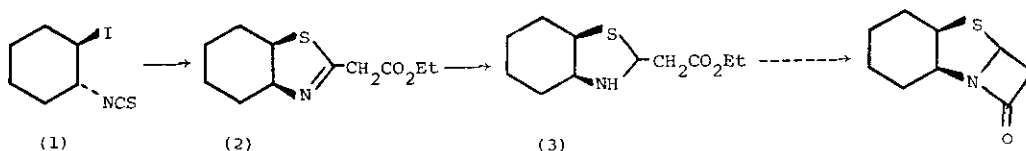


A SYNTHESIS OF ETHYL 2-(8-CIS-7-THIA-9-AZABICYCLO[4.3.0]NONANYL)ACETATE

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Abstract — A diastereomeric mixture of ethyl 2-(8-cis-7-thia-9-azabicyclo[4.3.0]nonanyl)acetate (3), a useful model for cepham synthesis, is readily prepared from 2-methyl-2-thiazoline via the tautomeric mixture of ethyl 2-(2-cis-3a,4,5,6,7,7a,-hexahydrobenzothiazolyl)acetate (2) and 8-(ethoxycarbonylmethylene)-cis-7-thia-9-azabicyclo[4.3.0]nonane (6).

Recently we reported the formation of 2-alkyl-2-thiazolines in high yield by the reaction of vic-iodoisothiocyanates with carbon nucleophiles.¹ We now report a utilization of the method to form the diastereomeric ethyl thia-azabicyclononanyl acetate (3), which can be envisaged (Scheme) as a potential precursor to a cepham-related nucleus.



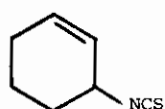
Scheme

An obvious route to the compound (2) involves the addition of the carbanion derived from ethyl acetate, to the vic-iodoisothiocyanate (1).² However, treatment of (1) with lithioethyl acetate, generated from ethyl acetate with lithium hexamethyldisilylamide³ or with the alternative non-nucleophilic base lithium 2,2,6,6-tetramethylpiperidide at -78 °C (at higher temperature the carbanion undergoes self-condensation³) gave no reaction. Likewise, the attempted addition of ethoxyethyne⁴ (a synthon for ethyl acetate) as ethoxyethynylmagnesium bromide⁵ in benzene—ether at 20° for 22 hr, or as ethoxyethynyl-lithium in tetrahydrofuran at -78° for 4 hr (or at 0° for 20 min) was also unsuccessful. Moreover, when the iodoisothiocyanate was treated with dilithioacetate (LiCH₂CO₂Li),⁶ the latter acted simply as a strong base, resulting in the formation of volatile 3-isothiocyanatocyclohexene (4).

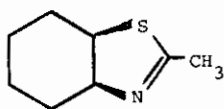
The compound (2) was ultimately prepared by treatment of the lithio- derivative of 2-methyl-2-thiazoline (5) [prepared from (1) and methylmagnesium bromide¹] with ethyl chloroformate. Since the product was more acidic than the starting material, provision was made in its preparation for proton transfer from the product to the unreacted carbanion.⁷ Thus, in order to utilize the starting material effectively, 2-methyl-2-thiazoline was treated with 1 mol. equiv. of butyl-lithium followed by the sequential addition of 0.5 mol. equiv. of acylating agent, 0.5 mol. equiv. of butyl-lithium, 0.25 mol. equiv. of acylating agent, and so on. Four repetitions of this cycle resulted in the formation in 80% yield of the desired product ethyl 2-(2-cis-3a,4,5,6,7,7a-hexahydrobenzothiazolyl)acetate (2), which existed as a 1:6 mixture with its tautomer, 8-(ethoxycarbonylmethylene)-cis-7-thia-9-azabicyclo[4.3.0]nonane (6) (cf. ref. 8), $C_{11}H_{17}NO_2S$,⁹ b.p. 108° at 0.5 mmHg.

Reduction of the tautomeric mixture of (2) and (6) with aluminium amalgam¹⁰ in refluxing ether for 2 hr gave ethyl 2-(8-cis-7-thia-9-azabicyclo[4.3.0]nonanyl)acetate (3) in 97% yield as an inseparable mixture (ca. 1:1) of diastereomers (7) and (8), b.p. 130° at 0.8 mmHg. The presence of both isomers was indicated by the ¹H n.m.r. spectrum which showed two sets of signals for the C 2 protons. A doublet of doublets at δ 2.76 attributable to the C 2 protons of (7) arose from vicinal coupling (J 6.5 Hz) with the adjacent thiazolidine methine proton and a smaller (J 2.5 Hz) five-bond coupling with the cyclohexyl methine proton vicinal to nitrogen. In contrast, the C 2 protons of the isomer (8) appeared as a simple doublet (J 5.5 Hz) at δ 2.91. Moreover, two sets of triplets at δ 4.84 (J 5.5 Hz) and δ 5.20 (J 6.5 Hz) were observed for the C 8 protons.

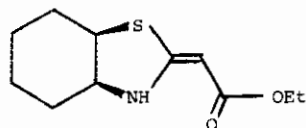
Attempts to effect β -lactam formation from the diastereomers (7) and (8) with methylmagnesium iodide,¹¹ butyl-lithium, or tributylaluminum,¹² resulted in recovery of starting material and/or formation of ring-opened tautomeric products. The predominant tautomer was ethyl 2-3-N-(cis-2-thiolocyclohexyl)amino-2-propenoate (9) and the minor isomer was ethyl 3-N-(cis-thiolocyclohexyl)-iminopropanoate (11); the mixture reverted to (7) and (8) on Kugelrohr distillation. Addition of iodomethane during the ring-opening reaction trapped the predominant tautomer as its S-methylated derivative (10). In order to ascertain if the preference for ring opening of (7) and (8) was a consequence of unfavourable strain that would result from formation of a tricyclic system, the monocyclic thiazidine analogue (12)¹³ of (2) was also treated with butyl-lithium and ethyl chloroformate. Reduction of the resulting tautomeric (1:2) mixture of (13) and (14), $C_8H_{13}NO_2S$,⁹ b.p. 120° at 0.8 mmHg, with aluminium amalgam gave racemic ethyl 2-[2-(1,3-thiazidinyl)]acetate (15), $C_8H_{15}NO_2S$,⁹ b.p. 116° at 0.8 mmHg, in 99% yield. Attempted cyclization of (15) with ethylmagnesium bromide, potassium t-butoxide, butyl-lithium, or tributylaluminum all gave starting material, ethyl 2-3-N-(3-thiolopropyl)amino-2-propenoate (16), and varying amounts of polymeric material.



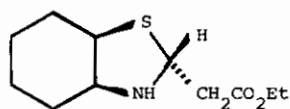
(4)



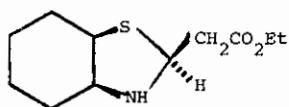
(5)



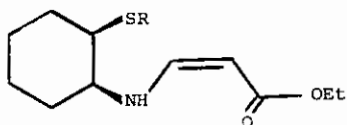
(6)



(7)

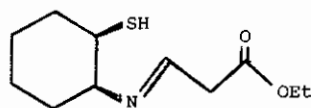


(8)

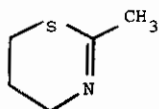


(9) R = H

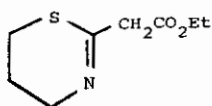
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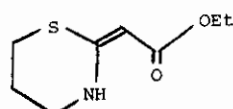
(11)



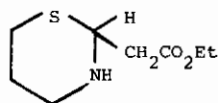
(12)



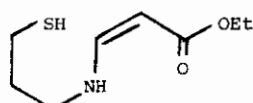
(13)



(14)



(15)



(16)

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