* 9 and 9 Hz, ArH); *m/e* 150 ($M^{+\cdot}$), 135 ($M^{+\cdot}$ − Me), and 107 ($M^{+\cdot}$ − MeCO·).

Reaction of trans-1-*Iodo*-2-*isothiocyanatocyclohexane with Phenylethynyl-lithium.*—*trans*-1-Iodo-2-isothiocyanatocyclohexane (1) (0.20 g, 0.749 mmol) was added to a cooled (0 °C) solution of phenylethynyl-lithium [from butyl-lithium (0.6 ml, 0.89 mmol) and phenylacetylene (76 mg, 0.75 mmol)] in benzene–TMEDA (10 : 1, 5.5 ml). The mixture was stirred at 0 °C for 50 min and worked up to yield *N*-(*trans*-2-iodocyclohexyl)(phenylethynyl)thioformamide (18); $\nu_{max.}$ ($CHCl_3$) 3 380 (NH), and 2 210 cm^{-1} (C≡C); δ 0.67—2.76 (m, CH_2), 4.44 (m, CHN and CHI), 7.38 (m, ArH), and 9.0 (m, NH, exchanged with D_2O), as an unstable yellow oil which was treated immediately with potassium carbonate (*ca.* 0.30 g) in acetone (5 ml) at 20 °C for 22 h. Work-up by dilution with ether and filtration, followed by p.l.c. [hexane–chloroform (2 : 1)] gave 1-(cis-3a,4,5,6,7,7a-*hexahydrobenzothiazol*-2-*yl*)-2-*phenylacetylene* (8) (0.13 g, 68%), b.p. 140 °C at 0.35 mmHg (Found: C, 74.4; H, 6.3; N, 5.7; S, 13.1. $C_{15}H_{15}NS$ requires C, 74.6; H, 6.3; N, 5.8; S, 13.3%); $\nu_{max.}$ ($CHCl_3$) 2 217 (C≡C), and 1 560 cm^{-1} (C=N); δ 1.00—2.64 (m, CH_2), 3.85 (m, $W_{\frac{1}{2}}$ 29 Hz, CHS and CHN), and 7.42 (m, ArH), *m/e* 241 ($M^{+\cdot}$), 208 ($M^{+\cdot}$ − HS·), 128 ($M^{+\cdot}$ − $C_6H_{10}S$), and 114 ($C_6H_{10}S^{+\cdot}$); δ_C 21.5 (C-6′), 21.3 (C-5′), 28.2 (C-7′), 29.8 (C-4′), 52.3 (C-7a′), 74.7 (C-3a′), 82.9 (C-2), 93.4 (C-1), 121.0 (*ipso*-C), 128.4 (*m*-C),* 129.7 (*p*-C), 132.2 (*o*-C),* and 151.3 (C-2′).

* Assignments may be reversed.

Reaction of trans-1-*Iodo*-2-*isothiocyanatocyclohexane with Ethynyl-lithium*.[19]—(*a*) Acetylene (50 ml, 2.2 mmol) was added by gas syringe over 30 min to tetrahydrofuran (4 ml) cooled to −78 °C. Butyl-lithium (0.65 ml, 0.9 mmol) was then added dropwise and the solution was stirred for 5 min. *trans*-1-Iodo-2-isothiocyanatocyclohexane (1) (0.10 g, 0.37 mmol) dissolved in tetrahydrofuran (2 ml), was added and the mixture was stirred at −78 °C for 4 h, and then warmed to 20 °C. T.l.c. analysis showed no starting material but a very unstable compound tentatively identified as *N*-(*trans*-2-iodocyclohexyl)ethynylthioformamide (19). Work-up gave a dark brown oil (0.10 g) composed of many products (t.l.c.).

(*b*) *trans*-1-Iodo-2-isothiocyanatocyclohexane (1) (0.10 g, 0.37 mmol) was added to a benzene (5 ml)–TMEDA (0.2 ml) solution of ethynyl-lithium [from butyl-lithium (0.65 ml, 0.9 mmol) and acetylene (50 ml)] at 0 °C. Within 3 min, a yellow coloured solution was obtained which turned dark brown after 30 min. T.l.c. analysis showed no starting material, and only product(s) of decomposition.

Reaction of trans-1-*Iodo*-2-*isothiocyanatocyclohexane with Trimethylsilylethynyl-lithium*.—Purified acetylene was bubbled through a solution of ethylmagnesium bromide [from bromomethane (0.82 g, 7.49 mmol) and magnesium (0.22 g, 8.88 mmol)] in tetrahydrofuran (8 ml) maintained at 20 °C for 25 min. Chlorotrimethylsilane (0.65 g, 5.98 mmol) was added to the cooled (10 °C) solution. The mixture was stirred for 1 h, and ca. 80% of the solution was distilled directly under argon to yield trimethylsilylacetylene [22] [b.p. 53°, δ 2.60 (C≡CH)] in tetrahydrofuran. This solution was cooled to −78 °C, butyl-lithium (1.4 ml, 2.24 mmol) was added dropwise, and the solution was stirred for 15 min. *trans*-1-Iodo-2-isothiocyanatocyclohexane (1) (0.40 g, 1.49 mmol) in tetrahydrofuran (1 ml) was added, and the mixture was stirred at −78 °C for 3 h and then warmed to 20 °C for 5 min. Work-up yielded *N*-(*trans*-2-iodocyclohexyl)(trimethylsilylethynyl)thioformamide (20) (0.60 g, 100%) as an unstable yellow oil. The product (0.45 g) was stirred with potassium carbonate (*ca.* 0.40 g) in acetone (10 ml) at 20 °C for 48 h. Work-up yielded an unstable solid (0.22 g) which after several distillations (Kugelrohr) gave 2-*ethynyl*-cis-3a,4,5,6,7,7a-*hexahydrobenzothiazole* (9) (83 mg, 41%), m.p. 55—57 °C (Found: C, 65.2; H, 6.6; N, 8.7; S, 19.5. $C_9H_{11}NS$ requires C, 65.4; H, 6.7; N, 8.5; S, 19.4%); $\nu_{max.}$ 3 310 (C≡CH), 2 115 (C≡C), and 1 560 cm^{-1} (C=N); δ 1.10—2.50 (m, CH_2), 3.15 (s, C≡CH), and 3.85 (m, $W_{\frac{1}{2}}$ 29 Hz, CHS and CHN); *m/e* 165.062 4 ($M^{+\cdot}$), and 114.049 0 ($C_6H_{10}S^{+\cdot}$).

Reaction of trans-1-*Iodo*-2-*isothiocyanatocyclohexane with Butyl-lithium*.—(a) *In ether*. *trans*-1-Iodo-2-isothiocyanatocyclohexane (1) (0.20 g, 0.75 mmol) was added to a cooled (−78 °C) solution of butyl-lithium (0.56 ml, 0.89 mmol) in ether (5 ml). The mixture was stirred at −78 °C for 15 min and worked up to give cis-7-*azabicyclo*[4.2.0]*octane*-8-*thione* (24) (89 mg, 84%) which crystallized from ether–pentane as prisms, m.p. 111—114 °C (Found: C, 59.4, H, 8.1; N, 9.7; S, 23.0. $C_7H_{11}NS$ requires C, 59.5; H, 7.9; N, 9.9; S, 22.7%); $\nu_{max.}$ 3 390 cm^{-1} (NH); δ 1.68 (m, CH_2), 2.73 (m, $W_{\frac{1}{2}}$ 18.5 Hz, 1-H), 3.69 (m, $W_{\frac{1}{2}}$ 17 Hz, 6-H), and 7.90 (br s, NH, exchanged with D_2O); *m/e* 141.061 3 ($M^{+\cdot}$; *M* requires 141.061 2), 112 ($M^{+\cdot}$ − CH_2=NH), 89 (*m**, 141→112), 82.078 4 ($M^{+\cdot}$ − HNCS, requires 82.078 2), 67.054 6 [$M^{+\cdot}$ − (HNCS + Me·), requires 67.054 8], 54 [$M^{+\cdot}$ − (HNCS + C_2H_4)], 54 (*m**, 82→67), and 48 (*m**, 141→82).

Repetition of this experiment at 0 °C gave lower yields (30—50%) of the thioxo-β-lactam (24).

(b) *In tetrahydrofuran*. *trans*-1-Iodo-2-isothiocyanatocyclohexane (1) (0.20 g, 0.75 mmol) dissolved in tetrahydrofuran (5 ml) was cooled to −78 °C. Butyl-lithium (0.56 ml, 0.89 mmol) was added dropwise and the mixture was stirred at −78 °C for 30 min. T.l.c. analysis showed no starting material, and no spots developed on exposure of the plate to iodine. After 1 h the solution was warmed to 20 °C and an excess of bromine was added. The mixture was stirred for 10 min and worked up to give an oil (0.10 g), containing (^{1}H n.m.r. analysis) *trans*-1,2-dibromocyclohexane; δ 4.48 (m, $W_{\frac{1}{2}}$ 7 Hz, CHBr [42]), contaminated with products arising from bromine or hydrogen bromide attack on the solvent. Inverse addition gave the same result.

Reactions of a Regioisomeric Mixture of Iodoisothiocyanates of 5α-Androst-2-ene.—(a) *With butyl-lithium*. A mixture (7 : 1, 60 mg, 0.135 mmol) of 3α-iodo-2β-isothiocyanato-5α-androstane (25) and 2β-iodo-3α-isothiocyanato-5α-androstane (26) [25] in ether (3 ml) was cooled to −78 °C. Butyl-lithium (0.15 ml, 0.21 mmol) was added, and the mixture was stirred at −78 °C. T.l.c. analysis showed only starting material after 30 min. After a further 70 min the reaction mixture was warmed to 20 °C for 20 min and then worked-up to give 5α-androst-2-ene [43] (35 mg, 100%).

(b) *With butylmagnesium bromide*. An ether (2 ml) solution of a mixture (7 : 1, 94 mg, 0.21 mmol) of (25) and (26) was added to butylmagnesium bromide [from bromobutane (0.11 g, 0.8 mmol) and magnesium (25 mg, 1 mmol)] in ether (2 ml) and the mixture was stirred at 20 °C for 4 h. Work-up gave 5α-androst-2-ene (56 mg, 100%).

Reaction of a Regiosomeric Mixture of Iodoisothiocyanates of 4-t-Butylcyclohexene with Butyl-lithium.—Butyl-lithium (1 ml, 1.6 mmol) was added to a mixture (5 : 4, 0.43 g, 1.34 mmol) of *c*-4-iodo-*t*-3-isothiocyanato-*r*-1-t-butylcyclohexane and *t*-3-iodo-*c*-4-isothiocyanato-*r*-1-t-butylcyclohexane [2] cooled to −78 °C in ether (5 ml). The reaction mixture was stirred at −78 °C for 40 min and then worked up to give a volatile oil (0.27 g) containing 4-t-butylcyclohexene and 1-iodobutane in the ratio 1.6 : 1.

Reaction of 3α-*Iodo*-2β-*thiocyanato*-5α-*androstane with Butyl-lithium*.—Butyl-lithium (0.15 ml, 0.21 mmol) was added to a cooled (−78 °C) solution of 3α-iodo-2β-thiocyanato-5α-androstane (27) [1] (59 mg, 0.13 mmol) in ether (3 ml) and the mixture was stirred at −78 °C for 40 min. Work-up gave an oil (35 mg) composed of 5α-androst-2-ene (75%) and 2β,3β-epithio-5α-androstane (28) (25%) (correct ^{1}H n.m.r. spectrum [1]).

1-*Iodo*-3-*isothiocyanatopropane*.—1-Chloro-3-isothiocyanatopropane (1.0 g, 7.4 mmol) and sodium iodide (5.5 g, 36.9 mmol) were stirred and heated under reflux in acetone (15 ml) for 24 h. Work-up gave 1-*iodo*-3-*isothiocyanatopropane* (1.65 g, 98%) as an oil, b.p. 92 °C at 1.5 mmHg (Found: C, 21.4; H, 2.8; N, 6.4; S, 14.7. C_4H_6INS requires C, 21.2; H, 2.7; N, 6.2; S, 14.1%); $\nu_{max.}$ (neat) 2 070 cm^{-1} (NCS); δ 1.90—2.62 (m, CH_2), 3.31 (t, *J* 6.5 Hz, CH_2NCS), and 3.72 (t, *J* 6.5 Hz, CH_2I); *m/e* 227 ($M^{+\cdot}$), and 100 ($M^{+\cdot}$ − I·).

Reactions of 1-*Iodo*-3-*isothiocyanatopropane*.—(a) *With butyl-lithium*. Butyl-lithium (1.2 ml, 1.76 mmol) was added dropwise to a solution of 1-iodo-3-isothiocyanatopropane (0.37 g, 1.62 mmol) in ether (5 ml), cooled to −78 °C. The mixture was stirred at −78 °C for 15 min and the reaction was quenched and worked up to give a tautomeric mixture (*ca.* 7 : 3) of 4,5-dihydro-2-mercapto-1-pyrroline (29) and

2-thioxopyrrolidine (31) as an unstable oil (0.12 g, 75%); δ 2.27 [m, overlapping 4-H_2 of (29) and (31)], 2.96 [m, overlapping 3-H_2 of (29) and (31)], 3.75 [m, overlapping 5-H_2 of (29) and (31)], 5.00 [br s, SH of (29)], and 9.48 [br s, NH of (31)].

(b) *With butyl-lithium and iodomethane.* A solution of 1-iodo-3-isothiocyanatopropane (0.69 g, 3.05 mmol), HMPT (0.55 g, 3.05 mmol), and ether (10 ml) was cooled to −78 °C. Butyl-lithium (2.3 ml, 3.2 mmol) was added slowly and the mixture was stirred at −78 °C for 5 min. Iodomethane (2.15 g, 15 mmol) was then added, and the reaction mixture was warmed to 20 °C and stirred for 1 h. Work-up gave a malodorous oil (0.54 g) containing: (*i*) 4,5-dihydro-2-(methylthio)-1-pyrroline (30) [26] (0.29 g, 92%) (^{1}H n.m.r. analysis), b.p. 98 °C at 25 mmHg: $\nu_{max.}$ (neat) 1 580 cm^{-1} (C=N); δ 1.78—2.27 (m, 4-H_2), 2.44 (s, SMe), 2.60 (tt, $J_{3,4}$ 7 Hz, $J_{3,5}$ 1.5 Hz, 3-H_2), and 3.83 (tt, $J_{5,4}$ 7 Hz, and $J_{5,3}$ 1.5 Hz, 5-H_2); *m/e* 115 ($M^{+\cdot}$): and (ii) 1-iodobutane (0.25 g).

Reaction of 1-*Chloro*-3-*isothiocyanatopropane with Butyl-lithium.*—Butyl-lithium (1.7 ml, 2.5 mmol) was added dropwise to a cooled (−78 °C) solution of 1-chloro-3-isothiocyanatopropane (0.30 g, 2.2 mmol) in ether (5 ml) and the mixture was stirred at −78 °C for 15 min. Work-up gave *N*-(3-chloropropyl)thiopentanamide (33) (0.40 g, 93%) as an oil; δ 0.93 (t, Me), 1.50 (m, CH_2), 2.22 (m, 2′-H_2), 2.90 [poorly resolved t, $W_{\frac{1}{2}}$ 10.5 Hz, C(:S)CH_2], 3.39 (poorly resolved t, $W_{\frac{1}{2}}$ 14 Hz, CH_2Cl), 3.80 (poorly resolved t, $W_{\frac{1}{2}}$ 13.5 Hz, CH_2N), and 10.42 (br s, NH). Attempted distillation (Kugelrohr) (105 °C at 1 mmHg) of the uncyclized product (33) gave 2-butyl-5,6-dihydro-4*H*-1,3-thiazinium chloride (34) as a dark-red water-soluble solid. Treatment of the salt with saturated sodium hydrogencarbonate followed by partition with ether gave 2-*butyl*-5,6-*dihydro*-4H-1,3-*thiazine* (35) (0.27 g, 71%) as an oil, b.p. 85 °C at 0.8 mmHg (Found: C, 61.0; H, 9.7; N, 9.1; S, 19.9. $C_8H_{15}NS$ requires, 61.1; H, 9.6; N, 8.9; S, 20.4%); $\nu_{max.}$ (neat) 1 630 cm^{-1} (C=N); δ 0.96 (t, *J* 7 Hz, Me), 1.57 (m, CH_3), 2.40 (poorly resolved t, $W_{\frac{1}{2}}$ 13 Hz, 1′-H_2), 3.03 (poorly resolved t, $W_{\frac{1}{2}}$ 19 Hz, CH_2S), and 3.75 (poorly resolved t, $W_{\frac{1}{2}}$ 15 Hz, CH_2N); *m/e* 157 ($M^{+\cdot}$), and 115 ($M^{+\cdot} - C_3H_6$); δ_C 13.9 (C-4′), 19.2 (C-3′), 22.2 (C-2′), 26.4 (C-5), 29.7 (C-1′), 41.8 (C-6), 47.3 (C-4), and 161.3 (C-2).

Reactions of erythro-3-*Iodo*-4-*isothiocyanatohexane.*—(a) *With butyl-lithium.* Butyl-lithium (1.3 ml, 1.84 mmol) was added dropwise with stirring to a cooled (−78 °C) solution of *erythro*-3-iodo-4-isothiocyanato-hexane [2] (0.45 g, 1.68 mmol) in ether (5 ml). Analysis (t.l.c.) of the reaction mixture after 2 min showed one polar product [probably *cis*- and/or *trans*-3,4-diethyl-2-thioxoazetidine (36)]. Work-up after a further 8 min gave a volatile oil (73 mg) containing mostly 1-iodobutane and a complex mixture of products (t.l.c. analysis).

(b) *With butyl-lithium and iodomethane.* A solution of *erythro*-3-iodo-4-isothiocyanatohexane (0.17 g, 0.43 mmol) in ether (5 ml)–HMPT (77 mg, 0.43 mmol) was treated with butyl-lithium (0.33 ml, 0.47 mmol) at −78 °C for 2 min followed by iodomethane (0.30 g, 21.5 mmol) at 20 °C for 1 h. Work-up gave a malodorous oil (13 mg) containing unidentified products.

Reaction of trans-1-*Iodo*-2-*isothiocyanatocyclohexane with Methylmagnesium Iodide.*—Methylmagnesium iodide [from iodomethane (9.08 g, 64.7 mmol) and magnesium (1.7 g, 70.4 mmol)] in ether (25 ml) was added to a solution of *trans*-1-iodo-2-isothiocyanatocyclohexane (1) (8.65 g, 32.4 mmol) in ether (10 ml) and the mixture was stirred at 20 °C in the dark for 18 h. The reaction was quenched with aqueous ammonium chloride and extracted with ether. Removal of solvent from the dried extract yielded a malodorous oil, which, after two distillations, gave 2-methyl-*cis*-3a,4,5,6,7,7a-hexahydrobenzothiazole (10) (3.53 g, 70%), b.p. 53 °C at 0.9 mmHg (lit.,[29] 85—90 °C at 15 mmHg) (Found: C, 61.7; H, 8.8; N, 9.2. Calc. for $C_8H_{13}NS$: C, 61.9; H, 8.4; N, 9.2%); $\nu_{max.}$ 1 610 cm^{-1} (C=N); δ 1.00—2.43 (m, CH_2), 2.16 (d, *J* 2 Hz, Me), and 3.70 (m, $W_{\frac{1}{2}}$ 28 Hz, CHS and CHN); *m/e* 155 ($M^{+\cdot}$), 140 ($M^{+\cdot}$—Me·), and 114 ($M^{+\cdot}$ — MeCN); δ_C 21.5 (C-6), 23.0 (C-5), 28.4 (C-7), 30.1 (C-4), 33.2 (C-1′), 52,4 (C-7a), 74.1 (C-3a), and 167.5 (C-2).

Reaction of trans-1-*Iodo*-2-*isothiocyanatocyclohexane with Ethylmagnesium Iodide.*—Ethylmagnesium iodide [from iodoethane (0.58 g, 3.74 mmol) and magnesium (72 mg, 2.69 mmol)] in ether (10 ml) was added to a solution of *trans*-1-iodo-2-isothiocyanatocyclohexane (1) (0.20 g, 0.75 mmol) in ether (1 ml) and the mixture was stirred at 20 °C in the dark for 3 h. Work-up gave an oil (0.11 g, 88%) which after p.l.c. [hexane–chloroform (3 : 7)] afforded 2-ethyl-*cis*-3a,4,5,6,7,7a-hexahydrobenzothiazole (11) (91 mg, 72%), b.p. 100 °C at 0.37 mmHg (lit.,[29] 100—110 °C at 10 mmHg) (Found: C, 63.7; H, 9.0; N, 8.1; S, 18.7. Calc. for $C_9H_{15}NS$: C, 63.9; H, 8.9; N, 8.3; S, 18.9%); $\nu_{max.}$ (neat) 1 607 cm^{-1} (C=N); δ 0.96—2.23 (m, CH_2), 1.19 (t, *J* 7 Hz, Me), 2.46 (br q, *J* 7 Hz, CH_2Me), and 3.70 (m, $W_{\frac{1}{2}}$ 30 Hz, CHS and CHN); *m/e* 169 ($M^{+\cdot}$), 154 ($M^{+\cdot}$ — Me·), 140 ($M^{+\cdot}$ — Et·), and 114 ($C_6H_{10}S^{+\cdot}$); δ_C 12.1 (C-2′), 21.6 (C-6), 23.0 (C-5), 28.4 (C-7), 28.7 (C-1′), 30.0 (C-4), 51.5 (C-7a), 74.0 (C-3a), and 173.0 (C-2).

Reaction of trans-1-*Iodo*-2-*isothiocyanatocyclohexane with Butylmagnesium Bromide.*—Butylmagnesium bromide [from bromoethane (0.41 g, 2.99 mmol) and magnesium (91 mg, 3.7 mmol)] in ether (8 ml) was added to *trans*-1-iodo-2-isothiocyanatocyclohexane (1) (0.20 g, 0.75 mmol) and the mixture was stirred at 20 °C for 30 min. Work-up yielded an oil (0.18 g) which after p.l.c. [hexane–chloroform (7 : 3)] gave in order of decreasing R_F: (i) starting material (43 mg, 22%): (ii) cis-1-*iodo*-2-*isothiocyanatocyclohexane* (37) (17 mg, 91%), b.p. 100 °C at 0.5 mmHg (Found: C, 31.8; H, 3.8; N, 5.5. $C_7H_{10}INS$ requires C, 31.5; H, 3.8; N, 5.2%); $\nu_{max.}$ ($CHCl_3$) 2 065 cm^{-1} (NCS); δ 1.05—2.39 (m, CH_2) 3.75 (m, $W_{\frac{1}{2}}$ 11 Hz, CHNCS), and 4.36 (m, $W_{\frac{1}{2}}$ 15 Hz, CHI); *m/e* 267 ($M^{+\cdot}$), 235 ($M^{+\cdot}$ — S), 209 ($M^{+\cdot}$ — NCS·) 140 ($M^{+\cdot}$ — I), and 81 [$M^{+\cdot}$ — (HNCS + I·)]: and (iii) 2-*butyl*-cis-3a,4,5,6,7,7a-*hexahydrobenzothiazole* (12) (73 mg, 50%), b.p. 100 °C at 0.5 mmHg (Found: C, 67.1; H, 9.6; N, 6.8; S, 16.1. $C_{11}H_{19}NS$ requires C, 67.0; H, 9.7; N, 7.1; S, 16.2%); $\nu_{max.}$ (neat) 1 607 cm^{-1} (C=N); δ 0.64—2.17 (m, CH_2), 0.96 (t, *J* 7 Hz, Me), 2.44 (br t, *J* 7 Hz, CH_2Pr), and 3.70 (m, $W_{\frac{1}{2}}$ 30 Hz, CHS and CHN); *m/e* 197 ($M^{+\cdot}$), 182 ($M^{+\cdot}$ — Me·), 168 ($M^{+\cdot}$ — Et·), and 155 ($M^{+\cdot} - C_3H_6$); δ_C 13.8 (C-4′), 21.6 (C-6), 22.3 (C-3′), 23.1 (C-5), 28.5 (C-7), 29.7 (C-2′), 30.1 (C-4), 35.0 (C-1′), 51.5 (C-7a), 74.0 (C-3a), and 172.0 (C-2).

Repetition of the reaction for 3 h gave only the butyl-2-thiazoline (12) (83%, from p.l.c.).

Reaction of trans-1-*Iodo*-2-*isothiocyanatocyclohexane with Butylmagnesium Iodide.*—*trans*-1-Iodo-2-isothiocyanatocyclohexane (1) (0.20 g, 0.75 mmol) was treated with butylmagnesium iodide [from iodobutane (0.55 g, 3.0 mmol) and magnesium (91 mg, 3.7 mmol)] in ether (8 ml) and the mixture was kept at 20 °C for 43 h. Work-up gave an oi (0.17 g) which after p.l.c. [hexane–chloroform (7 : 3)

afforded: (*i*) starting material (24 mg, 12%): (*ii*) the *cis*-iodoisothiocyanate (37) (18 mg, 9%): and (*iii*) the butyl-2-thiazoline (12) (60 mg, 41%). Repetition of this reaction at 20 °C for varying times gave the following results (Table 5).

TABLE 5

	Yield (%) [a]		
Time/h	(1)	(37)	(12)
1.5	33	6	34
4.3	12	9	41
6			61

[a] After p.l.c.

Attempted Isomerization of trans-1-*Iodo*-2-*isothiocyanatocyclohexane with Magnesium Bromide.*—A stirred mixture of magnesium powder (0.10 g, 4.1 mmol) and mercury(II) bromide (0.72 g, 2 mmol) in ether (30 ml) was refluxed for 3 h. The resulting suspension was transferred by syringe and centrifuged under argon for several minutes, giving a clear supernatant liquid containing magnesium bromide. This was added to *trans*-1-iodo-2-isothiocyanatocyclohexane (1) (0.20 g, 0.75 mmol) and the mixture was stirred at 20 °C for 22 h. T.l.c. analysis showed the presence of only the *trans*-iodoisothiocyanate (1) and none of the *cis*-iodoisothiocyanate (37).

Reactions of trans-1-*Iodo*-2-*isothiocyanatocyclohexane.*—(a) *With exogenous phenyl-lithium.* Phenyl-lithium (1 ml of a 0.866 mol l^{-1} solution in ether, 0.866 mmol) [33] was added dropwise to a cooled (−78 °C) solution of *trans*-1-iodo-2-isothiocyanatocyclohexane (1) (0.20 g, 0.75 mmol) in ether (4 ml) and the mixture was stirred at −78 °C for 25 min. Work-up yielded *N*-(*trans*-2-iodocyclohexyl)thiobenzamide (21) (0.27 g, 100%) which crystallized from ethanol as yellow needles, m.p. 179—182 °C; δ 1.00—2.79 (m, CH_2), 4.22 (ddd, *J* 10, 10, and 4.5 Hz, CHI), 4.78 (m, CHN), 7.59 (m, ArH), and 8.39 (m, NH, exchanged with D_2O); *m/e* 345 ($M^{+\cdot}$), 218 ($M^{+\cdot}$ − I·), 217 ($M^{+\cdot}$ − HI), and 114 ($C_6H_{10}S^{+\cdot}$).

The thiobenzamide (21) was stirred with potassium carbonate (0.40 g) in acetone (20 ml) at 20 °C for 15 h. Work-up afforded an oil (0.17 g) which after p.l.c. [hexane–chloroform 1 : 1)] gave 2-*phenyl*-cis-3a,4,5,6,7,7a-*hexahydrobenzothiazole* (13) (0.13 g, 80%), b.p. 120 °C at 0.5 mmHg (Found: C, 72.0; H, 6.8; H, 6.8; N, 6.3; S, 14.5. $C_{13}H_{15}NS$ requires C, 71.8; H, 7.0; N, 6.4; S, 14.8%); $\nu_{max.}$ (neat) 1 600 (C=N), and 1 580 cm^{-1} (C=C); δ 0.76—2.56 (m, CH_2), 3.65 (m, $W_{\frac{1}{2}}$ 19 Hz, CHS), 4.14 (m, $W_{\frac{1}{2}}$ 11.5 Hz, CHN), and 7.55 (m, ArH); *m/e* 217 ($M^{+\cdot}$); δ_C 21.8 (C-6), 23.1 (C-5), 28.6 (C-7), 29.9 (C-4), 51.2 (C-7a), 74.9 (C-3a), 128.1 (C-2′ and C-6′),* 128.4 (C-3′ and C-5′),* and 130.9 (C-4′), 134.1 (C-1′), and 168.3 (C-2).

(b) *With phenyl-lithium generated* in situ. Butyl-lithium (0.6 ml, 0.89 mmol) was added dropwise to a cooled (0 °C) solution of iodobenzene (0.15 g, 0.75 mmol) in ether (5 ml). This solution was stirred for 30 min, *trans*-1-iodo-2-isothiocyanatocyclohexane (1) (0.20 g, 0.75 mmol) was added, and the stirring was continued at 0 °C for 72 min. Work-up gave a yellow solid (0.23 g) which after p.l.c. afforded: (*i*) starting material (56 mg, 28%): (*ii*) the phenyl-2-thiazoline (13) (24 mg, 15%): and (*iii*) the thiobenzamide (21) (0.11 g, 43%) which cyclized to the phenyl-2-thiazoline (13) (55 mg, 34%) upon further multiple p.l.c.

(c) *With phenylmagnesium bromide.* A mixture of *trans*-1-iodo-2-isothiocyanatocyclohexane (1) (0.20 g, 0.75 mmol) and phenylmagnesium bromide [from bromobenzene (0.46 g, 2.96 mmol) and magnesium (72 mg, 2.96 mmol)] in ether (10 ml) was stirred at 20 °C for 1.5 h. Work-up gave a yellow solid (0.49 g) which after p.l.c. gave: (*i*) biphenyl (32 mg); δ 7.20—7.67 (m, 10, ArH); *m/e* 154 ($M^{+\cdot}$): (*ii*) several unidentified compounds: and (*iii*) the thiobenzamide (21) (0.13 g) which after further multiple p.l.c. gave the phenyl-2-thiazoline (13) (50 mg, 31%).

*Assignments may be reversed.

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