Gem. Dithiols

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In 1960 Nomura and Takeuchi [1] described a synthesis of thioketones from hydrogen sulphide and enamines. This method was later found to give *gem.*dithiols, an earlier difficultly available class of compounds.

At that time investigations were in progress at this laboratory concerning the reaction between ammonium polysulphide and carbonyl compounds. The intention was to prepare 1,2,4,5-tetrathianes and other cyclic systems with several sulphur atoms. Thioketones prepared according to Sen [2], however, did not give tetrathianes with ammonium polysulphide.

Work has instead been concentrated upon a method to obtain *gem.*dithiols and thus tetrathianes by oxidation. The first successful attempts were made in May this year when *gem.*dithiols were obtained from ketimines and hydrogen sulphide. Meanwhile Djerassi [3] in Stanford and Jentzsch [4] in Dresden observed that the Nomura method gave *gem.*dithiols; however the first report concerning this work was not available at this institute until Aug. 16.

Due to the great interest in this field, no less than seven reports [3-9] about *gem.*-dithiols have appeared in the litterature this year. This communication is a short report of our results.

It appears possible to obtain *gem.*dithiols from simple aliphatic ketones if the corresponding ketimine can be prepared. In most cases it is easily done according to the method of Norton *et al.*[10], but sometimes it is necessary to resort to boiling and continuous water separation.

Sterically hindered ketones failed to give ketimines, *i.e.* dicyclopropyl-, dicyclohexyl-, diisopropyl-, and di-*tert.*-butylketone. The *gem.*dithiols are easily prepared from the ketimines by the reaction with hydrogen sulphide according to method A in the first preliminary report [7]. The difficulties arise when the boiling points are above 80°, when the *gem.*dithiols decompose. Thus the *gem.*dithiol from cyclooctanone decomposed by more than 50 %. From the analyses it appears that cycloheptanone gives an impure product. 2,2-Dimercapto-4-methyl-pentane also decomposed during attempted distillation. Phenylacetone gave *via* the ketimine a slightly pink-coloured oil with an onion-like odour in addition to mercaptane and unchanged starting material. It showed a strong SH-absorbtion at 3.98 μ and showed a positive lead acetate test for *gem.*dithiol [13]; however it could not be obtained in crystalline form and decomposed during distillation.

The ketimines from acetophenone and phenyl-cyclohexyl-ketone gave thioketones with hydrogen sulphide and no *gem.*dithiols. Aromatic aldehydes gave a deep blue colour when the corresponding Schiff bases were treated with hydrogen sulphide in ether solution at $-70°$, but the colour persisted only as long as the reaction continued. When the Schiff base had been consumed the colour faded out and a viscous polymer of thioaldehyde separated from the solution. In the case of the aromatic carbonyl compounds the amine part of the reaction product between the Schiff base and hydrogen sulphide is eliminated under the formation of the thiocarbonyl compound prior to substitution by the SH-group.

Aliphatic aldimines give poor yields of *gem.*dithiols due to polymer formation, but optimum experimental conditions have presumably not been used.

The most remarkable compound in this series is perhaps the 2,2-dimercapto-3,3-dimethyl-butane, which has a melting point of about 200°. In addition to the method *via* the ketimine, this *gem.*dithiol is readily prepared from pinacolone, hydrogen sulphide and hydrogen chloride according to the method given by Berchtold *et al.*[11] for 2,2-dimercapto-1,3,-diphenyl-propane. It immediately gives a black precipitate with lead acetate, no red or yellow colours being observed. NMR gives three peaks at 2.43, 1.84 and 1.16 ppm with the relative intensities 2:3:9, which is consistent with structure proposed. Molecular weight determinations give values which are about 10 % too high, indicating some association. This is also consistent with the high melting point. The dithiol has a faint odour of camphor distinctly perceptible through the mercaptane odour which is not particulary strong. In the case of the lower dithiols, however, the odour is extremely penetrating. In higher concentrations the *gem.*-dithiols are somewhat lachrymatory.

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Table 1. *gem*.Dithiols

	Yield %	n_D^{20}	b.p./mm	Formula	Analyses Calculated C	H	S	Found C	H	S	Ketimines from the corresponding ketone with butylamine Yield %	n_D^{20}	b.p./mm
2,2-Dimercapto-propane [a]	56	1.5088	57/100	$C_3H_8S_2$	33.29	7.45	59.26	33.38	7.36	59.13	73	1.4228	131/760
2,2-Dimercapto-butane	72	1.5100	46/19	$C_4H_{10}S_2$	39.30	8.24	52.46	39.66	8.28	51.89	72	1.4263	145/760
3,2-dimercapto-2-methyl-butane [c]	81	—	51/13	$C_5H_{12}S_2$	44.07	8.88	47.06	44.25	8.85	46.58	37[b]	1.4223	140/760
2,2-Dimercapto-3,3-dimethyl-butane [e]	53	—	—	$C_6H_{14}S_2$	47.94	9.39	42.67	47.99	9.41	41.57	60[d]	1.4291	55/2
3,3-Dimercapto-pentane	83	1.5052	54/12	$C_5H_{12}S_2$	44.07	8.88	47.06	44.16	8.80	47.03	63[f]	1.4323	58/2
1,1-Dimercapto-cyclopentane	73	1.5492	62/13	$C_5H_{10}S_2$	44.73	7.51	47.76	45.24	7.52	47.82	50	1.4608	78/13
1,1-Dimercapto-cyclohexane	80	1.5476	51/2,3	$C_6H_{12}S_2$	48.60	8.16	43.25	48.40	8.13	42.97	78	1.4665	80/10
1,1-Dimercapto-cycloheptane	71	1.5523	70/3	$C_7H_{14}S_2$	51.80	8.69	39.51	54.09	8.34	37.04	75	1.4729	116/17
1,1-Dimercapto-2-methyl-cyclohexane	81	1.5432	48/0,3	$C_7H_{14}S_2$	51.80	8.69	39.51	50.23	7.65	40.34	71	1.4163	103/17

a) m.p. 4—6°. *b*) Ketimine with propylamine, Ref.[10] *c*) m.p. 37—40°. The *gem*.dithiol may also be prepared in 10 % yield according to the method of Berchtold *et al.*[11] *d*) Water was removed by continuous water separation, *cf.* Ref.[12] *e*) m.p. in a sealed capillary tube 195—203° d. The substance sublimes easily. Mol. weight: Calc. 150.3; found 166 by freezing point depression in benzene; 165 by boiling point determination in acetone.

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The Fractionation of Ethanolamine Phosphatides of Ox Brain

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In 1961 Hanahan and Watts [1] reported that acylated alkoxy glycerophosphorylethanolamines are deacylated more slowly than phosphatidylethanolamines under mild alkaline conditions. This finding allowed the final purification of the "native alkoxy cephalins" of bovine erythrocytes. In 1962 Renkonen [2] isolated "native alkoxy lecithins" from human serum by removing quite large amounts of phosphatidylcholine with a similar method. In addition, Renkonen [3] recently found conditions where the diacyl phosphatides can be eliminated with mild alkaline treatment from native plasmalogens too. This report describes preparative fractionation of highly purified ox brain ethanolamine phosphatides with mild alkaline and mild acid [4] treatments, which yielded fairly good concentrates of all the three component lipids of the original mixture, *i.e.* of phosphatidylethanolamines, corresponding native plasmalogens, and "native alkoxy cephalins".

Ox brain cephalins were isolated and fractionated essentially as described by Folch [5]. The fraction V was further purified on DEAE cellulose [6] and on silicic acid [3], which gave a pure preparation of ethanolamine phosphatides (Table 1) containing 57 ± 8 % native plasmalogens, about 4 % native alkoxy phosphatides and 37 ± 8 % phosphatidylethanolamines *.

This sample was treated with 0.05 N NaOH in moist chloroform-methanol (3:4, v/v) at 20° for 23 min, and the hydrolysate was fractionated by solvent partition, and by silicic acid chromatography essentially as described previously [3]. In addition to lysoplasmalogens a phosphatide preparation was thus obtained which contained one third of the original phosphorus and consisted of 83 ± 8 % of native plasmalogens, of about 6 % of native alkoxy phosphatides, and of 11 ± 8 % of phosphatidylethanolamines *. Renewed alkaline treatment gave an even more satisfactory preparation of native ethanolamine plasmalogens, which was nearly free of phosphatidylethanolamines. Analytical characterization of this sample (Table 1) showed that it was, however, contaminated by about 8 % of alkoxy phosphatides.

Treatment of the pure native ethanolamine plasmalogens (276 μg P) with 0.05 N HCl in moist chloroform-methanol (1:1, v/v) at 20° for 60 min, and partitioning of the hydrolysate gave 4 % water soluble and 94 % lipid soluble phosphorus. Silicic acid chromatography of the lipid soluble fraction gave two phosphatide preparations, one of which (23 μg P) contained mainly acylated alkoxy glycerophosphorylethanolamines, *i.e.* native "cephalin B" [11], the other (220 μg P) was pure lysophosphatidylethanolamine **. Analytical char-

* The quantitative estimation of the different phosphatides was based on analysis of carboxylic esters [7], enolethers [8], phosphorus [9], alkali stable phosphorus [3], as well as acid and alkali stable phosphorus [10], and also on results of preparative mild acid hydrolysis.

** The purity of the lysophosphatidylethanolamines was ascertained by thin layer chromatography [3], and analysis of enolethers, carboxylic esters, glycerol [12], phosphorus and alkali labile as well as acid stable phosphorus [10].