

THE SYNTHESIS OF PRIMOCARCIN

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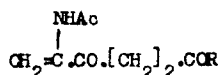
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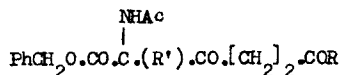
We wish to report the synthesis of primocarcin, an antitumour antibiotic isolated(1) from *Nocardia fukayae*, which has been assigned structure (I; R = NH₂).(2)

Reduction of α -benzyl δ -ethyl α -hydroxyimino- β -oxoadipate(3) with zinc-acetic acid-acetic anhydride afforded (91%) the acetamido-compound (II; R = OEt, R' = H), m.p. 69-70°, which was hydrolysed with concentrated hydrochloric acid at 0° to the acid (II; R = OH, R' = H) (72%), m.p. 99-101° [Lit.(3) m.p. 105.5-106° or 130-131.5°]. Treatment of the latter with ethyl chloroformate and triethylamine at 0° furnished the lactone (III), m.p. 119-120° [ν_{\max} 1826 cm⁻¹ (lactone C = O), λ_{\max} 235 μ (ϵ 11,900)], which with ammonia in dioxan gave the amide (II; R = NH₂, R' = H), m.p. 143-144°. Hydroxymethylation with formaldehyde and sodium bicarbonate(4) gave the amide (II; R = NH₂, R' = CH₂OH), m.p. 122-123.5°. A suspension of the foregoing amide in ethanol was hydrogenated over 10% palladium on strontium carbonate with rapid shaking (when 1.1 mol. had been taken up, the rate of absorption fell from 135 to 5 c.c./min.). Evaporation of the filtered solution was accompanied by decarboxylation and dehydration, and the precipitation of colourless needles, m.p. 116-118° (53%). Recrystallization from methanol afforded primocarcin (I; R = NH₂),

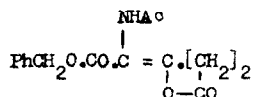
m.p. and mixed m.p. $127^{\circ}\text{--}128^{\circ}$, λ_{max} 253 μ (ϵ 3,600) [Lit.(1) m.p. $130\text{--}131^{\circ}$, λ_{max} 253 μ (ϵ 3,420)], whose infrared spectrum was identical with that of an authentic sample.



(I)



(II)



(III)

The analogues (I; R = OH, NHMe, NMe₂, NHPH) have been synthesized in a similar manner from the lactone (III).

Satisfactory spectral and analytical data have been obtained for all new compounds. The authors thank Dr. K. Isono for a sample of natural primocarcin.

REFERENCES

1. J. Nagatsu, K. Isono, and S. Suzuki, J. Antibiotics (Ser. A), 15, 75 (1962); K. Isono, and S. Suzuki, ibid., p. 77.
2. K. Isono, J. Antibiotics (Ser. A), 15, 80 (1962).
3. W. G. Laver, A. Neuberger, and J. J. Scott, J. Chem. Soc., 1474 (1959).
4. L. M. Long, and H. D. Troutman, J. Amer. Chem. Soc., 71, 2473 (1949).