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The Reduction of 5,6-Dihydro-1,3-thiazines to 1,3-Thiazanes by Sodium Borohydride (I)

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Sir:

We have observed during our studies in the cephalosporin series a facile reduction of the C=N linkage in 5,6-dihydro-1,3-thiazines (I) using sodium borohydride in mildly acidic aqueous ethanol at 0-10°. The resulting 1,3-thiazanes (II) were obtained in yields ranging from 66-84% with no significant ring cleavage accompanying the process. Previous attempts (2) to perform this reduction using metal hydrides have resulted in ring opening by cleavage of the N-C-S moiety. Eliel (3) reported that thiazolidines were effectively cleaved to mercaptoalkyl amines using metal hydrides. To date, the most widely utilized reagent to successfully reduce dihydro-1,3-thiazines to 1,3-thiazanes is amalgamated aluminum in moist ether (4), a technique which in many instances gives rather unsatisfactory yields. We have employed sodium borohydride successfully to reduce a series of dihydro-1,3-thiazines, the products of which are shown in Table I. It is noteworthy that the ester grouping present during the reduction of I ($R_1=R_2=CH_3$, $R_3=CH_2COOEt$) was completely untouched (IIe). Also evident from the table is the fact that the absence of *gem*-methyl substituents does not appear to cause any instability to the ring system under the conditions of reduction. The sole limitation observed regarding the scope of the technique was in the case of the 2-phenyl derivative, I ($R_1=R_2=H$, $R_3=C_6H_5$). The only product isolated was the open chain mercaptoamine, III [b.p. 96-99° (0.5 mm), n_D^{25} 1.5615, ν max (film) 3336 cm^{-1} (NH), 2550 cm^{-1} (SH), two proton singlet, 6.38 τ ($C_6H_5-CH_2-N-$), two proton broad singlet, 8.55 τ , which exchanges with heavy water (SH, NH)]. In an additional attempt to determine which reducible groups may be present while the C=N linkage is attacked, we examined the reduction of a 2-vinyl derivative, I ($R_1=R_2=CH_3$, $R_3=-CH=CH_2$). Only

the 2-ethyl-1,3-thiazane (II d) was obtained from this experiment in 30% yield along with unreacted starting material. Comparison of the product obtained by the reduction of the 2-ethyl derivative (I, $R_1=R_2=CH_3$, $R_3=C_2H_5$) showed they were identical in every respect. This result is not entirely unexpected, in view of the fact that 1,4-addition by metal hydrides is well known (5). If this had occurred, it would give rise to the enamine, IV, which, in acidic medium, would be protonated on carbon (6) to give V. The latter is identical to the protonated form of the 2-ethyl-5,6-dihydro-1,3-thiazine (I, $R_1=R_2=CH_3$, $R_3=C_2H_5$).

The method is best illustrated by the following typical experimental procedure leading to II d.

A solution of 4.70 g. (0.03 mole) of the thiazine in 30 ml. 3N hydrochloric acid and 15 ml. ethanol was adjusted to pH 6 by the addition of 6N sodium hydroxide and then cooled to 0-5°. While stirring was maintained, a solution of 1.7 g. (0.045 mole) sodium borohydride in 20 ml. water containing one drop of 10% sodium hydroxide was added dropwise. The pH of the reaction solution was kept within the limits (monitored by a pH meter) of 5-7 by the periodic addition of 3N hydrochloric acid and the temperature was never allowed to exceed 10°. The addition took 1.5 hours and the mixture stirred for an additional hour at 0-5°. After making the solution alkaline (pH 10-12), it was extracted with ether, the extracts dried and concentrated and the product distilled. The 1,3-thiazane (II d), 3.86 g. (81%) showed no absorption in the 6 μ region and its n. m. r. spectrum exhibited a well defined triplet at 6.12 τ

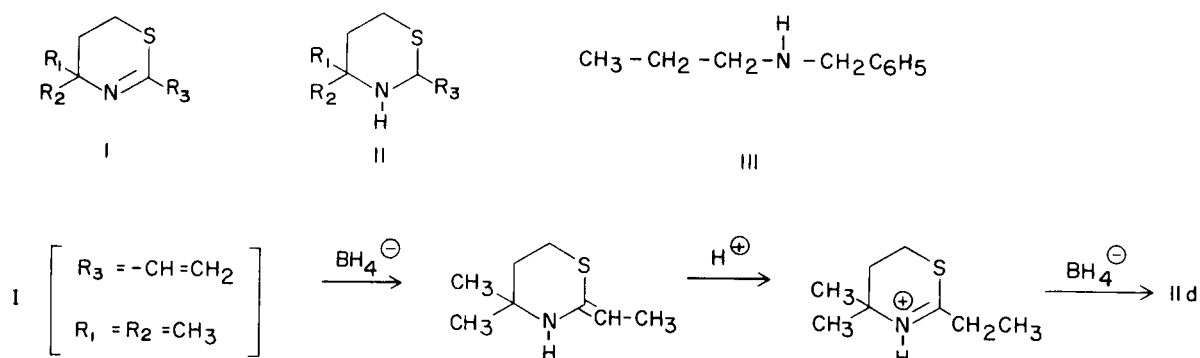
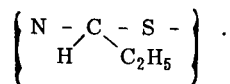


TABLE I

1,3-Thiazanes (II) Obtained From the Reduction of 5,6-Dihydro-1,3-thiazines (I) (a)

	R ₁	R ₂	R ₃	b. p. °C (mmHg)	n _D ²⁵	picrate (b)	% Yield (c)
IIa	H	H	C ₂ H ₅	45 (1.2)	1.5016	179-180	66
IIb	H	H	C ₃ H ₇	50-51 (1.5)	1.5050	167-169	71
IIc	CH ₃	CH ₃	CH ₃	44-45 (0.65)	1.5030	196-197	80
IId	CH ₃	CH ₃	C ₂ H ₅	54-55 (0.50)	1.4945	160-162	81
IIe	CH ₃	CH ₃	CH ₂ COOEt (d)	91-92 (0.60)	1.4966	133-135	87

(a) The thiazines (I) were prepared according to P. A. S. Smith and J. M. Sullivan, *J. Org. Chem.*, **26**, 1132 (1961), and the procedure given by A. I. Meyers, *ibid.*, **25**, 1147 (1960). (b) All melting points are uncorrected. (c) Correct elemental analysis was obtained for all compounds. (d) The constants for Ie are: b.p. 110-112° (0.75 mm), n_D²⁴ 1.5445, picrate, m.p. 138°.

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