SYNTHESIS OF ALKALOIDS, TORTUOSAMINE, N-FORMYLTORTUOSAMINE, AND RELATED COMPOUND

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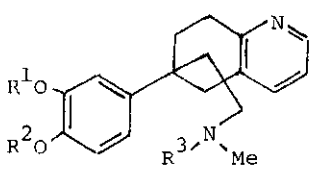
Synthesis of alkaloids, tortuosamine, N-formyltortuosamine, and related compound , was accomplished by application of a new method constructing cycloalkenopyridines by thermal rearrangement of oxime O-allyl ethers as a key step.

Tortuosamine[1a), 1b)] (1) and N-formyltortuosamine[1b)] (2), alkaloids isolated from Sceletium tortuosam N.E.Br.(Aizoaceae), were characterised by seco-mesembrane structure by Jeffs and Wiechers and their co-workers, and the former has been transformed from an alkaloid sceletium A_4 (3) by hydrogenolysis of the C-N bond. We report here a straightforward synthesis of these alkaloids in recemic modification as an extension of our recent work concerning a synthetic method of some cycloalkenopyridines.[2),3)]

Preliminary experiment was carried out using the cyano-cyclohexanone (4)[4)] in our hands. Thus, treatment of (4) with O-allyl-hydroxylamine[2)] in ethanol in the presence of sodium acetate gave the oxime O-allyl ether (5) in 97% yield. Thermolysis of the ether (5) in a sealed tube under air at 170-180 °C (bath temperature) for 24 hr yielded the cyclohexenopyridine (6) in 40% yield. Confirmation of the structure was provided by spectral properties: M^+(m/z) 278; ν_{max}(Nujol),2245cm^{-1} (CN); $\delta^{\#}$ 5.81 (2H, s, O-CH_2-O), 7.13 (1H, dd, J=5 and 8Hz, pyr-β), 7.42 (1H, dd, J=2 and 8Hz, pyr-γH), and 8.43 (1H, dd J=2 and 5Hz, pyr-αH).

Based on the above result, the congener (9) of (4) was synthesised. Treatment of 3,4-dimethoxybenzylcyanide with methyl acrylate in the presence of Triton B in t-butanol gave the pimelate (8) (m.p. 72-74 °C) in 80% yield. The Dieckmann cyclisation with sodium hydride in benzene gave the β-keto-ester (7) (m.p. 111-112 °C).

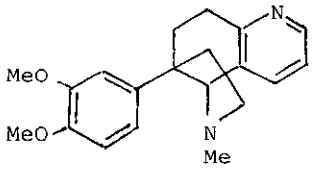
Hydrolysis and decarboxylation of (7) gave the cyanohexanone (9)[(m.p. 116-117 °C) ν_{max} 2230 (CN) and 1729cm^{-1} (CO)] in 75% yield from the pimelate (8). Treatment of (9) with O-allyl-hydroxylamine gave the oxime O-allyl ether (10) as an oil [ν_{max} ($CHCl_3$); 2250cm^{-1} (CN); Mass, M^+=314.164 corresponding to $C_{18}H_{22}N_2O_3$(314.163), δ, 3.88 and 3.99 (3H each, s, 2xOMe), 4.58-6.28 (5H, typical allyl grouping) and 6.98 (3H, m, arom-Hs)] which was subjected to the thermolysis in the same manner as mentioned above to give the cyclohexenopyridine (11) [(m.p.117-118 °C), ν_{max} ($CHCl_3$) 2230cm^{-1} (CN); δ, 3.90 (6H, s, 2xOMe), 6.95-7.72 (4H, m, 3 arom-Hs and pyr-βH), 7.45 (1H, dd, J=2 and 8Hz, pyr-γH), and 8.42 (1H, dd, J=2 and 5Hz, pyr-αH)] in 37% isolated yield.



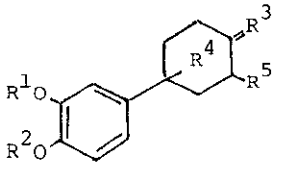
(1) R^1=R^2=Me; R^3=H

(2) R^1=R^2=Me; R^3=CHO

(19) R^1,R^2=-CH_2-; R^3=H



(3)



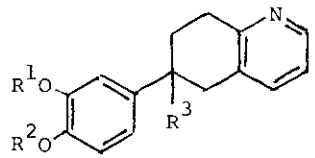
(4) R^1,R^2=-CH_2-; R^3=O; R^4=CN; R^5=H

(5) R^1,R^2=-CH_2-; R^4=CN; R^5=H; R^3=N-O-CH_2-CH=CH_2

(7) R^1=R^2=Me; R^3=O; R^4=CN; R^5=CO_2Me

(9) R^1=R^2=Me; R^3=O; R^4=CN; R^5=H

(10) R^1=R^2=Me; R^4=CN; R^5=H; R^3=N-O-CH_2-CH=CH_2



(6) R^1,R^2=-CH_2-; R^3=CN

(11) R^1=R^2=Me; R^3=CN

(12) R^1=R^2=Me; R^3=CHO

(13) R^1=R^2=Me; R^3=CH=CH-CO_2Et

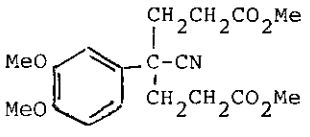
(14) R^1=R^2=Me; R^3=$CH_2CH_2CO_2$Et

(15) R^1=R^2=Me; R^3=$CH_2CH_2CONHNH_2$

(16) R^1=R^2=Me; R^3=$CH_2CH_2CON_3$

(17) R^1=R^3=Me; R^3=CH_2CH_2N=C=O

(18) R^1=R^2=Me; R^3=$CH_2CH_2NHCO_2$Et



(8)

Reduction of the cyclohexenopyridine (11) with di-isobutylaluminium hydride in benzene at -5 °C for half an hour followed by acid hydrolysis with dilute sulphuric acid gave the aldehyde (12) as an oil [ν_{max} ($CHCl_3$), 1720cm^{-1}; δ, 3.82 and 3.84 (3H each, s, 2xOMe), 6.82 (3H, m, arom-Hs), 7.06 (1H, dd, J=5 and 8Hz, pyr-βH), 7.50 (1H, dd, J=2 and 8Hz, pyr-γH), 8.36 (1H, dd J=2 and 5 Hz, pyr-αH) and 9.51 (1H, s, CHO); Mass, M^+=297.138 corresponding to $C_{18}H_{19}NO_3$(297.137)] in 88% yield. The Wittig reaction of the aldehyde with Wadsworth- Emmons reagent[5] in benzene gave the trans-acrylate (13) as an oil [ν_{max} 1700cm^{-1}(CO); δ, 1.23 (3H, t. CH_2-CH_3), 4.16 (2H, t, CH_2-CH_3), 3.80 (6H, s, 2xOMe), 5.68 (1H, d, J=15Hz, CH=CHCO$_2$Et), 7.11 (1H, d, J=15Hz, CH=CHCO$_2$Et), 6.79 (3H, m, arom-Hs), 7.08 (1H, dd, J=5 and 8Hz, pyr-βH), 7.48 (1H, dd, J=2 and 8Hz, pyr-γH), and 8.35 (1H, dd, J=2 and 5Hz, pyr-αH); M^+=367.180 corresponding to $C_{22}H_{25}NO_4$ (367.178)] in 90% yield, which was smoothly hydrogenated (Pt in ethanol) to the propionate (14) as an oil [M^+=369.200 corresponding to $C_{22}H_{27}NO_4$ (369.194)]. Treatment of (14) with hydrazine hydrate in ethanol yielded the hydrazide (15) in 90% yield. The hydrazide (15) was converted to the urethane (18) in 70% yield in the conventional way [i) treatment of the hydrazide with sodium nitrite gave the azide (16), ii) the Curtius rearrangement of (16) gave the isocyanate (17), and iii) treatment of (17) with ethanol gave the urethane (18)]. The urethane (18) has the following spectroscopic properties; (m.p. 110-112 °C) ν_{max} 3460 (NH) and 1710cm^{-1} (CO); δ, 1.18 (3H, t, CH_2CH_3), 4.04 (2H, q, CH_2-CH_3), 3.79 and 3.82 (3H each, s, 2xOMe), 4.38 (1H, broad s, NH), 6.78 (3H, m, arom-Hs) 7.05 (1H, dd, J=5 and 8Hz, pyr-βH), 7.48 (1H, dd, J=2 and 8Hz, pyr-γH), and 8.35 (1H, dd, J=2 and 5Hz, pyr-αH); Mass, M^+= 384.208 corresponding to $C_{22}H_{28}N_2O_4$ (384.205). Lithium aluminium hydride reduction of the urethane furnished (±)-tortuosamine as an oil [ν_{max} ($CHCl_3$) 1600, 1580, 1570, and 1510 (aromatic); δ, 1.52 (1H, s, NH), 2.32 (3H, s, NMe), 3.79 and 3.82 (3H each, s, 2xOMe), 6.80 (3H, m, arom-Hs) 7.04 (1H, dd, J=5 and 8Hz, pyr-βH), 7.47 (1H, dd, J=2 and 8Hz, pyr-γH), and 8.34 (1H, dd, J=2 and 5Hz, pyr-αH); Mass, M^+=326.198 corresponding to $C_{20}H_{26}N_2O_2$ (326.199)]. ^{1}H-n.m.r. spectrum of (±)-tortuosamine was identical with that of tortuosamine kindly provided by Professor P.W. Feffs in North Carolina University,[6] confirming the synthesis of (±)-tortuosamine.

Formylation of the synthetic alkaloid with acetic-formic anhydride at 0 °C for 45 min. gave (±)-N-formyltortuosamine [(oil), Mass, M^+=354.193 corresponding

to $C_{21}H_{26}N_2O_3$ (354.194); δ(DMSO-d_6) at 120 °C, 3.71 and 3.72 (3H each, s, 2xOMe), 6.85-6.94 (3H, arom-Hs), 7.09 (1H, dd, J=4.5 and 8Hz, pyr-βH), 7.55 (1H, d, J=8Hz, pyr-γH), 7.85 (1H, broad s, CHO), and 8.27 (1H, d, J=4.5Hz, pyr-αH)] in 65% yield which showed identical spectroscopic properties with those described in literature.[1b)]

Application of the same reaction sequence on the methylenedioxy-cyclohexenopyridine (6) gave the compound (19) as an oil, m.n.r. spectrum of which was quite similar to that of tortuosamine except displacement of two methoxyl groups to methylenedioxy-group.

References and Note

1) a) F.O. Snyckers, F. Strelow, and A. Wiechers, J.C.S., Chem. Commun., 1971, 1467; b) P.W. Jeffs, T. Capps, D.B. Johnson, J.M. Karle, N.H. Martin, and B. Rauckman, J. Org. Chem., 39, 2703 (1974).

2) H. Irie, I. Katayama, Y. Mizuno, J. Koyama, and Y. Suzuta, Heterocycles, 12, 771 (1979).

3) Professor Kakisawa (Tsukuba University) reported a similar method for synthesis of cycloalkenopyridine, when our report was in press: T. Kusumi, K. Yoneda, and H. Kakisawa, Synthesis, 1979, 221

4) H. Irie, S. Uyeo, and A. Yoshitake, J. Chem. Soc., (C), 1968, 1802.

5) S.W. Wodsworth and W.D. Emmons, J. Am. Chem. Soc., 83, 1733 (1961).

6) We are indebted to Professor P.W. Jeffs for his generous supply of a copy of n.m.r. spectrum of tortuosamine.

N.m.r. spectra were taken in deuteriochloroform unless otherwise stated.

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