New Synthesis of the Amino-acid (±)-Cucurbitine

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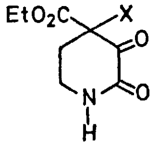
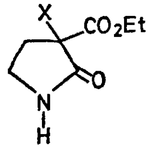
Summary Stepwise reduction of ethyl 3-azido-2-oxopyrrolidine-3-carboxylate (**5**), readily available from ethyl 2,3-dioxopiperidine-4-carboxylate (**1**) through a novel ring contraction, leads to (±)-cucurbitine (**9**).

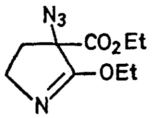
(−)-Cucurbitine (**9**), an unusual amino-acid isolated[1] from the seeds of several species of *Cucurbitaceae* is known to inhibit[2] the growth of immature *Schistosoma japonicum.* Although its synthesis has been described,[3] we required more efficient synthetic routes to cucurbitine and analogues in view of our interest[4] in potentially useful chemotherapeutic agents against schistosomiasis.



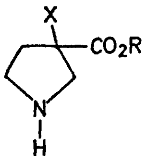
(**1**) X = H
(**2**) X = Br
(**3**) X = N_3



(**4**) X = Br
(**5**) X = N_3



(**6**)



(**7**) R = Et, X = N_3
(**8**) R = Et, X = NH_2
(**9**) R = H, X = NH_2

Bromination of the ester (**1**)[5] afforded the bromo-derivative (**2**) (95%), m.p. 70—72°, which gave the azide (**3**) (80%), m.p. 82—84°, with sodium azide in boiling 1,2-dimethoxyethane. On treatment with peroxyacetic acid ($CHCl_3$; room temperature), (**3**) underwent smooth ring contraction affording the azido-ester (**5**) (80%), m.p. 47—49°. Alternatively, treatment of (**2**) with peroxy-acid led to the bromo-ester (**4**) (60%), m.p. 112—113°, which was converted into the azide (**5**) (*ca.* 100%) as described above.

Reaction of (**5**) with triethyloxonium fluoroborate afforded the oily imino-ether (**6**), b.p. 58° at 2·5 mmHg, quantitatively. Attempted reduction of (**6**) with $NaBH_4$ in EtOH or AcOH failed to give the desired pyrrolidine (**7**) in appreciable yield. However, (**7**), b.p. 40° at 0·5 mmHg, could be obtained in 40% yield by reduction with diborane (generated *in situ*), followed by work-up with ethanolic hydrogen chloride according to the procedure of Kornet *et al.*,[6] by which the pyrrolidone (**5**) could also be directly reduced to (**7**), albeit in lower yields.

Catalytic hydrogenation (PtO_2) of (**7**) led to (±)-cucurbitine ethyl ester (**8**), which was hydrolysed to (±)-cucurbitine (**9**) (70%) and characterized as its hydrochloride (decomp. *ca.* 280°), diacetate (m.p.[3] 237—240°), and dibenzoate (m.p.[3] 224—226°).

All new compounds gave satisfactory spectral and microanalytical data.

We acknowledge support from the Conselho Nacional de Pesquisas.

(*Received*, 6*th November* 1972; *Com.* 1867.)

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