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THE REACTION OF 3,4-DIBROMOSULFOLANE WITH AMINES. A NEW METHOD FOR THE PREPARATION OF BIOTIN PRECURSOR

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It was found that 3,4-dibromosulfolane reacted with amines to give the corresponding 3,4-diaminosulfolane or 4-amino-2-sulfolene derivatives. Also, it was established that N,N'-dibenzyl-cis-ureylene-tetrahydrothiophene as a precursor of biotin was derived from cis-3,4-bis(benzylamino)sulfolane prepared by the above reaction.

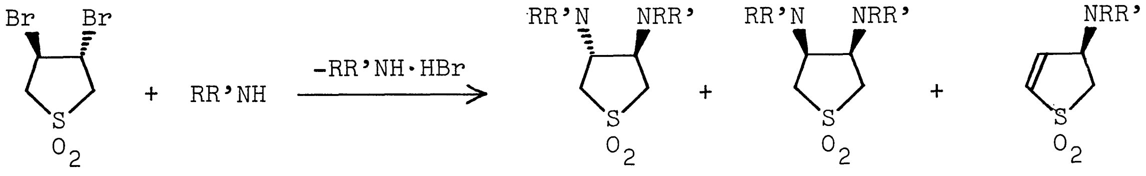
It is noteworthy that readily available 3-sulfolene has the useful skelton for biotin synthesis but no attempt was made to use this compound as a starting material for the preparation of biotin.

We wish to report in this paper about the reaction of 3,4-dibromosulfolane(I), prepared by bromination of 3-sulfolene, with amines to give the corresponding 3,4-diaminosulfolane derivatives which lead to the production of a precursor of biotin.

Bailey and Cummins have reported[1)] that I reacted with excess dimethylamine in benzene to give 3,4-bis(dimethylamino)sulfolane in excellent yield, but whole stereochemical character of the product has not been discussed. Then we tried initially the similar reaction using benzylamine in place of dimethylamine in various solvents such as benzene, methylenechloride, dioxane, tetrahydrofuran, ether, methanol, n-propanol and iso-propanol and found that protic solvents were superior to aprotic solvents for the production of 3,4-bis(benzylamino)sulfolane.

The following procedure is representative for the reaction of I with benzylamine (IIc) using methanol as solvent. To a methanol(1 ml) solution of I(0.278g, 1 mmol) was added a methanol solution(4 ml) of IIc(1.072g, 10 mmol) at room temperature, then the mixture was refluxed for 6 hrs. After cooling, the solution was evaporated under reduced pressure, and the residue was treated with 4.8 ml of 1 N HCl to remove excess of IIc followed by extraction with methylene chloride. The organic layer was dried over Na_2SO_4, filtered, and evaporated to dryness under reduced pressure. The residue was separated by preparative tlc to afford cis- and trans-3,4-bis(benzylamino)sulfolane(cisIIIc and transIIIc) in 30%(99 mg) and 58%(191 mg) yields, respectively.

By the similar procedure, cis- and trans-3,4-bis(methylamino)sulfolane(cisIIIb and transIIIb) were prepared by the reaction of I with methylamine,2) while only trans-3,4-bis(dimethylamino)sulfolane was obtained from I and dimethylamine.2) The reaction of I with aniline, however, did not give the expected 3,4-diaminosulfolane (IIId) but 4-anilino-2-sulfolene(IVd). The results are listed in the following Table.



I IIa-d transIIIa-d cisIIIa-d IVa-d

Amines	R	R'	Conditions	Isolated yield,*1,2 % transIIIa-d	cisIIIa-d	IVa-d
IIa	CH_3	CH_3	r.t. 1hr then reflux 1hr	quant.	–	–
IIb	CH_3	H	reflux 7hr	67	17	–
IIc	$PhCH_2$	H	reflux 6hr	58	30	–
IId	Ph	H	reflux 6hr	–	–	70

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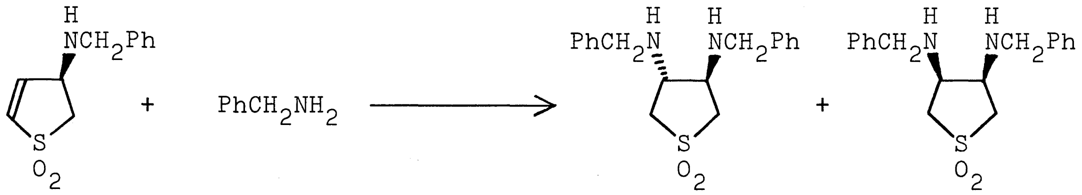
*1 transIIIa, mp 60.5-61.5°(lit.1) 63.4-63.6°); transIIIc, mp 114-115°; cisIIIc, mp 111.0-111.5°; IVd, mp 135-136°; cis and transIIIb are liquid.

*2 All compounds exhibited ir and pmr spectral data in accordance with assigned structure.

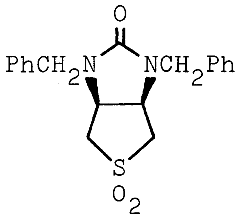
From the results of formation of cisIIIb,c as well as IVd in the reactions of trans-3,4-dibromosulfolane with amines, we assumed that the reaction proceeded through the initial formation of 4-amino-2-sulfolene(IV). This assumption was supported by the fact obtained from the reaction of IVc and benzylamine under the similar condition as follows.



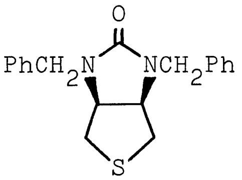
IVc transIIIc, 56% cisIIIc, 29%

Formation of IVd may be based on the steric hindrance and the poor nucleophilicity of aniline. On the other hand, I was treated with methylamine and dimethylamine under the same reaction condition to give trans isomers predominantly. These results suggested that both S_N2 process and addition reaction process occured competitively in these reactions owing to the high nucleophilicity of these amines.

Treatment of cisIIIc with phosgene and triethylamine in methylene chloride at room temperature afforded N,N'-dibenzyl-cis-3,4-ureylenesulfone(V) in quantitative yield. It was found that the ureylenesulfone(V) thus obtained further reacted with lithium aluminum hydride in dry ether at room temperature to afford the expected product, N,N'-dibenzyl-cis-3,4-ureylenetetrahydrothiophene(VI), as a precursor of biotin.3) The structure of this product was confirmed by direct comparison with an authentic sample prepared from fumaric acid.3,4)



V, mp 184°



VI, mp 110-111°

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2) About 40% aqueous solution was used.

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