LETTERS TO THE EDITORS

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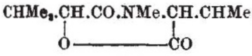
Antibiotics Produced by Fungi, and a New Phenomenon in Optical Resolution

It was reported earlier[1] that a strain of *Fusarium lateritium* produced an antibiotic, lateritiin-I, which was representative of a group of related compounds in presenting several remarkable chemical features. These features were elaborated in a communication to the Eleventh International Congress of Pure and Applied Chemistry held in London in July 1947, in which it was stated that lateritiin-I gave rise on hydrolysis to *D*(−)-α-hydroxy*iso*valeric acid and *L*(+)-N-methylvaline (II). The different configurations of these products were an indication, taking

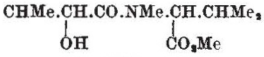
$\mathrm{CHMe_2.CH(OH.)CO_2H}$ (I) $\qquad$ $\mathrm{CHMe_2.CH(NHMe)CO_2H}$ (II)

their configurational stabilities into account, that these units had an individual existence in the original antibiotic. This conclusion was supported by the isolation from lateritiin-I, after mild alkaline hydrolysis, of a lactone from which a crystalline methyl ester was prepared, the properties of these compounds being compatible with the structures (III) and (IV) respectively.



$$\mathrm{CHMe_2.\underset{\displaystyle O}{\underset{|}{CH}}.CO.NMe.\underset{\displaystyle CO}{\underset{|}{CH}}.CHMe_2}$$

(III)



$$\mathrm{CHMe.\underset{\displaystyle OH}{\underset{|}{CH}}.CO.NMe.\underset{\displaystyle CO_2Me}{\underset{|}{CH}}.CHMe_2}$$

(IV)

Meanwhile Gaumann, Roth, Plattner, Ettlinger and Nager[2] had, unknown to us, reported the production by a strain of *F. orthoceras* of enniatin, which appeared to be closely related to, if not identical with, lateritiin-I. After exchanging samples of the two materials, it is agreed by Prof. Plattner and by us that a mixture of them is undepressed in melting point and that they must be regarded as identical. However, in a paper which has only recently reached us[3], it is concluded that the simple nitrogenous acid hydrolytic fragment of enniatin is probably identical with the higher homologue of (II), namely, N-methylleucine.

It seems, therefore, desirable to report that the structure of the fission product under discussion has been completely established by oxidation and by synthesis. Oxidation afforded *iso*butyraldehyde, which was identified as its 2 : 4-dinitrophenylhydrazone and 2 : 4-dinitrophenylsemicarbazone. Interaction of methylamine and lævo-α-bromo*iso*valeric acid afforded *L*(+)-N-methylvaline, identical in all respects with the material of natural origin; this was also obtained by the methylation of *L*(+)-valine in the usual way. Any remaining structural doubt has been removed by the synthesis of the lactone (III) and the derived ester (IV) in the following way. *lævo*-α-Brom*iso*valeryl chloride and *DL*-N-methylvaline were condensed together and the product was refluxed with pyridine and water, when the hydroxy-acid condensation product was formed. This was extracted and heated for several hours on the steam bath under reduced pressure, when the lactone (III) was obtained as a viscous oil similar to the natural material. This had the rotation $[\alpha]_D = +52°$ (ethanol); but on passing it through an acid-washed column in ethereal solution, about half the material was lost and the remainder had the rotation $[\alpha]_D = +79°$ (ethanol). The natural lactone has the rotation $[\alpha]_D = +82°$ (ethanol). On mild alkaline hydrolysis the synthetic material reverted to the hydroxy-acid, which on treatment with diazomethane gave the methyl ester (IV) identical in melting point with the ester of natural origin, with which it gave no depression on admixture; it was identical in all other respects with the material obtained by degradation, both showing the same optical activity, $[\alpha]_D = -128°$ (chloroform). Finally, the synthetic material yielded *L*(+)-N-methylvaline on hydrolysis.

The above reactions virtually constitute a facile resolution of N-methylvaline; apparently the lactone derived from *D*-α-hydroxy*iso*valeryl-*D*-N-methylvaline is more strongly absorbed on the alumina than that derived from *D*-α-hydroxy*iso*valeryl-N-methylvaline and undergoes hydrolysis. The lactone and derived hydroxy-acid pairs are, of course, not mirror images and no new theoretical principle is involved, nor is this an asymmetric synthesis in the conventional sense. The process is, however, unexpectedly simple; it might have considerable utility if it were general, and it clearly offers interesting speculation on the genesis of optically active amino-acids from existing optically active compounds.

Using the same procedure and starting with *DL*-α-brom*iso*valeryl chloride and *DL*-N-methylvaline, a crystalline optically inactive lactone was obtained, which was also formed by mixing equal amounts of the natural lactone with that derived from *L*-α-hydroxy*iso*valeryl-*D*-N-methylvaline.

A number of lactones similar to (III) have been made and are being studied, and full details of the present and related work will be published elsewhere.

Note added in proof.—Since the above was written a further communication (Plattner, Pl. A., and Nager, U., *Helv. chim. Acta*, 31, 665; 1948) has come to our notice in which 'enniatin A' and 'enniatin B' were described. Of these 'enniatin A', which appeared to be identical with lateritiin-I, afforded N-methylleucine, while N-methylvaline arose from 'enniatin B'. The above authors suggested that lateritiin-I was highly contaminated with 'enniatin B'. It must be emphasized, however, that we find no evidence to support this contention, the various degradation products affording no sign of heterogeneity.

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[1] Cook, A. H., Cox, S. F., Farmer, T. H., and Lacey, M. S., *Nature*, **160**, 31 (1947).

[2] Gaumann, E., Roth, S., Plattner, Pl. A., Ettlinger, L., and Nager, U., *Experientia*, **3**, 202 (1947).

[3] Plattner, Pl. A., and Nager, U., *Experientia*, **3**, 325 (1947).

The Antibiotic Agent from *Marasmius ramealis*

It has earlier been shown that species of the genus *Marasmius* produce substances inhibiting the growth of *Staphylococcus aureus*[1]. Our investigations now show that *Marasmius ramealis* Fr. exercises an antibiotic effect upon various pathogenic bacteria *in vitro*.

The *Marasmius* strain used was isolated and investigated for nutritional requirements by Lindeberg[2]. The fungus was grown upon different media, the most suitable one being a modification of the Czapek-Dox substrate. Erlenmeyer flasks containing 25 ml. of the nutrient solution were inoculated and incubated at 25° C., and the culture liquid tested for anti-