It would seem justified to reserve the term "neat soap structure" for the types of lamellar mesophase composed of double amphiphilic layers, and to call the mesophase structure encountered in the sodium caprylate—octanediol—water system the "single layered lamellar type" with the designation type D_s.

Acknowledgement. The investigation has been supported by grants from *Malmfonden (The Swedish Foundation for Scientific Research and Industrial Development)* and from the *Swedish Council for Applied Research.*

1. Rosevear, F. B. *J. Am. Oil Chemists' Soc.* **31** (1954) 628.
2. Fontell, K., Ekwall, P., Mandell, L. and Danielsson, I. *Acta Chem. Scand.* **16** (1962) 2294.
3. Mandell, L., Fontell, K. and Ekwall, P. *Ordered Fluids and Liquid Crystals, Advan. Chemistry Series* **63** (1967) 89.
4. Fontell, K., Mandell, L., Lehtinen, H. and Ekwall, P. *Acta Polytech. Scand.* Ch. 74, III (1968).
5. Mandell, L. *Unpublished measurements.*
6. Ekwall, P., Mandell, L. and Fontell, K. *Acta Chem. Scand.* **22** (1968). *In press.*

Received December 23, 1967.

Semisynthetic Penicillins

VIII.* The Use of Tributyltin 6-Aminopenicillanate in Penicillin Synthesis**

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In a recent paper [1] we reported the convenient preparation of pyridylmethylpenicillins by acylation of phenacyl 6-aminopenicillanates with pyridylacetic acids in the presence of *N,N'*-dicyclohexylcarbodiimide (DCC).

During our investigations on other carboxyl protecting groups suitable in penicillin synthesis, we employed the tributyltin ester grouping which has recently been used by Frankel *et al.*[2] in the preparation of peptides. These authors prepared the triethyl- and tributyltin esters of free and N-protected amino acids. The esters were easily cleaved with acetic acid and other organic or inorganic acids or with bases such as methoxide or hydroxide. Tributyltin esters obtained from free amino acids were described as extremely sensitive to water or ethanol. Their instability made it impossible to use them in coupling reactions with DCC as the free acid present in the reaction mixture immediately cleaved the ester group.

We could prepare tributyltin 6-aminopenicillanate (I) from 6-APA and tributyltin oxide in high yield and purity by treatment of 6-APA with tributyltin oxide in boiling benzene and removal of the water formed by distillation. Partial evaporation of the remaining benzene and addition of petroleum ether precipitated the crystalline product.

The tributyltin ester of 6-APA was somewhat more stable than the α-amino acid tin esters described by Frankel *et al.* It could be stored unchanged for weeks at room temperature and in ethanolic solution it was stable for hours. The product was easily soluble in most organic solvents such as ether, ethyl acetate, benzene *etc.*

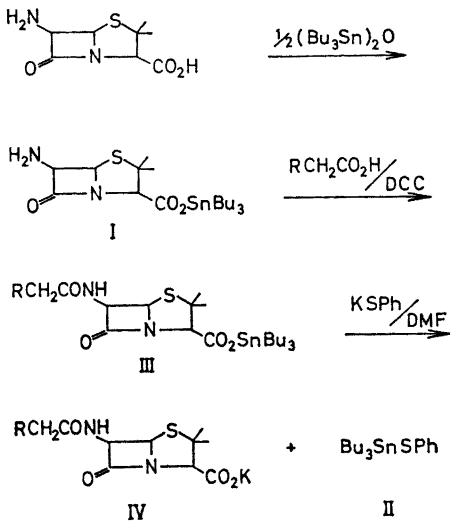
With one equivalent of potassium thiophenoxide (KSPh) in dimethylformamide (DMF), the ester was cleaved almost quantitatively within *ca.* 15 min to potassium 6-aminopenicillanate and phenyl tributyltin sulfide (II) without any appreciable destruction of the sensitive penicillin nucleus (Scheme 1).

We used the tributyltin 6-aminopenicillanate as a starting material in the synthesis of methylpenicillins carrying a nitrogen-containing heterocycle in the α-position in the manner described previously for phenacyl 6-aminopenicillanates.[1]

Tributyltin 6-aminopenicillanate was easily acylated with heterocyclic acetic acids using *N,N'*-dicyclohexylcarbodiimide (DCC) as the coupling reagent. In order to attain complete acylation of the 6-APA ester, a moderate excess of the carboxylic acid and DCC was used. The intermediate tributyltin penicillinates (III) were freed

* Paper VII. *Acta Chem. Scand.* **21** (1967) 2210.

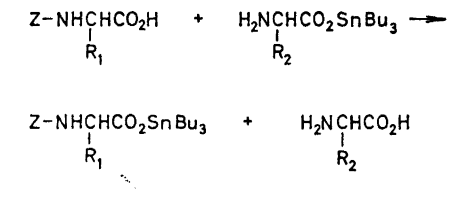
** Presented in part at the Svenska Kemistsamfundets Organikerdagar June 14—16, 1967, Gothenburg.



Scheme 1.

from excess carboxylic acid by washing with water at neutral pH and treated with KSPh in DMF to yield the potassium penicillinates (IV).

Under the experimental conditions used, the tributyltin 6-aminopenicillanate seemed to be stable and the side reaction described earlier in the case of α-amino acid tri-n-butyltin esters [2] (Scheme 2) seemed to be of minor importance. The suppression of the mentioned side reaction might be explained by the presence of a basic centre in the radical R (Scheme 1) which causes the acid to exist to some extent in the zwitterion form. Furthermore, the tributyltin 6-aminopenicillanate might be more stable than the corresponding α-amino acid esters in weakly protic media.



Scheme 2.

Several methylpenicillins with nitrogen-containing heterocycles in the α-position could be prepared in good yields and in many cases were of excellent purity. Experimental standard conditions are given below. The applicability of tributyltin 6-aminopenicillinate as an intermediate in the synthesis of methylpenicillins carrying other substituents in the α-position as well as a heterocycle is under investigation.

Tributyltin 6-aminopenicillanate. 6-APA (33.2 g, 0.154 mole) and tributyltin oxide (40 ml, 0.077 mole) were added to 1000 ml of boiling dry benzene.* The mixture was stirred while about 100 ml of the solvent was distilled off in the course of 5 min. After removal of a little unreacted 6-APA by filtration, the remaining solution was evaporated to about 200 ml. Chilling and addition of light petroleum ether precipitated white crystals 67.2 g (88 %), m.p. 84-85°, IR absorption (β-lactam) 1760 cm^{-1}. (Found: C 47.71; H 7.56; N 5.52; O 9.45; S 6.16. Calc. for $C_{30}H_{38}N_2O_3SSn$: C 47.54; H 7.58; N 5.55; O 9.50; S 6.35).

4-Phenylthiazolyl-5-methylpenicillin, (IV, R = 4-phenyl-5-thiazolyl). DCC (1.7 g, 0.0083 mole) in 10 ml of dry methylene chloride was added dropwise to an ice-cooled stirred suspension of 4-phenylthiazolyl-5-acetic acid [3] (2.0 g, 0.0091 mole) and tributyltin 6-aminopenicillanate (3.9 g, 0.0077 mole) in 20 ml of dry methylene chloride. The mixture was stirred at 4° for 15 h, diluted with 100 ml of ethyl acetate and the *N,N'*-dicyclohexylurea formed was removed by filtration. The clear solution was poured into 80 ml of ice water and the pH adjusted to 6.5 with 2 N NaOH. After drying the organic phase and complete evaporation of the solvent at reduced pressure, the residue was reprecipitated from benzene/petroleum ether yielding 4.8 g (0.0068 mole) of the intermediate tributyltin penicillinate. This was dissolved in 8 ml of dry DMF. KSPh (1.0 g, 0.0068 mole) was added and after allowing to stand for 30 min at room temperature, the solution was poured into dry acetone ether 1:4. The solvent was partly decanted from the resulting precipitate and more dry ether was added. Filtration yielded 2.2 g of product (63 %), purity determined alkalimetrically [4] 94.6 %.

The following compounds of purity 80—100 % were prepared in a similar way in yields

* Benzene from which most of the water had been removed azeotropically was adequate.

of 40–60 %. IV, R = 4- and 5-thiazolyl,[5] 2-phenyl-4-thiazolyl,* 2-chloro-4-thiazolyl,** 3-pyridyl, 3-quinolyl.[8] All products had a strong IR absorption band in the region 1755–1770 cm^{-1} corresponding to the β-lactam system.

Paper chromatograms of all the penicillins were run in a butanol-ethanol-water (4:1:5) top layer system and were developed microbiologically.[9] In all cases, only one zone corresponding to the pencillin was observed.

1. Bamberg, P., Ekström, B. and Sjöberg, B. *Acta Chem. Scand.* **21** (1967) 2210.
2. Frankel, M., Gertner, D., Wagner, D. and Zilkha, A. *J. Org. Chem.* **30** (1965) 1596.
3. U.S. Pat. 2,423,709.
4. Patterson, S. J. and Emery, W. B. *Analyst* **73** (1948) 207.
5. Mory, R. and Schenkel, H. *Helv. Chim. Acta* **33** (1950) 405; Erlenmeyer, H. and Morel, Ch. J. *Ibid.* **28** (1945) 362.
6. Burger, A. and Ullyot, G. E. *J. Org. Chem.* **12** (1947) 342.
7. Ganapathi, K. and Venkataraman, A. *Proc. Indian Acad. Sci* **22** (1945) 362.
8. Jones, R. G., Soper, Q. F., Behrens, O. K. and Corse, J. W. *J. Am. Chem. Soc.* **70** (1948) 2843.
9. Batchelor, F. R., Doyle, F. P., Nayler, J. H. C. and Rolinson, G. N. *Nature* **183** (1959) 257.

Received December 30, 1967.

* 2-Phenylthiazolyl-4-acetic acid was prepared from ethyl γ-bromoacetoacetate [6] and thiobenzamide according to a method given by Burger and Ullyot.[6]

** 2-Chlorothiazolyl-4-acetic acid was prepared from ethyl 2-aminothiazolyl-5-acetate following a method of Ganapathi and Venkataraman.[7]

The Vibrational Spectra of Tetramethylene Sulphoxide

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We have recently studied the vibrational spectra of two 5-membered cyclic molecules, ethylene trithiocarbonate and ethylene thiourea, and concluded that these molecules were not planar.[1] Since we have previously been interested in the sulphoxides as electron donors to iodine,[2] it seemed natural to extend these studies to tetramethylene sulphoxide (TMSO). This molecule represents another 5-membered aliphatic ring with an heteroatom, and the structurally related molecule tetramethylene sulphone has previously been reported by Katon and Feairheller.[3] A detailed vibrational analysis of dimethyl sulphoxide and the fully deuterated molecule has been carried out.[4] Since TMSO consists of 14 atoms and therefore has 36 normal vibrations, no complete interpretation of the spectra is possible, but a tentative assignment of most of the fundamentals will be proposed.

Experimental. TMSO from Aldrich was shaken with PCl_5 and fractionated three times over barium oxide in a Vigreux column under reduced pressure. No impurity peaks (including water) could be detected in a gas chromatogram.

The infrared spectra were recorded with Beckman models IR-9 and IR-12 in the region 4000–240 cm^{-1} as a capillary and in sealed cells. No vapour spectrum could be obtained even with a 10 m path cell, but a spectrum of the solid was recorded at −78°C.

The Raman spectrum was recorded with a Cary model 81 spectrometer, using the 7 mm tube and the 4358 Å radiation. Semiquantitative polarization measurements were obtained by the standard method.

Results. The infrared and the Raman spectra of TMSO are shown in Fig. 1 and the observed frequencies are listed in Table 1. It appears that there are no obvious cases of Raman bands without infrared counterparts. Therefore, the planar model with C_{2v} symmetry can be excluded, since the 7 fundamentals of species A_2 should be Raman active (and depolarized)