# N-Quaternary Compounds. Part XXXIV. ${ }^{1}$ Addition of Pyridine-2-thiones to $\alpha$-Bromo- $\alpha \beta$-unsaturated Cyclic Ketones 

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Adduct formation between pyridine-2-thiones and cyclic $\alpha$-bromo- $\alpha \beta$-unsaturated ketones is followed by rapid cyclisation to cis-dihydrothiazolo[3.2-a]pyridinium derivatives. It is suggested that the adduct is formed by cis-addition.

Michael addition of pyridine- 2 -thiones to $\alpha$-bromo- $\alpha \beta$ unsaturated acids is followed by cyclisation to dihydro-thiazolo[3,2-a]pyridinium-3-carboxylates. ${ }^{2}$ The 2 - and 3 -substituents in the cyclised products were found to have the trans-configuration, irrespective of the initial stereochemistry in the $\beta$-substituted $\alpha$-bromo- $\alpha \beta$-unsaturated acid. ${ }^{2-4}$ It was therefore of interest to prepare some cis-2,3-dihydrothiazolo[3,2-a]pyridinium derivatives, to gain further information on the reaction sequence and on the magnitude of the vicinal coupling constant in the products with cis stereochemistry. Derivatives with a small ring ortho-fused to the 2- and 3 -positions of the dihydrothiazole system will, for steric reasons, have the cis-configuration. 2-Bromoindenone, prepared from 2,3-dibromoindanone ${ }^{5}$ by elimination of hydrogen bromide in the presence of diethylamine in the cold, was treated with 6-methyl-pyridine-2-thione (Scheme 1). Adduct formation and cyclisation [to (4)] occurred readily in cold ethyl acetate solution. In accordance with evidence ${ }^{2}$ for $c i s$-addition to the double bond in related systems, it is suggested that the intermediate Michael adduct is formed by cisaddition. The cis-adduct (3) has the right stereochemistry for bromine displacement by the ring nitrogen atom; the trans-adduct would have to undergo epimerisation before cyclisation.

(1b)


Scheme 1

The vicinal coupling constant was 8.0 Hz for the ringjunction protons in the product (4) (cf. $0-1 \mathrm{~Hz}$ for

[^0]trans derivatives ${ }^{2}$ ). The torsion angle between the two $\mathrm{C}-\mathrm{H}$ bonds in structure (4) is expected to be small because of the stiffness of the indanone system; such a situation agrees well with the observed $J$ value. ${ }^{6,7}$


Models of derivatives with a six-membered ring ortho-fused at the dihydrothiazole 2 - and 3 -positions indicated that both cis- and trans-configurations are possible. Such compounds were formed from 2 -bromo-cyclohex-2-enone and pyridine-2-thiones in cold chloroform solution. The non-phenolic thiones ( $\mathrm{la}, \mathrm{b}$, and d) reacted faster than the 3 -phenolic analogue (lc). Similar differences in reactivity towards $\alpha$-bromo- $\alpha \beta$-unsaturated acids have been explained in terms of intramolecular hydrogen bonding, where the sulphur atom acts as acceptor for the phenolic hydrogen atom. ${ }^{2}$ The intermediate Michael adduct (6) was not seen in these reactions. Adduct formation is therefore the ratedetermining step in the overall sequence. Chromatography and n.m.r. spectroscopy showed the product to consist of only one configurational isomer. The n.m.r. spectra showed the dihydrothiazole 2 -proton signal at $\tau\left(\mathrm{CF}_{3} \cdot \mathrm{CO}_{2} \mathrm{H}\right) 4 \cdot 6-4 \cdot 7$ and that of the 3 -proton at $\tau 3.6-3.8(J 7.0-7.5 \mathrm{~Hz})$. No deuterium was incorporated at the 3 -position in (7a) after 1 day in $\mathrm{CF}_{3} \cdot \mathrm{CO}_{2} \mathrm{D}$ solution; however in deuterium oxide at room temperature the 3 -proton was fully exchanged

[^1]during this time. The n.m.r. spectrum of an aqueous solution of (7a) showed no change after 1 day. Since deuteriation occurs under these conditions, and since the intermediate carbanion must be reprotonated to give the thermodynamically more stable product, the product isolated must have the thermodynamically more stable configuration. Both the cis- and the trans-isomers apparently can assume cyclohexane conformations which fit the observed coupling constant for the dihydrothiazole ring protons. Application of the suggested cis-addition mechanism (Scheme 1), however, leads to the assignment of the cis-configuration to the product, since it has been established that cyclisation in related compounds proceeds with configurational inversion (Scheme 2). ${ }^{8}$ The question of relative stereochemistry was unambiguously solved for compound (7d) by $X$-ray analysis, and the cis-configuration was confirmed. ${ }^{9}$ All the members of the series must have the same configuration since the coupling constants for the vicinal dihydrothiazole protons are almost the same.

The $X$-ray analysis ${ }^{9}$ shows that the five-membered ring has the envelope conformation with C- $20.60 \AA$ out of the plane of the other four dihydrothiazole ring atoms. A similar envelope conformation has been seen in a trans-2,3-dicarboxy-analogue (C-2 $0.57 \AA$ out of plane ${ }^{4}$ ). The cyclohexanone ring has the chair conformation. The 2,3 -torsion angle ( $41 \pm 3^{\circ}$ ) is larger than expected 6,7 on the basis of the coupling constant $(7.0 \mathrm{~Hz})$ in $\mathrm{CF}_{3} \cdot \mathrm{CO}_{2} \mathrm{H}$ solution.

## EXPERIMENTAL

N.m.r. spectra were recorded for solutions in trifluoroacetic acid with a Varian A-60A instrument and u.v. spectra were obtained with a Perkin-Elmer 137-UV instrument.
4b,10a-Dihydro-9-methyl-11-oxoindeno $\left[2^{\prime}, 1^{\prime}-4,5\right]$ thiazolo-[3,2-a]pyridinium Bromide (4).-2,3-Dibromoindanone ${ }^{5}$ $(1.16 \mathrm{~g}, 0.004 \mathrm{~mol})$ was dissolved in ethyl acetate ( 30 ml ) and diethylamine ( $0.29 \mathrm{~g}, 0.004 \mathrm{~mol}$ ) was added. An immediate exothermic reaction ensued with precipitation of diethylamine hydrobromide. The precipitate was filtered off after 10 min under anhydrous conditions. The filtrate containing the generated 2 -bromoindenone was then

[^2]added dropwise to a solution of 6 -methylpyridine-2-thione $(0.50 \mathrm{~g}, 0.004 \mathrm{~mol})$ in ethyl acetate $(40 \mathrm{ml})$. The precipitate was collected after 1 day in the cold ( $0.60 \mathrm{~g}, 45 \%$ ) and recrystallised from ethanol; m.p. $246-248{ }^{\circ} \mathrm{C}$ (decomp.) (Found: C, $53.7 ; \mathrm{H}, 3.8 ; \mathrm{N}, 4.05 . \mathrm{C}_{15} \mathrm{H}_{12} \mathrm{BrNOS}$ requires C, $53.9 ; \mathrm{H}, 3 \cdot 6 ; \mathrm{N}, 4 \cdot 2 \%$ ), $\tau 3.47$ ( $4 \mathrm{~b}-\mathrm{H}$ ), $3 \cdot 18$ ( $10 \mathrm{a}-\mathrm{H}$ ) $(J 8.0 \mathrm{~Hz}), 6.80(\mathrm{Me})$, and $1.6-2.4$ (aromatic), $\lambda_{\max }(0 \cdot 1 \mathrm{~N}-$ $\mathrm{HCl}) 330(\log \varepsilon 3 \cdot 50)$ and $245 \mathrm{sh} \mathrm{nm}(4 \cdot 0)$.
5a,6,7,8,9,9a-Hexahydro-9-oxopyrido[2,1-b]benzothiazoliun Bromide and Derivatives (7).-A solution of 2-bromocyclo-hex-2-enone ${ }^{10}$ ( $0.83 \mathrm{~g}, 0.0047 \mathrm{~mol}$ ) in chloroform ( 30 ml ) was added dropwise to a chloroform solution ( 50 ml ) of a pyridine-2-thione (1) $(0.005 \mathrm{~mol})$. The chloroform was distilled off when the reaction was complete [ 1 day for ( $7 \mathrm{a}, \mathrm{b}$, and d ), 3 days for ( 7 c )] and the residual oil was dissolved in ethanol-acetone, from which the desired substance slowly crystallised out. Yellowish-white crystals were obtained on recrystallisation from acetone to which had been added a drop of hydrobromic acid.

Compound (7a) ( $71 \%$ ) had m.p. $155-156{ }^{\circ} \mathrm{C}$ (decomp.) (Found: $\mathrm{C}, \mathbf{4 5 \cdot 9} ; \mathrm{H}, 4 \cdot 45 ; \mathrm{N}, 5 \cdot 1 . \quad \mathrm{C}_{11} \mathrm{H}_{12} \mathrm{BrNOS}$ requires C, $46.15 ; \mathrm{H}, 4.2 ; \mathrm{N}, 4.9 \%), \tau 4.6$ ( $5 \mathrm{a}-\mathrm{H}), 3.73$ ( $9 \mathrm{a}-\mathrm{H})$ ( $J 7.5 \mathrm{~Hz}$ ), $1.2-2.4$ (pyridine H ), and $7 \cdot 1-8.0$ (cyclohexane H ), $\lambda_{\text {max. }}(0 \cdot 1 \mathrm{~N}-\mathrm{HCl}) 330(\log \varepsilon 3.74), 240(3.92)$, and $213 \mathrm{~nm}(3 \cdot 85)$.

The 1-methyl derivative (7b) ( $65 \%$ ) had m.p. 248$249{ }^{\circ} \mathrm{C}$ (decomp.) (Found: C, 47.75 ; H, 4.55 ; N, 4.7 . $\mathrm{C}_{12} \mathrm{H}_{14} \mathrm{BrNOS}$ requires C, $48.0 ; \mathrm{H}, 4 \cdot 7 ; \mathrm{N}, 4.65 \%$ ), $\tau 4.6$ ( $5 \mathrm{a}-\mathrm{H}$ ), $3.62(9 \mathrm{a}-\mathrm{H})(J 7.0 \mathrm{~Hz}), 7 \cdot 22(\mathrm{Me}), 1.6-2.5($ pyridine H ), and $6.9-7.8$ (cyclohexane H ), $\lambda_{\text {max. }}(0 \cdot 1 \mathrm{~N}-\mathrm{HCl}) 331$ ( $\log \varepsilon 3 \cdot 81$ ), $240(3 \cdot 88)$, and $211 \mathrm{~nm}(3 \cdot 88)$.

The 4-hydroxy-1-methyl derivative (7c) ( $78 \%$ ) had m.p. $243-244{ }^{\circ} \mathrm{C}$ (decomp.) (Found: C, $45.35 ; \mathrm{H}, 4.55$; N, 4.5. $\quad \mathrm{C}_{12} \mathrm{H}_{14} \mathrm{BrNO}_{2} \mathrm{~S}$ requires $\mathrm{C}, 45 \cdot 6 ; \mathrm{H}, 4 \cdot 45 ; \mathrm{N}, 4 \cdot 45 \%$ ), $\tau 4.7(5 \mathrm{a}-\mathrm{H}), 3.70(9 \mathrm{a}-\mathrm{H})(J 7 \cdot 0 \mathrm{~Hz}), 7.35(\mathrm{Me}), 2 \cdot 60(2-\mathrm{H})$, $2 \cdot 15(3-\mathrm{H})$, and $7 \cdot 0-7 \cdot 8$ (cyclohexane H ), $\lambda_{\text {max. }}(0 \cdot 1 \mathrm{~N}-\mathrm{HCl})$ 348 ( $\log \varepsilon 4 \cdot 00$ ), $241(3 \cdot 92)$, and $216 \mathrm{~nm}(4 \cdot 11)$.

The 4-ethoxy-1-methyl derivative (7d) ( $80 \%$ ) had m.p. $198-199{ }^{\circ} \mathrm{C}$ (decomp.) (Found: C, $48.6 ; \mathrm{H}, 5 \cdot 3 ; \mathrm{N}, 4.1$. $\mathrm{C}_{14} \mathrm{H}_{18} \mathrm{BrNO}_{2} \mathrm{~S}$ requires $\mathrm{C}, 48.85 ; \mathrm{H}, 5.3 ; \mathrm{N}, 4.05 \%$ ), $\tau 4.7(5 \mathrm{a}-\mathrm{H}), 3.80(9 \mathrm{a}-\mathrm{H})(J 7.0 \mathrm{~Hz}), 7.33(\mathrm{Me}), 2.53(2-\mathrm{H})$, $2.28(3-\mathrm{H}), 6.9-7.9$ (cyclohexane H ), and 5.63 and 8.45 (OEt), $\lambda_{\text {max. }}(0 \cdot 1 \mathrm{~N}-\mathrm{HCl}) 349$ ( $\log \varepsilon 3.95$ ), 243 (3.91), and $218 \mathrm{~nm}(3 \cdot 94)$.
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