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A NEW, SIMPLE ROUTE TO TETRACYCLIC INTERMEDIATES FOR THE SYNTHESIS OF DITERPENOID ALKALOIDS

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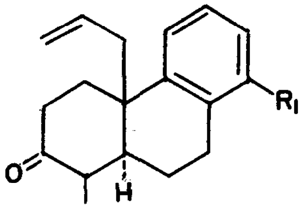
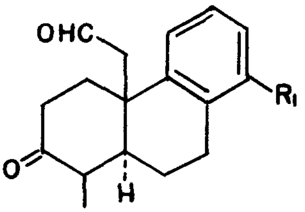
We should like to report a new, simple synthesis of the tetracyclic compounds 10A[1] and 10B[2], known as important key intermediates in the total synthesis of Garrya alkaloids and supposed to be promising substances in the synthesis of aconitine type compounds.

The allyl ketone 1A, m.p. 83-84° ($\nu_{max.}^{nujol}$ 1713, 1638, 999, 910 cm^{-1}, τ^{CDCl_3} 8.90(3H, d., J=5cps), 3.7-5.2(3H, m.)) prepared from 1-methoxynaphthalene by the known procedure[3], was oxidized[4] by sodium periodate with a catalytic amount of osmium tetroxide in aqueous tert-butanol at room temperature to the keto aldehyde 2A, m.p. 91-92° (ν_{max}^{nujol} 2740, 1703 cm^{-1}, τ^{CDCl_3} 8.85(3H, d., J=6cps), 0.50(1H, t., J=3cps) in 70% yield. The methoxyl derivative 2B of 2A has been obtained by Turner et al.[3] and they reported that in all their attempts the aldol cyclization of 2B under both acidic and basic conditions took place inveriably at C_2 to give the undesired 3D.

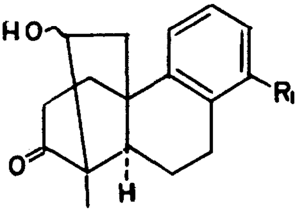
In an attempt to control the direction of the cyclization to C_4, base catalyzed aldol condensation of 2A and 2B was examined in polar aprotic solvents, such as DMSO, DME, HMPA, and potassium tert-butoxide in DMSO was found to be quite effective for this purpose. Thus treatment of 2A in DMSO with



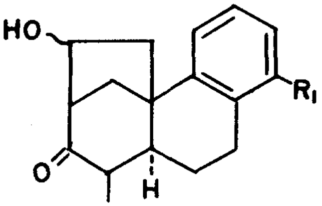
1A;1B



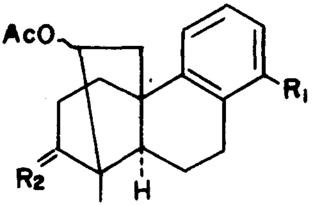
2A,2B



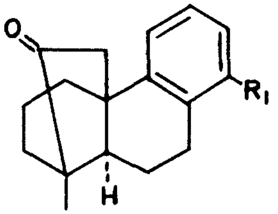
3A,3B



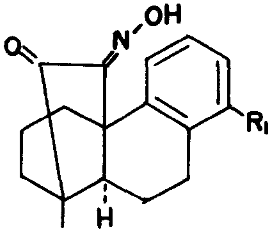
3C,3D



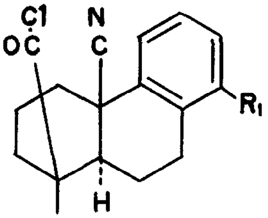
4A,4B(R_2= O)
5A,5B(R_2=$\langle^S_S]$)



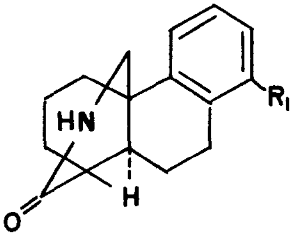
6A,6B



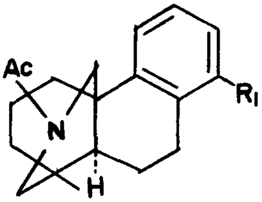
7A,7B



8A,8B



9A,9B



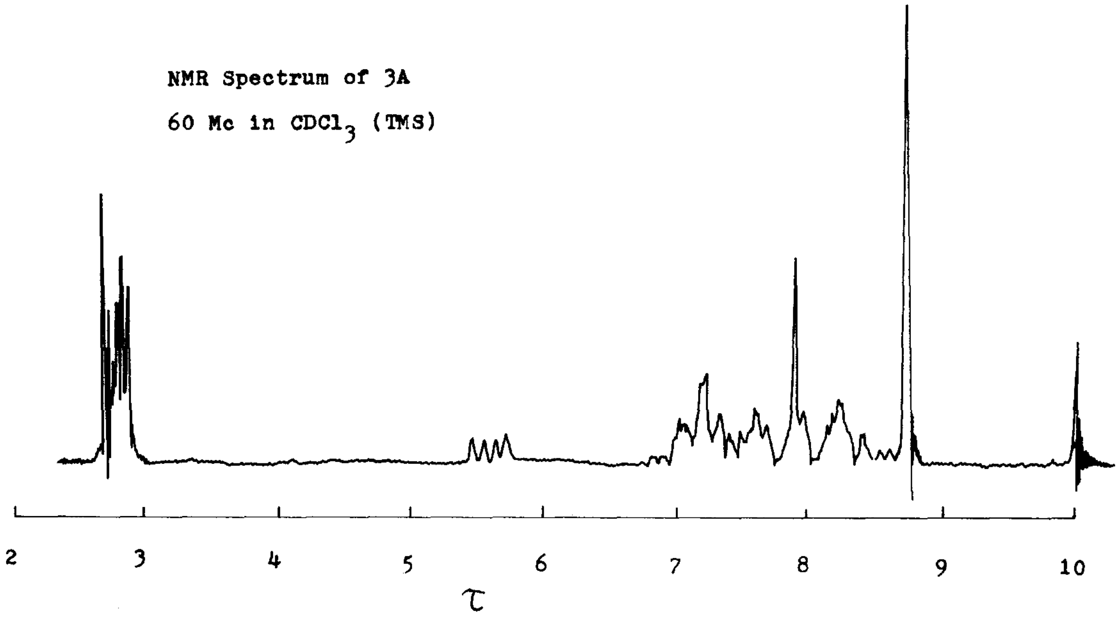
10A,10B

R_1=H in A series and 3C

R_1=OCH_3in B series and 3D

butanol-free tert-butoxide under nitrogen atmosphere at 70° led to the formation of 3A*, m.p. 203.5-205° (ν_{max}^{nujol} 3420, 1680 cm^{-1}, τ^{CDCl_3} 8.77(3H, s.), 5.55(1H, q.)) together with 3C, m.p. 183.5-184.5° (ν_{max}^{nujol} 3420, 1690 cm^{-1}, τ^{CDCl_3} 8.90(3H, d., J=6cps)). The both compounds were separated by fractional crystallization from ethyl acetate and obtained in almost equal amount. Similarly 2B afforded 3B, m.p. 249-251° (ν_{max}^{nujol} 3500, 3420, 1695, 1260 cm^{-1}, τ^{CDCl_3} 8.95(3H, s.), 6.18(3H, s.), 5.85(1H, q.)) and 3D$^{3)}$ in about the same yield. The presence of protic species in the reaction medium seems to have a remarkable effect on the course of the reaction: treatment of 2A (or 2B) in DMSO containing even a small amount of tert-butanol with potassium tert-butoxide afforded exclusively 3C (or 3D), in contrast with the butanol free case.

The keto aldehydes 3A and 3B were next converted into the acetates 4A, m.p. 135.5-136.5° (ν_{max}^{nujol} 1737, 1720 cm^{-1}, τ^{CDCl_3} 8.80(3H, s.), 7.93(3H, s.)) and 4B, m.p. 181-182° (ν_{max}^{nujol} 1741, 1705, 1255, 1240 cm^{-1}, τ^{CDCl_3} 8.80(3H, s.), 7.95(3H, s.), 6.18(3H, s.), 4.75(1H, q.)), which in turn were treated with ethanedithiol


NMR Spectrum of 3A
60 Mc in $CDCl_3$ (TMS)

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* Satisfactory analyses were obtained for all new compounds characterized.

and borontrifluoride etherate to give thioketals 5A, m.p. 152-153° (ν_{max}^{nujol} 1735 cm^{-1}, τ^{CDCl_3} 8.55(3H, s.), 7.80(3H, s.), 6.80(4H, m.), 4.65(1H, q.)) and 5B, m.p. 209-210° (ν_{max}^{nujol} 1740 cm^{-1}, τ^{CDCl_3} 8.55(3H, s.), 7.80(3H, s.), 6.15(3H, s.), 6.80 (4H, m.), 4.65(1H, q.)) respectively. These compounds were successively treated with Raney-nickel in refluxing ethanol, with lithium aluminum hydride in ether and then oxidized with chromium trioxide-pyridine to produce the tetracyclic ketones 6A, m.p. 117-118° (ν_{max}^{nujol} 1743 cm^{-1}, τ^{CDCl_3} 8.90(3H, s.)) and 6B**, m.p. 152-153° in overall 75% in both cases based on 3A and 3B.

The conversion of the cyclopentanone system thus produced to the nitrogeneous six membered ring was effected by the following new sequence of reactions. Treatment of the ketone 6A (or 6B) with isoamyl nitrite and potassium tert-butoxide in tert-butanol (in the case of 6B, sufficient amount of DME was added to dissolve the reactant) gave the isonitroso ketone 7A, m.p. 173-174° (ν_{max}^{nujol} 3240, 1740, 1640 cm^{-1}, τ^{CDCl_3} 8.83(3H, s.) or 7B, m.p. 175-177° (ν_{max}^{nujol} 3240, 1740, 1640 cm^{-1}, τ^{CDCl_3} 8.82(3H, s.), 6.15(3H, s.)) in 70% yield in both cases. On treatment with thionyl chloride, 7A and 7B underwent Beckmann fission to give the nitrile acid chlorides 8A (ν_{max}^{film} 2220, 1800 cm^{-1}, in 70% yield) and 8B (ν_{max}^{film} 2220, 1780 cm^{-1}, in 65% yield), and subsequent treatment of these two products with diborane led directly to the formation of lactams 9A, m.p. 239.5-242° (ν_{max}^{nujol} 3200, 1660 cm^{-1}, τ^{CDCl_3} 8.70(3H, s.), 6.55(2H, b.s.), 3.80(1H, b.)) and 9B***, m.p. 307-310° (ν_{max}^{nujol} 3160, 1660, 1255 cm^{-1}). The compounds 9A and 9B were then reduced with lithium aluminum hydride in dioxane and resulted amines (m.p. 94-96° and oil respectively) were characterized as N-acetyl compounds 10A, m.p. 125-126.5° ($\nu_{max}^{CCl_4}$ 1643 cm^{-1}, τ^{CDCl_3} 9.02(3H, s.), 7.82(3H, s.)) and 10B, m.p. 145-147° (ν_{max}^{nujol} 1638, 1260 cm^{-1}).

The compound 10A was completely identical in IR spectrum with the optical active form with known stereochemistry derived from abietic acid$^{1)}$.

** The compound 6B has been obtained by Turner et al.$^{3)}$ Reported m.p. 152-152.5°.

*** Because of low solubility in common organic solvents, NMR spectrum has not been measured.

The conversion of 10A and 10B to Garrya alkaloids has been already described by Tahara et al.[1)] and by Wiesner et al.[2)] respectively.

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REFERENCES

1) A. Tahara and K. Hirao, Tetrahedron Letters, 1453 (1966).
2) R. W. Guthrie, A. Phillipp, Z. Valenta and K. Wiesner, Tetrahedron Letters, 2945 (1965). Z. Valenta, K. Wiesner and C. M. Wong, ibid., 2437 (1964).
3) R. B. Turner, G. D. Diana, G. E. Fodor, K. Gerbert, D. L. Simmons, A. S. Rao, O. Roos and W. Wirth, J. Am. Chem. Soc., 88, 1786 (1966).
4) R. Pappo, D. S. Allen, Jr., R. U. Lumieux and W. S. Johnson, J. Org. Chem., 21, 478 (1956).
5) H. C. Brown and B. C. Subba Rao, J. Am. Chem. Soc., 82, 681 (1960).