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SYNTHESIS OF 1-METHYLENEPYRROLIZIDINE

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LATELY a considerable increase has been observed in the number of pyrrolizidine alkaloids not containing necinic acid. A new addition is 1-methylenepyrrolizidine recently isolated by Culvenor and Smith from Crotolaria anagyroides.[1]

In line with our programme for the synthesis of pyrrolizidine alkaloids[2-4] we have carried out the synthesis of natural 1-methylenepyrrolizidine. Condensation of ethyl prolinate with methyl acrylate (boiling time, 24 hours) yielded ethyl β-(N-2-ethoxycarbonylpyrrolidine) propionate (1), 74%, b.p.$_{1\ \mathrm{mm}}$ 92-94°, n_D^{20}1.4571 (Found: C, 57.78; H,8.40, N, 6.08. Calc. for $C_{11}H_{19}O_4N$: C, 57.58: H, 8.39; N, 6.11). Picrate, m.p. 74.5 - 75.5° (EtOH) (Found: N, 12.14. Calc. for $C_{17}H_{22}O_{11}N_4$: N, 12.22). I was heated with dry C_2H_5ONa in xylene (150-160°, 1.5 hours)

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[1] C.C. Culvenor and L.W. Smith, Austr. J. Chem. 12, 255 (1959).

[2] N.K. Kochetkov, A. M. Likhosherstov and E.I. Budovskii, Khim. Nauka i Prom. 4, 678 (1959); Zh. Obshch. Khim. 30, 2077 (1960).

[3] N.K. Kochetkov, A.M. Likhosherstov and L.M. Likhosherstov, Zh. VKhO.im. Mendeleeva 5, 109 (1960).

[4] N.K. Kochetkov and A.M. Likhosherstov, Zh. VKhO. im. Mendeleeva, 5, 477 (1960).

and the crude ketoester on heating with 10% HCl (boiling time, 3 hours) was converted to pyrrolizidone-1 (II)[5]; yield 65%, b.p.$_{3\ \mathrm{mm}}$ 55-56°, n_D^{20} 1.4884 (Found: N, 11.49. Calc. for $C_7H_{11}ON$: N, 11.19). Picrate m.p. 162-164° (abs. EtOH, decomp.) (Found: C, 44.04; H, 4.12. Calc. for $C_{13}H_{14}O_8N$: C,44.06; H, 3.98).

In order to pass over to methylenepyrrolizidine use was made of Wittig's reaction. As far as we know this is the first time it has been applied in the field of alkaloids. By reaction with excess freshly-prepared triphenylphosphinomethylene[6] in ether (boiling time, 6 hours, standing at room temperature for 2 days) II was transformed to racemic 1-methylenepyrrolizidine (III). Yield 63%, colorless, hygroscopic liquid, b.p.$_{168\ \mathrm{mm}}$ 114-116°, n_D^{20} 1.4880 (Found: C,77.95; H, 10.60; N, 11.15. Calc. for $C_8H_{13}N$:C, 77.99; H,10.64; N, 11.37). Picrate m.p. 213-213.5° (EtOH. Found: C,47.50; H,4.57. Calc. for $C_{14}H_{16}O_7N_4$: C, 47.73; H, 4.58). The I.R. spectrum of III completely coincided with that of the natural product.[1] It contains an intensive 884 cm^{-1} methylene band and does not contain the 1385 cm^{-1} band characteristic of isoheliotridene-1,2 derivatives, thus proving the absence of isomerization during the Wittig reaction.

Racemic III was resolved by conversion to the tartrate with d-tartaric acid and after crystallization from ethanol-ethyl acetate (1:2) mixture the

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[5] This compound has also been used by us in the synthesis of isoretronecanol.[4] It was simultaneously prepared by Adams, employing another method [R. Adams, S. Miyano and D. Flis, J. Amer. Chem. Soc. 82, 1466 (1960)].

[6] G. Wittig, H. Eggers and P. Duffner, Liebigs Ann. 619, 10 (1958).

less soluble tartrate of m.p. 103-104° was isolated, $[\alpha]_D^{21}$ +8° (c 3.52, 96% EtOH) (Found: C, 52.90; H,6.93. Calc. for $C_{12}H_{19}O_6N$ C, 52.72; H,7.01). The 1-methylenepyrrolizidine base was liberated from the tartrate by the action of K_2CO_3 or NH_3 in aqueous solution. It was found to completely coincide with the natural alkaloid, $[\alpha]$ -39° (Found: C,77.99; H,10.58; N, 11.37). Picrolonate m.p. 171.5-172° (EtOH. Found: C,55.79; H,5.43; N, 17.80. Calc. for $C_{18}H_{21}O_5N_5$: C,55.81; H,5.46; N,18.07) Picrate m.p. 214-215° (Found: C, 47.58; H, 4.55; N, 15.85. Calc. for $C_{14}H_{16}O_7N_4$: C, 47.74; H, 4.58; N, 15.91) (Reported data:[1] $[\alpha]_D^{20}$ -43.1° (c 1.07, EtOH). Picrolonate m.p. 171-172.5°. Picrate m.p. 217.5-218°.