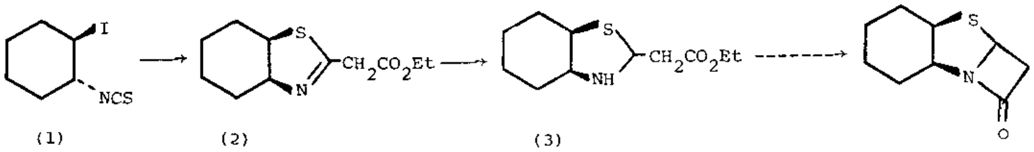
HETEROCYCLES, Vol 14, No 5, 1980

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

Paul D. Woodgate,* David Chambers, Peter S. Rutledge, and Richard C. Cambie
Department of Chemistry, University of Auckland, Auckland, New Zealand

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.



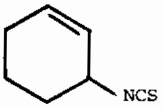
Scheme

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 hexamethyldisilylamide[3] or with the alternative non-nucleophilic base lithium 2,2,6,6-tetramethylpiperidide at -78 °C (at higher temperature the carbanion undergoes self-condensation[3]) gave no reaction. Likewise, the attempted addition of ethoxyethyne[4] (a synthon for ethyl acetate) as ethoxyethynylmagnesium bromide[5] 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 ($LiCH_2CO_2Li$),[6] the latter acted simply as a strong base, resulting in the formation of volatile 3-isothiocyanatocyclohexene (4).

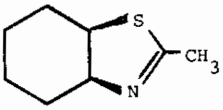
The compound (2) was ultimately prepared by treatment of the lithio- derivative of 2-methyl-2-thiazoline (5) [prepared from (1) and methylmagnesium bromide[1]] with ethyl chloroformate. Since the product was more acidic than the starting material, provision was made in its preparation for proton transfer 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 amalgam[10] 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 ^{1}H 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.

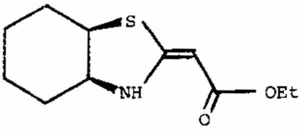
Attempts to effect β-lactam formation from the diastereomers (7) and (8) with methylmagnesium iodide,[11] butyl-lithium, or tributylaluminium,[12] resulted in recovery of starting material and/or formation of ring-opened tautomeric products. The predominant tautomer was ethyl Z-3-*N*-(*cis*-2-thiolocyclohexyl)amino-2-propenoate (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), $C_8H_{13}NO_2$,[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 tributylaluminium all gave starting material, ethyl Z-3-N-(3-thiolopropyl)amino-2-propenoate (16), and varying amounts of polymeric material.



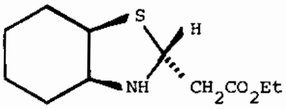
(4)



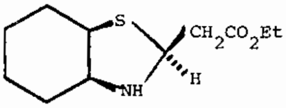
(5)



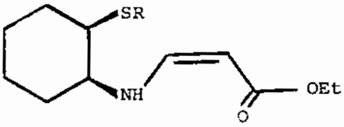
(6)



(7)

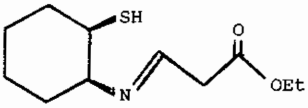


(8)

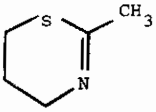


(9) R = H

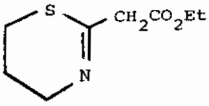
(10) R = Me



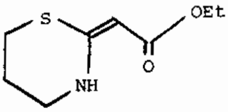
(11)



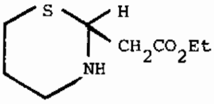
(12)



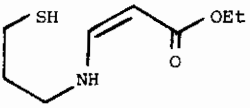
(13)



(14)



(15)



(16)

REFERENCES

1. R.C. Cambie, D. Chambers, P.S. Rutledge, and P.D. Woodgate, J.C.S. Perkin I, in the press.
2. R.C. Cambie, H.H. Lee, P.S. Rutledge, and P.D. Woodgate, J.C.S. Perkin I, 1979, 757.
3. M.W. Rathke, J. Amer. Chem. Soc., 1970, 92, 3222.
4. J.F. Arens, Adv. Org. Chem., 1960, 2, 117.
5. G.E. Arth, G.I. Poos, R.M. Lukes, F.M. Robinson, W.F. Johns, and L.H. Sarett, J. Amer. Chem. Soc., 1954, 76, 1715.
6. P.L. Creger, J. Org. Chem., 1972, 37, 1907; S. Danishefsky, P.F. Schuda, T. Kitahara, and S.J. Etheredge, J. Amer. Chem. Soc., 1977, 99, 6066.
7. P.A. Bartlett, F.R. Green, and E.H. Rose, J. Amer. Chem. Soc., 1978, 100, 4852.
8. C. Rocheville-Divorne and J-P. Roggero, Compt. rend. Acad. Sc., 1977, 285, 257.
9. Satisfactory elemental analyses were obtained.
10. A.I. Meyers, R. Munavu, and J. Durandetta, Tetrahedron Letters, 1972, 3929.
11. E. Testa, L. Fontanella, G.F. Cristiani, and F. Fava, Annalen, 1958, 614, 158; E. Testa, G. Pagani, and E. Gatti, ibid., 1961, 647, 92.
12. E.G. Rochow, D.T. Hurd, and R.N. Lewis, 'The Chemistry of Organometallic Compounds,' Wiley and Sons, Inc., New York, 1957; G.E. Coates, M.L.H. Green, and K. Wade, 'Organometallic Compounds,' Vol. 1, 3rd Ed., Methuen, London, 1967, pp. 295-343; D.W. Harney, A. Meisters, and T. Mole, Aust. J. Chem., 1974, 27, 1639.
13. E. Cherbuliez, Br. Baehler, O. Espejo, H. Jindra, B. Willhalm, and J. Rabinowitz, Helv. Chim. Acta., 1967, 50, 331.

Received, 23rd January, 1980