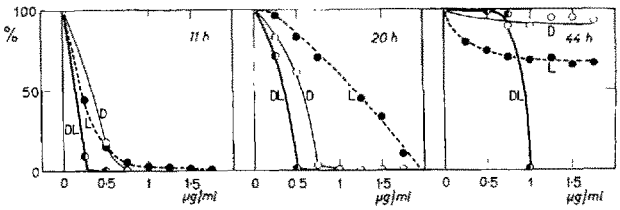
Synthesis of L-4-Amino-3-isoxazolidinone, the Unnatural Stereoisomer of Cycloserine and its Antibiotic Activity

The antibiotic cycloserine, 4-amino-3-isoxazolidinone, is configurationally related to D-serine. We now wish to report the direct synthesis of L-4-amino-3-isoxazolidinone from L-serine. The synthesis was modelled on a procedure which we have developed for the preparation of the racemate and which will be reported in detail shortly. This synthesis (cf. FLOWSHEET), with 1-triphenylmethyl-2-carbomethoxyethyleneimine as the key intermediate, appears to possess some advantages over the synthesis published in outline by KUEHL, WOLF *et al.*[1]. Though setting out from the same starting material, serine, our synthesis is shorter by two steps and all intermediates are stable, readily crystalline compounds and the yields are very satisfactory. The present synthesis was carried out essentially according to the sequence outlined in the FLOWSHEET, starting from L-serine. The synthesis does not involve an attack on the asymmetric centre and indeed the rotation of the final product $[\alpha]_D^{20} - 114{\cdot}5°$ ($c = 0{\cdot}9$ water) corresponds exactly to the value reported for the natural product $[\alpha]_D^{20} + 115°$ ($c = 1$, water). The D-isomer was prepared analogously from D-serine.

A comparison of the activities of the D-, L- and DL-forms of 4-amino-3-isoxazolidinone against *Escherichia coli* B on synthetic medium (glucose and inorganic salts) has yielded interesting results. As may be seen from the Figure, after 11 h of cultivation the racemate inhibits growth more powerfully than does either of the optically active forms; the growth-concentration curves of these two forms differ from each other. In subsequent stages of growth (20 h) this differentiation of the antibacterial effects of the three forms becomes still more pronounced. In the final phase (44 h) both optically active forms are practically without effect whereas the racemate still exhibits marked inhibitory activity. To remove any doubts as to the authentic nature of any of the compounds used in these tests, the results for the racemate were checked against a mixture made up of equal parts of the D- and L-forms used above; the two curves obtained were found practically to coincide.

[1] F. A. KUEHL, F. J. WOLF *et al.*, J. Amer. chem. Soc. *77*, 2344 (1955).



One possible explanation of these findings could be furnished by assuming the emergence of resistance towards both the D- and the L-forms of the antibiotic individually. In the racemate, on the other hand, the two antipodes – which evidently have different modes of action – would mutually prevent the emergence of resistance. Our findings represent the first case of synergism between stereoisomeric forms of an antibiotic.

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Zusammenfassung

Eine direkte Synthese von L- und D-Cycloserin aus L- und D-Serin wurde beschrieben. Die bakteriostatischen Effekte der drei Formen von Cycloserin (D-, L- und DL-) auf *E. coli* in synthetischem Medium wurden verglichen.

Über pharmakodynamisch interessante Aminoalkylderivate von Acridan- und Phenthiazinhomologen[1]

Es ist bekannt, dass die N-Aminoalkylderivate des Acridans[2], Phenthiazins[3] und Iminodibenzyls[4] in-

[1] 40. Mitt. *Antihistamin-Substanzen*, 39. Mitt. siehe Československ. farm. *6* (1957), im Druck; 8. Mitt. *Lokalanästhetika*, 7. Mitt. siehe Chem. listy *51*, 547 (1957).

[2] J. MILLS, E. ROHRMANN, W. G. DINWIDDIE und H. M. LEE, Arch. int. pharmacodyn. *80*, 119 (1949). – M. PROTIVA, J. O. JÍLEK, Z. J. VEJDĚLEK und O. EXNER, Chem. listy *46*, 551 (1952).

[3] P. VIAUD, J. Pharm. Pharmacol. London *6*, 361 (1954).

[4] W. SCHINDLER und F. HAEFLIGER, Helv. chim. Acta *37*, 472 (1954).