Tetrahedron Letters No.46, pp. 4601-4603, 1967. Pergamon Press Ltd. Printed in Great Britain.

TOTAL SYNTHESIS OF ALBONOURSIN

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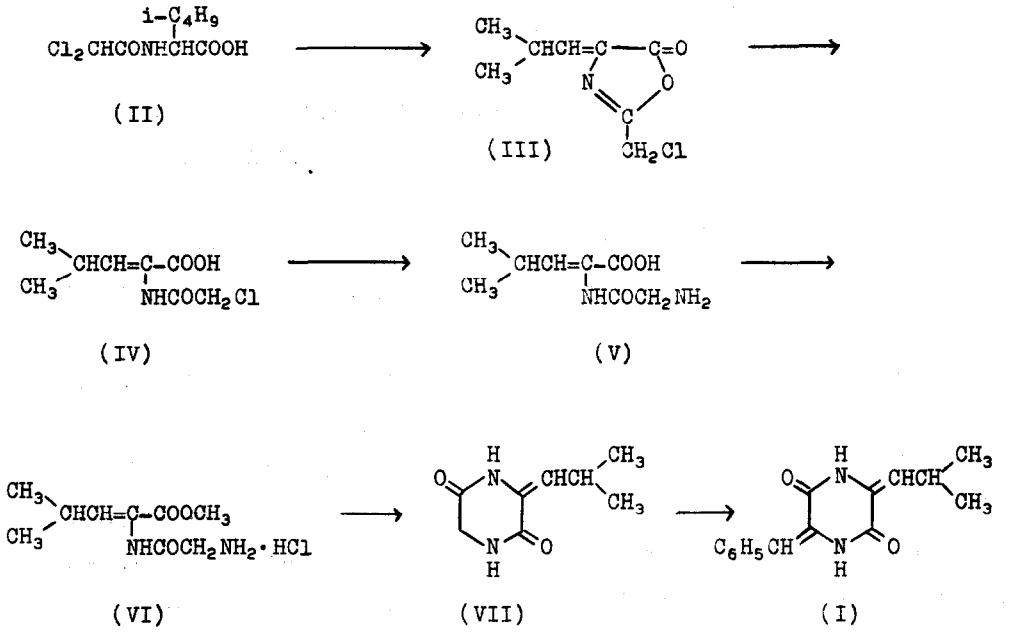
(Received in Japan 27 July 1967)

In 1963, Khokhlov and Lokshin (1) isolated a new substance from Streptomyces albus var. fungatus and St. noursei and named it albonoursin. Brown and Kelley (2) had reported that St. noursei produces a new metabolite 'Component 2'. Also Rao and Cullen (3) isolated the substance B-73 from St. albus. The two substances have been shown to be identical with albonoursin. Two independent studies by Brown et al. (4) and Vondracek and Vanek (5) have suggested 3-isobutylidene-6-benzylidene-2,5-piperazinedione structure (I) for albonoursin. Although arylidene 2,5-piperazinediones are known to be readily obtainable by condensation of 2,5-piperazinediones with aromatic aldehyde, no preparative method of monoalkylidene 2,5-piperazinedione has been reported except 3-methylene derivatives (6). Therefore, synthetic methods of 3-monoalkylidene 2,5-piperazinediones have been sought in our laboratory (7). In the present paper, we wish to communicate the first total synthesis of albonoursin by a new and simple method as illustrated in Scheme I.

The starting material, 2-chloromethyl-4-isobutylidene-5-oxazolone (III) was synthesized by heating dichloroacetyl-L-leucine (II) in acetic anhydride at 90°, as a yellow oil with a bp 90-93° (3 mm) (8). The oxazolone III was, upon being suspended in water, hydrolyzed to afford N-(chloroacetyl)dehydroleucine (IV) as colorless needles in a 35% yield, mp 128-129°, which was treated with ammonia in methanol to yield glycyldehydroleucine (V), mp 266-267°.



Scheme I

The leucine V was esterified with methanol-hydrogen chloride to give the corresponding methyl ester hydrochloride (VI), which, upon being heated with an aqueous solution of sodium bicarbonate, gave 3-isobutylidene-2,5-piperazinedione (VII) in a 28% yield (calcd. from VI), mp 277-278°. When condensation reaction of VII with benzaldehyde was carried out by heating in acetic anhydride at 130° for 6 hrs. in the presence of sodium acetate, I was obtained in a 56% yield. Recrystallization from acetic acid and then acetone gave colorless needles with a mp 271-272°. The product was characterized by elementary analysis (Calcd. for $C_{15}H_{16}N_2O_2$: C, 70.27; H, 6.29; N, 10.93. Found: C, 70.02; H, 6.39; N, 11.00.) and UV spectrum [λ_{max}^{DMF} 320 mμ ($\log \epsilon = 4.4$)] as well as IR spectrum (ν_{max}^{KBr} 3180, 1680, 1635, 1420, 1355 and 690 cm^{-1}).

These constants are essentially identical with those recorded for the natural product [mp 272°, λ_{max} 234 mμ ($\log \epsilon = 3.9$) and 318 (4.4) (9), ν_{max} 3184, 1680, 1638, 1424, 1358 and 690 cm^{-1} (4) and mp 263-265°, λ_{max} 201, 236 and 316 mμ (9) (5)].

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(9) Unfortunately, solvents used for the determination of the absorption maxima were not described in literatures (4) and (5).