A New Stereospecific Synthesis of 5,6-Dihydro-4*H*-1,3-thiazines by Polar 1,4-Cycloaddition of Thioamidoalkyl Ions to Olefins. Configurational and Conformational Nuclear Magnetic Resonance Analysis of the Products

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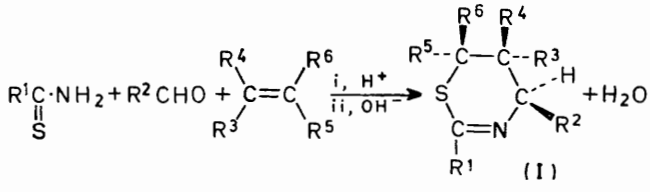
5,6-Dihydro-4*H*-1,3-thiazines with a wide variety of substituents have been obtained by a one-step condensation of a thioamide, an aldehyde, and an olefin. The reaction proceeds through polar 1,4-cycloaddition of the thioamidoalkyl ion (generated *in situ* from the aldehyde and the thioamide) to the olefin and is stereospecific and regiospecific. Conformational and configurational n.m.r. analysis has been carried out on the diastereoisomeric pairs of 5,6-dihydro-4*H*-1,3-thiazines so obtained.

THE known methods of synthesis of 5,6-dihydro-4*H*-1,3-thiazines suffer from the disadvantages of requiring starting materials which are not readily available and/or of low yields. Results obtained during the study of thioamidoalkylation of olefins [1] prompt us to report a new method of synthesis from a thioamide, an aldehyde, and an olefin (Scheme) (substituents



(I)

are shown in Table 1). The reaction is stereospecific and regiospecific [2] and is of good synthetic applicability for a wide range of substituents.

Conformational and configurational n.m.r. analysis of the products helped us elucidate the stereochemical course of reaction, and also provided new information on the configuration and conformation of 5,6-dihydro-4*H*-1,3-thiazine derivatives.

RESULTS AND DISCUSSION

Two different experimental procedures gave satisfactory results. *Method A* consists of adding at room temperature a solution of aldehyde, thioamide, and a strong protic acid (100% H_2SO_4 or HCl gas) in acetic acid to a solution of olefin in acetic acid. After several hours, alkaline hydrolysis gives the 5,6-dihydro-4*H*-1,3-thiazines.

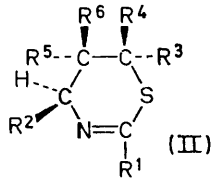
Method B, the alternative procedure, consists of adding boron trifluoride–ether complex at room temperature to a solution or suspension of aldehyde, thioamide, and olefin in chloroform; in many cases this method yields thiazines of higher purity than obtained in method A.

No effort was made to optimise the yields reported in Table 1.

The adducts (1)—(4) obtained from propylene, but-1-ene, dodec-1-ene, and styrene, respectively (Table 1) were completely free from type (II) isomers as shown by the n.m.r. evidence given later; the regiospecificity [2] of the reaction is thus established.

[1] C. Giordano, *Synthesis*, 1972, 34.
[2] A. Hassner, *J. Org. Chem.*, 1968, **33**, 2684.

Configurational analysis of the diastereoisomeric pairs obtained from *cis*- and *trans*-butene, respectively



(II)

[compounds (5)—(8), Tables 1 and 2] indicates the stereochemical course of the reaction. In fact *trans*-butene (methods A and B, Table 1) gives only the 5,6-dihydro-4*H*-1,3-thiazines with *trans* methyl groups at C-5 and C-6 [compounds (5), (7), and (8); Tables 1 and 2], and *cis*-butene (method B) gives only the *cis*-5,6-dimethyl compound (6) (Tables 1 and 2). When the thiazine (6) is prepared by method A, the isomer (5) (16% yield) is also formed, *cis*-butene being isomerized to *trans*-butene.* *trans*-Butene reacts about three times faster than *cis*-butene (method A).

These observations suggest that the reaction is *cis*-stereospecific and that the same mechanism applies for both methods (A and B). Further support of this conclusion derives from the observed parallel values of the diastereoisomeric ratio of the thiazines (5)—(7) obtained by methods A and B.

On the basis of the *cis*-stereospecificity and the regiospecificity of the reaction and of the available knowledge on amido- and thioamido-methylation of olefins,[1,3] we deduce that in both methods A and B the reaction proceeds through a *cis* electrophilic cycloaddition of the thioamidoalkyl ion (c), present probably as an ion-pair, to the olefin. Production of the intermediate (d) involves the concerted formation of two new σ-bonds without necessarily implying the same kinetics of bond formation.

It is not possible on the basis of the available data to offer an interpretation of the stereoselectivity observed

TABLE 1 [a-c]

5,6-Dihydro-4*H*-1,3-thiazines obtained by thioamidoalkylation of olefins

Compound	Olefin	R^1	R^2	R^3	R^4	R^5	R^6	Yield (%) (a + b)	a/b	Method
(1) a	Propene	*p*-MeC_6H_4	Ph	H-5	H-5′	H-6	Me	52	1	A
(1) b						Me	H-6			
(2) a	But-1-ene	*p*-MeC_6H_4	Ph	H-5	H-5′	H-6	Et	44	1	A
(2) b						Et	H-6			
(3) a	Dodec-1-ene	*p*-MeC_6H_4	Ph	H-5	H-5′	H-6	$[CH_2]_9Me$	44	1·5	A
(3) b						$[CH_2]_9Me$	H-6			
(4)	Styrene	Ph	Ph	H-5	H-5′	H-6	Ph	52	*d*	B
(5) a	*trans*-But-2-ene	*p*-MeC_6H_4	Ph	H-5	Me (a)	Me	H-6	75	4·4	A [e]
(5) b				Me (a)	H-5	H-6	Me (b)	75	5·2	A [f]
								53	4	A
								85	4·3	B
(6) a	*cis*-But-2-ene	*p*-MeC_6H_4	Ph	H-5	Me (a)	H-6	Me (b)	33 [g]	1·3	A
(6) b				Me (a)	H-5	Me (b)	H-6	77	1	B
(7) a	*trans*-But-2-ene	Me	Ph	H-5	Me (a)	Me (b)	H-6	48	7	A
(7) b				Me (a)	H-5	H-6	Me (b)	90	6·9	B
(8)	*trans*-But-2-ene	Ph	Me	H-5	Me (a)	Me (b)	H-6	83	*d*	B

[a] Method A: Acetic acid (300 ml), thioamide (0·1 mol), aldehyde (0·1 mol), olefin (0·1 mol), 100% H_2SO_4 (0·24 mol), *T* 15 °C, time 22 h. Method B: Chloroform (50 ml), thioamide (0·1 mol), aldehyde (0·1 mol), olefin (0·1 mol), BF_3,Et_2O (0·2 mol), *T* 15 °C, time 22 h. [b] In the i.r. spectra the –C=N stretching for all compounds gives a strong band at 6·2—6·3 μm, with the exception of (7) (6·1—6·2 μm). [c] Analytical data are reported in Supplementary Publication No. SUP 20640 (2 pp.) [See Notice to Authors No. 7 in *J. Chem. Soc.* (*A*), 1970, Issue No. 20]. [d] Only one isomer present; n.m.r. analysis did not reveal the other. [e] Temp. 35 °C. [f] Double concentration for all reagents with respect to acetic acid. [g] The *trans*-isomer (5) (a + b) is also obtained (16% yield).

TABLE 2

N.m.r. data

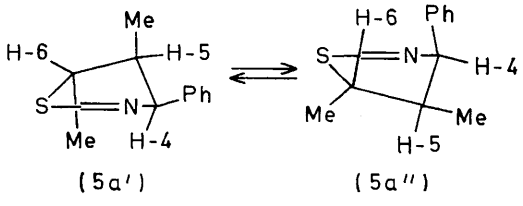
Compd.	δ($CDCl_3$)	*J*/Hz
(1a)	H-4 4·61	$J_{4,5} = 3·4$, $J_{4,5'} = 11·5$
(1b)	H-4 5·18	$J_{4,5} = 4·7$, $J_{4,5'} = 4·7$
(4)	H-4 4·81, H-5 2·43, H-5 1·84, H-6 4·67	$J_{4,5} = 3·3$, $J_{4,5'} = 11·4$, $J_{5,6} = 3·3$, $J_{5',6} = 12·4$, $J_{5,5'} = 13·7$
(5a)	H-4 4·76, H-5 1·9, H-6 3·09, Me(a) 0·70, Me(b) 1·37	$J_{4,5} = 3·4$, $J_{5,6} = 5·0$, $J_{5,Me(a)} = 6·8$, $J_{6,Me(b)} = 6·8$
(5b)	H-4 4·25, H-6 3·20, Me(a) 0·83, Me(b) 1·34	$J_{4,5} = 9·5$, $J_{5,6} = 10·0$, $J_{5,Me(a)} = 6·9$, $J_{6,Me(b)} = 6·9$
(6a)	H-4 4·70, H-5 2·0, H-6 3·80, Me(a) 0·50, Me(b) 1·15	$J_{4,5} = 2·9$, $J_{5,6} = 3·5$, $J_{5,Me(a)} = 6·8$, $J_{6,Me(b)} = 7·0$
(6b)	H-4 5·10, H-5 2·0, H-6 3·15, Me(a) 0·93, Me(b) 1·06	$J_{4,5} = 3·8$, $J_{5,6} = 3·2$, $J_{5,Me(a)} = 6·8$, $J_{6,Me(b)} = 6·9$
(7a)	H-4 4·55, H-5 1·77, H-6 2·97, Me(a) 0·68, Me(b) 1·35	$J_{4,5} = 3·3$, $J_{5,6} = 5·4$, $J_{5,Me(a)} = 6·9$, $J_{6,Me(b)} = 6·9$
(7b)	H-4 3·96	$J_{4,5} = 9·6$
(8)	H-4 3·81, H-5 1·51, H-6 3·1, Me 1·33, Me(a) 0·91, Me(b) 1·25	$J_{4,5} = 3·1$, $J_{5,6} = 6·6$, $J_{4,Me} = 6·8$, $J_{5,Me(a)} = 6·6$, $J_{6,Me(b)} = 6·6$

* Under the conditions of reaction and work-up there is no isomerization of the reported thiazines.

[3] R. R. Schmidt, *Chem. Ber.*, 1970, **103**, 3242.

in the reactions under discussion [thiazines (5), (7), and (8)]; this is a normal problem in αα′-diastereogenic [4] reactions.

N.m.r. Analysis.[5]—The spectra for compound (5a) have been measured for solutions in $CDCl_3$, $CD_3{\cdot}CO_2D$, and CS_2. The value of $J_{5,6}$ in $CDCl_3$ (5·0 Hz) does not make possible a clear attribution of the relative position of H-5 and H-6; on the other hand $J_{5,6}$ in $CD_3{\cdot}CO_2D$ (9·4 Hz) is in agreement with a *trans* relationship.* The difference between these values of $J_{5,6}$ could well be due to the existence of a conformational equilibrium between the two conformers (5a′) and (5a″). The

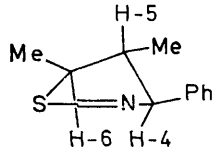


observed values could be explained in terms of a more significant role of form (5a′) (with diequatorial H-5 and H-6) in $CDCl_3$ solution than in $CD_3{\cdot}CO_2D$ solution, where form (5a″) (with diaxial H-5 and H-6) might predominate.†

* Dreiding models of the 5,6-dihydro-4H-1,3-thiazines show that the torsion angles between C(4)–C(5), and C(5)–C(6) are *ca.* 60 or 180°; on account of this, to show the position of the substituents relative to one another or relative to the ring, we have adopted the same nomenclature as has been used for cyclohexane and derivatives. Specifically, *cis* and *trans* refer to the configuration of substituents on C-5 and C-6, and *syn* and *anti* to substituents on C-4 and C-5.

To characterize the equilibrium we have investigated the influence of solvents and temperature. On passing from room temperature to −90 °C in an apolar solvent such as CS_2 a clear broadening of the signals in comparison to the Me_4Si reference peak (which remained virtually unchanged) was noticed. This may indicate the presence of a conformational equilibrium. The coupling constant $J_{4,5}$ behaves differently from $J_{5,6}$ in that it is practically the same in $CDCl_3$ (3·3 Hz) and in $CD_3{\cdot}CO_2D$ (4·1 Hz). If the foregoing considerations are correct, this is compatible only with a *syn*-relationship for H-4 and H-5.

In compound (5b), whose spectra in $CD_3{\cdot}CO_2D$ (as well as in benzene, dimethyl sulphoxide and pyridine) show similar features, $J_{5,6}$ (10 Hz) and $J_{4,5}$ (9·7 Hz) are both typical of axial–axial interaction. This means that the molecule has a *trans,anti*-configuration and a conformation such that all the substituents lie in



equatorial positions. The other conformer is less probable as the bulky substituents on C-4 and C-6 would then be present in diaxal positions with high steric compression.

In $CF_3{\cdot}CO_2H$, the coupling constants for both compounds (5a) and (5b) show that in this solvent the conformational equilibrium lies in a position similar to that in $CD_3{\cdot}CO_2D$. Moreover the consequences of protonation of the nitrogen atom support the previous attribution of conformation. In fact, $J_{NH,4}$ in compound (5a) is 4 Hz and in (5b) is less than 1 Hz; if the Karplus equation holds in this case, the values are in agreement with an equatorial position of H-4 in compound (5a) and an axial position in compound (5b).

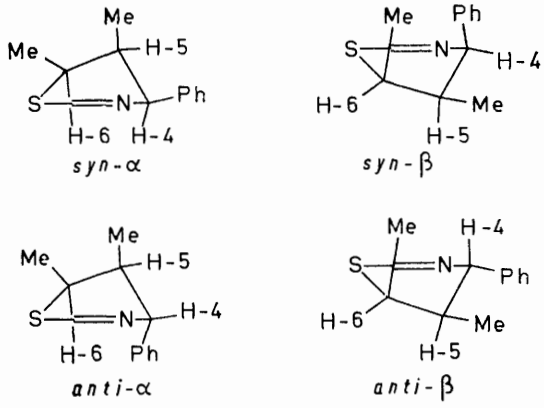
In the pair of diastereoisomers (6a and b) the values of $J_{5,6}$ indicate a *cis*-configuration [(6a) 3·5; (6b) 3·2 Hz]. However it is not possible to decide between *syn*- and *anti*-configurations (for H-4 and H-5) simply on the basis of $J_{4,5}$, this being of similar magnitude in the two compounds [(6a) 2·9; (6b) 3·8 Hz].

Each of the two diastereoisomers can exist in two conformations (α and β). The *anti*-β-conformation is improbable, being incompatible with the low observed values of $J_{4,5}$, and the *syn*-β-conformation is also unlikely because of diaxial interaction between the phenyl and 6-methyl groups. In other words, the *syn*-α- and *anti*-α-conformers are by far the most probable in $CHCl_3$ solution. Data obtained from $CF_3{\cdot}CO_2H$ solutions are consistent with this deduction, $J_{4,5}$ and $J_{5,6}$ being of similar magnitude to those for $CDCl_3$ solutions.

† In the diagrams the thiazines are projected on to the plane perpendicular to the S–C=N–C plane (Dreiding models).

[4] H. Schlosser, *Bull. Soc. chim. France*, 1971, 453.
[5] H. Booth, *Progr. N.M.R. Spectroscopy*, 1969, **5**, ch. 3.

Moreover, in analogy to our conclusions for compounds (5a and b), $J_{NH,4}$ in $CF_3{\cdot}CO_2H$ solution is 5·7 Hz for compound (6b) and 1 Hz for compound (6a). This indicates that H-4 is in an equatorial position in (6b)



and in an axial position in (6a). In other words the *syn*-α-conformer for compound (6a) is the only one which complies with all the n.m.r. data for different solvents. Analogously, only the *anti*-α-conformer appears compatible with the spectral data for compound (6b).

The coupling constants reported in Table 2 indicate that the substituents on C(4)–C(5) and C(5)–C(6) are staggered (Newman projection). Consequently we conclude that steric effects prevent significant contributions by eclipsed forms to the conformational equilibrium.

Configurations have been attributed to the other compounds by use of the same criteria as for compounds (5a), (5b), (6a), and (6b) (see Table 1).

EXPERIMENTAL

I.r. spectra were recorded with a Perkin-Elmer 137 spectrophotometer, and n.m.r. spectra with a JEOL C-60 HL instrument, with Me_4Si as internal standard. M.p.s were determined with a Kofler hot-stage apparatus. Butenes were analysed on a column (8 m) of dimethylsulpholane (20%) on Chromosorb W. Chloroform, used as solvent in method B, was free of ethyl alcohol.

5,6-Dihydro-4H-1,3-thiazines.—Methods A and B are illustrated by the preparation of *cis*-5,6-dihydro-5,6-dimethyl-2-(*p*-tolyl)-4-phenyl-4*H*-1,3-thiazine (6). *Method A.* A solution of 4-methyl(thiobenzamide) (22·68 g, 0·15 mol), benzaldehyde (15·9 g, 0·15 mol), and 100% sulphuric acid (35·3 g, 0·36 mol) in acetic acid (150 ml) was added to a solution of *cis*-butene (8·4 g, 0·15 mol) in acetic acid (300 ml) during 10 min with the temperature kept at 15 °C. A sample of the mixture taken after 3 h and treated with an excess of sodium hydroxide evolved a gas containing *ca.* 13% of *trans*-butene and 87% of *cis*-butene.

After 22 h the reaction mixture was poured on ice, made alkaline with aqueous 40% sodium hydroxide (at *ca.* 10°), and extracted with ether (3 × 100 ml). The extract was washed with 2N-hydrochloric acid (4 × 50 ml). The acidic aqueous extract was made alkaline with aqueous 40% sodium hydroxide at *ca.* 10° and extracted with ether (3 × 100 ml). This extract was evaporated to give compounds [(5) + (6)] (21·7 g) [n.m.r. analysis indicated the presence of 16% of (5) and 33% of (6)].

Treatment of the thiazine mixture with acetonitrile (*ca.* 30 ml) at room temperature followed by filtration gave the *isomer* (6a) as a crystalline powder, m.p. 102—103 °C.

Method B. Boron trifluoride–ether complex (24·5 ml; *d* 1·13; 0·2 mol) was added dropwise during 15 min to a mixture of 4-methyl(thiobenzamide) (15·1 g, 0·1 mol), benzaldehyde (10·6 g, 0·1 mol), and *cis*-butene (5·6 g, 0·1 mol) in chloroform (50 ml) at *ca.* 5 °C. The resulting solution was kept for 1 h at 5 °C and for 20 h at 15 °C, poured on ice, made alkaline with aqueous 40% sodium hydroxide (at *ca.* 10 °C), and extracted with chloroform (3 × 100 ml). The extract was dried (Na_2CO_3) and evaporated to give an oil which was dissolved in ether. The ethereal solution was washed with 2N-hydrochloric acid (3 × 50 ml). The acid aqueous extracts were made alkaline with aqueous 40% sodium hydroxide at 10 °C and extracted with ether (3 × 100 ml). The ethereal extract was evaporated to give compound (6) (22·6 g, 77%) (diastereoisomeric ratio a : b = 1 : 1).

Diastereoisomeric trans-*5,6-Dihydro-5,6-dimethyl-2-(p-tolyl)-4-phenyl-4H-1,3-thiazines* (5a *and* b); *Separation of the Isomer* (5a).—*Method A.**—An acetic acid solution (70 ml) of 4-methyl(thiobenzamide) (15·1 g, 0·1 mol), benzaldehyde (10·6 g, 0·1 mol), and 100% sulphuric acid (23·5 g, 0·24 mol) was added dropwise, with stirring, during 5 min, to a solution of *cis*-butene (5·6 g, 0·1 mol) in acetic acid (80 ml) at 15 °C. The solution was then kept at this temperature for 22 h. The mixture was poured on crushed ice, made alkaline with aqueous 40% sodium hydroxide (at *ca.* 10°), and extracted with ether (3 × 100 ml). The extract was washed with 2N-hydrochloric acid (4 × 50 ml). The acid aqueous extract was made alkaline with aqueous 40% sodium hydroxide at *ca.* 10° and extracted with ether (3 × 100 ml). This extract was evaporated to give compound (5) (23·1 g, 78%) [from n.m.r. data (5a) : (5b) = 5·2 : 1].

Treatment of the crude product with acetonitrile (*ca.* 50 ml) at room temperature followed by filtration gave a crystalline powder (14 g), m.p. 73—76 °C [from n.m.r. data (5a : (5b) = 10 : 1].

Determination of the Relative Rates of Reaction of cis- *and* trans-*Butene.*—*cis-* and *trans*-Butene were treated separately under the conditions used in the preparation of compound (6) (method A). The reaction was stopped after 3 h and the thiazines were isolated as previously described. *cis*-Butene gave a yield of 6% of (6), and *trans*-butene 22% of (5).

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* This reaction was carried out with concentrations double the normal ones employed for method A (see note to Table 1).