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FURTHER APPLICATIONS OF ENDOCYCLIC ENAMINE–ENONE ANNULATIONS

THE TOTAL SYNTHESES[1] OF *RAC*-SCELETIUM ALKALOID A_4 AND 3'-DEMETHOXY SCELETIUM ALKALOID A_4

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Abstract—The total synthesis of *rac*-sceletium alkaloid A_4 1a and of its 3'-demethoxy analogue 1b via the annulation of endocyclic enamines 4a–b is presented. The Michael acceptor 5a is a useful synthon for the two-step synthesis of 2,3-disubstituted pyridines from Δ^2-pyrrolines.

The growing interest in the alkaloids obtained from various *Sceletium* species of the family Aizoaceae is reflected in the increasing number of papers dealing with their isolation and structural elucidation[1–4] synthesis[5] and biosynthesis.[6] Although we have isolated relatively large quantities of some of these alkaloids from *S. joubertii*, several of them are not available in sufficient quantities for dilution studies in radio-active tracer analysis or biological screening experiments. Of these we have been particularly interested in the pyridine alkaloids sceletium alkaloid A_4[1,4d,e,g] 1a, tortuosamine[4g] 2a and N-formyl tortuosamine 2b. Furthermore, the recent isolation of a 3'-deoxygenated mesembrane alkaloid, sceletenone[4e] 6 from *S. namaquense*, a plant from which dioxyaryl alkaloids (e.g. mesembranone) have also been extracted, and the proven intermediacy of sceletenone in the biogenesis of the *cis* - 3 - (3,4 - dimethoxyphenyl) - octahydroindole alkaloids,[4e] prompted us to undertake the total synthesis of the 3'-demethoxy analogue of sceletium alkaloid A_4 as well. This compound has hitherto not been isolated from natural sources.

The acid-catalysed thermal rearrangements of cyclopropyl imines 3 to Δ^2-pyrrolines 4, followed by annulation with methyl vinyl ketone or an analogue of it, a reaction sequence developed primarily by Stevens,[5f,h] has been utilized as the key step in the total syntheses of a variety of alkaloids.[7] Accordingly, we chose 6 - (5,5 - dimethyl - 1,3 - dioxan - 2 - yl)hex - 1 - en - 3 - one 5a and 6 - (1,3 - dioxolan - 2 - yl)hex - 1 - en - 3 - one 5b as Michael-acceptors which, after annulation with 3 - veratryl - 2 - pyrroline[5h] 4a and 3 - anisyl - 2 - pyrroline[5g] 4b, provided the masked 1,5-dicarbonyl systems 7a–d, which subsequently were readily converted to sceletium alkaloid A_4 1a and 3'-demethoxy sceletium alkaloid A_4 1b in good yields by treatment with an excess of hydroxylamine hydrochloride in refluxing 96% ethanol.

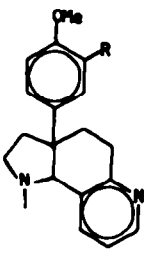
The preparation of the cyclopropyl imine 3a by cyclopropanation of 3,4-dimethoxyphenyl acetonitrile, reduction to the aldehyde with diisobutylaluminium hydride and imine formation, followed by acid-catalysed thermal rearrangement to the enamine 4a was readily accomplished by the method of Stevens.[5h] The preparation of the 3'-demethoxy analogue 4b[5g] was similarly achieved.

Annulation of the hydrochloride salts of Δ^2-pyrrolines 4a and 4b with enones 5a and 5b proceeded readily in refluxing acetonitrile in 75–80% yield over 15 hr. The resulting annulation products 7a–d were separately converted to sceletium alkaloid A_4 1a and 3'-demethoxy sceletium alkaloid A_4. 1b in 60–81% yields by refluxing them with a threefold excess of hydroxylamine hydrochloride in 96% aqueous ethanol. Sceletium alkaloid A_4 obtained in this way was identical in all respects (IR, UV, PMR, MS, m.p.) with the natural product. This two step conversion of the enone 5a to sceletium alkaloid A_4 is a marked improvement on the four step procedure employed by Stevens utilizing methyl - 5 - oxo - hept - 6 - enoate[5h] 8.

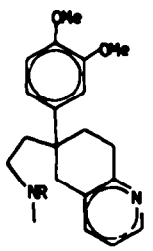
Enone 5a is in fact potentially useful as a *general precursor in the synthesis of 2,3-disubstituted pyridines*[8] via enolate or enamine annulations.† The syntheses of the enones 5a and 5b were accomplished by two different pathways. The first approach involved the regiospecific alkylation of the dianion of 3-phenylsulphinyl-butanone[9] 9 with 2 - (2 - bromopropyl) - 1,3 - dioxolane[10] to give the intermediate sulphoxide 10 as a pair of diastereomeric racemates which underwent thermal elimination of benzenesulphenic acid in refluxing carbon tetrachloride to afford the enone 5b. However a more efficient synthesis involved as a key step the Grignard reaction either of 2 - (3 - chloropropyl) - 1,3 - dioxolane 11a or 2 - (3 - chloropropyl) - 5,5 - dimethyl - 1,3 - dioxane 11b with acrolein to afford in high yield (84% and 89% respectively) the allylic alcohols 12a and 12b which were readily oxidized with pyridinium chlorochromate[11] to enones 5a and 5b in satisfactory yields. The acetals 11a and 11b were readily prepared from 4-chlorobutanol by oxidation to the aldehyde with pyridinium chlorochromate and subsequent acetalization.[12] The above mentioned Grignard reaction is, to the best of our knowledge, the first example of the high yield utilization of acetal substituted alkyl halides and forms the subject of a note published elsewhere.[13]

This total synthesis of sceletium alkaloid A_4 also formally constitutes a total synthesis of tortuosamine 2a which has previously been derived from natural sceletium alkaloid A_4 by catalytic hydrogenolysis.[4g]

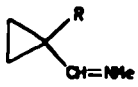
†Enone 5a is more stable to storage than enone 5b, although both compounds are labile and are used directly after their preparation [see Ref. (1)].



1. (a) R = OMe
(b) R = H



2. (a) R = H
(b) R = CHO



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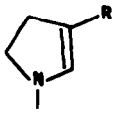
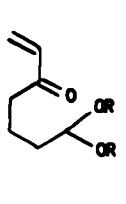
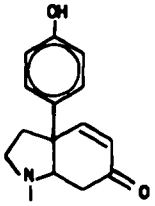


4.

(a) R = 3,4-dimethoxyphenyl
(b) R = 4-methoxyphenyl



5. (a) RR = $CH_2CMe_2CH_2$
(b) RR = CH_2CH_2



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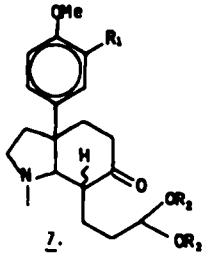
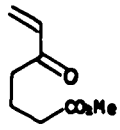


7. (a) R_1 = OMe, R_2R_2 = $CH_2CMe_2CH_2$
(b) R_1 = H, R_2R_2 = $CH_2CMe_2CH_2$
(c) R_1 = OMe, R_2R_2 = CH_2CH_2
(d) R_1 = H, R_2R_2 = CH_2CH_2



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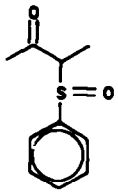

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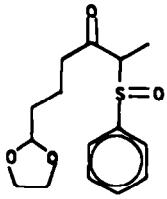
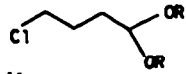
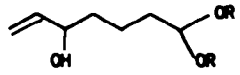


10.



11. (a) RR = CH_2CH_2
(b) RR = $CH_2CMe_2CH_2$



12. (a) RR = CH_2CH_2
(b) RR = $CH_2CMe_2CH_2$

EXPERIMENTAL

IR spectra were obtained on a Unicam SP200 spectrophotometer. PMR spectra were obtained on a Varian HA100 spectrometer. Mass spectra and accurate mass measurements were made on a Du Pont 21.492 B mass spectrometer. Qualitative tlc was carried out on silica gel (G 254) or on aluminium oxide (F254 type E) developed with varying concentrations of petrol in EtOAc. Column chromatography was carried out with silica gel 60 (70–230 mesh, Merck) or aluminium oxide 90 (active neutral, grade III, Merck). Solvents were purified and dried by standard procedures. All IR spectra were run as thin films between sodium chloride discs unless otherwise specified.

Sceletium alkaloid A_4 1a. A soln of 7a (79 mg; 0.81 mmol; 1 equiv) in 96% aqueous EtOH (12 ml) was treated with hydroxylamine hydrochloride (62.5 mg; 0.90 mmol; 5 equiv) and refluxed under N_2 for 22 hr. The mixture was cooled and treated with KOH (7 equiv) in MeOH (1.5 ml). The resulting mixture was evaporated under reduced pressure and twice azeotroped with dry benzene. The residue was filtered through neutral grade III alumina 10g with 50% benzene in EtOAc to give *rac*-1a (35 mg; 60%), m.p. 152–156°[5b] (EtOAc), identical (IR, UV, 100 MHz PMR, MS) with an authentic specimen (Found: M, 324.1830. $C_{20}H_{24}N_2O_2$ requires: M, 324.1837).

Similarly, 7c (100 mg; 0.25 mmol), produced after chromatography as before *rac*-1a (52 mg; 65%), identical as before with an authentic specimen.

3'-Demethoxy sceletium alkaloid A_4 1b. The keto-acetal 7b (216 mg; 0.54 mmol) treated as above, gave after chromatography as before, *rac*-1b (110 mg; 81%) as a chromatographically homogeneous oil, ν_{max} (neat) 750, 785, 1030, 1173, 1245, 1445, 1519, 1572, 1603 and 2900 cm^{-1}; δ (CCl_4) 1.70–3.35 (m, 12H, including an NCH_3 singlet at 2.24), 3.65 (s, OMe), 6.55–7.00 (AA'BB', *p*-methoxyphenyl ring protons), 7.1 (dd, H, J = 8 and 5 Hz, Hx of AMX), 7.41 (dd, H, J = 8 and 2 Hz, Hm of AMX), and 8.36 (dd, H, J = 5 and 2 Hz, Ha of AMX); mass spectrum[14] (chemical ionization 100°) *m/e* (rel intensity) 295 (100, M + 1), 294 (45, M^+), 279 (4, M–CH_3), 251 (13, M–C_2H_5N), 236 (14, M–C_3H_9N); (Found: M, 294.1720. $C_{19}H_{22}N_2O$ requires: M, 294.1732), (Found: C, 77.6; H, 7.32; N, 9.25%. $C_{19}H_{22}N_2O$ requires: C, 77.5; H, 7.5; N, 9.5%).

Similarly, 7d (150 mg; 0.41 mmol), produced after chromatography as before, *rac*-1b (82 mg, 70%) identical in all respects with the compound obtained before.

Annulation products 7a–d.† The pyrroline 4a[5b] (129 mg; 0.59 mmol; 1 equiv) was dissolved in anhyd ether (5 ml) and treated with a sat HCl–ether soln (0.1 ml; 1 equiv HCl) at 0°. The ether was removed under reduced pressure to give the corresponding gummy pyrroline hydrochloride. The hydrochloride was dissolved in anhyd acetonitrile (5 ml), treated with 5a (125 mg, 0.59 mmol, 1 equiv) and refluxed under dry N_2 for 15 hr. The mixture was cooled, diluted with ether (25 ml) and washed successively with 5% $NaHCO_3$ aq (2 × 5 ml) and water (2 × 5 ml). The organic phase was dried ($MgSO_4$) and concentrated to give the *cis*-[7(vi)] annulation product 7a as a chromatographically (tlc)

†The mass spectra of the annulation products 7a–d all showed the stable and diagnostic aryl conjugated pyrrolidinium ion (see Ref. 14) and the resonance stabilised cyclic oxonium ion due to C2 fragmentation of the acetal moiety as prominent or base peaks.

homogeneous oil in quantitative yield; ν_{max} (neat) 803, 1035, 1125, 1248, 1460, 1510, 1605, 1680, 1700 and 2900 cm^{-1}; δ (CCl_4)† 0.65 and 0.66 (two s, 3H, CH_3), 1.07 and 1.12 (two s, 3H, CH_3), 1.12–2.80 (m, 17H, including an NCH_3 singlet at 2.33), 3.15–3.60 (m, 4H, $CH_2CMe_2CH_2$), 3.75–3.77 (two s, 6H, two OCH_3), 4.15–4.40 (m, H, acetal proton), 6.60–6.90 (m, 3H, aromatic) (Found: M, 431.2618. $C_{25}H_{37}NO_5$ requires: M, 431.2671).‡

The pyrroline 4b[2a] (480 mg, 2.5 mmol), was converted to its hydrochloride and treated with 5a (1 equiv) in the same way to produce the *cis*-annulation product[7a,b] 7b (770 mg, 76%), ν_{max} (neat) 786, 1040, 1117, 1255, 1470, 1522, 1618, 1710, 2830 and 2950 cm^{-1}, δ (CCl_4)† 0.65 and 0.67 (two s, 3H, two CH_3), 1.08 and 1.12 (two s, 3H, two CH_3), 1.10–2.60 (m, 15H, including an $-NCH_3$ singlet at 2.34), 2.70–2.80 (d, H, angular proton), 3.10–3.60 (m, 4H, $CH_2CMe_2CH_2$), 3.75 (s, 3H, OCH_3), 4.17–4.35 (m, H, acetal proton), 6.63–7.30 (AA'BB', *p*-methoxyphenyl ring protons) (Found: M, 401.2562. $C_{26}H_{35}NO_4$ requires: M, 401.2566).‡

Pyrrolines 4a and 4b were similarly transformed to the annulation products 7c and 7d by annulation with the enone acetal 5b in 80% and 84% yields respectively. 7c had ν_{max} 760, 790, 1030, 1145, 1255, 1470, 1523, 1595, 1675, 1708 and 2940 cm^{-1}; δ ($CDCl_3$)† 1.40–1.80 (m, 15H including an $-NCH_3$ singlet at 2.40), 2.85 (d, H, angular proton), 3.80–4.00 (m, 10H, two OCH_3, OCH_2CH_2O), 4.70–4.93 (m, H, acetal proton), 6.70–7.00 (m, 3H, aromatic protons), (Found: M − 1, 388.2215. $C_{22}H_{31}NO_5$ requires: M − 1, 388.2203).‡ 7d had ν_{max} 762, 795, 836, 1035, 1140, 1185, 1255, 1465, 1618, 1678, 1710 and 2950 cm^{-1}; δ (CCl_4)† 1.35–2.60 (m, 15H, including two overlapping $-NCH_3$ singlets at 2.30 and 2.37), 2.78 (d, H, acetal proton), 6.65–7.32 (AA'BB', *p*-methoxyphenyl ring protons) (Fouhd: M − 1, 358.2085. $C_{21}H_{29}NO_4$ requires: M − 1, 358.2096).‡

2-(4-Keto-5-phenylsulphinylhexyl)-1,3-dioxolane 10. BuLi in hexane (20.6 ml; 33 mmol BuLi; 1.6 M) was concentrated to a small volume at 0° under vacuum, diluted with dry THF (15 ml), cooled to −25° and treated with diisopropylamine (2.45 ml; 36.2 mmol). The resulting soln of lithium diisopropylamide was added dropwise to a mixture of 9[9] (2.94 g; 14.9 mmol) and hexamethyl phosphoric triamide (6 ml) in dry THF (6 ml) under dry N_2. The resulting deep orange-red soln of the dianion was stirred for 30 min at −25° and treated dropwise with a soln of 2-(2-bromoethyl)-1,3-dioxolane[10] (5.44 g; 30.2 mmol) in dry THF (3 ml) over 20 min. The intensely coloured soln became pale yellow on completion of the addition. The mixture was stirred for an additional 1 hr at −25°, poured into cold sat NH_4Cl aq. (300 ml) and extracted with CH_2Cl_2 (5 × 50 ml). The organic phase was washed once with sat NaCl aq. (75 ml), dried ($MgSO_4$), and concentrated to an oil (9.5 g). Chromatography over silica gel with increasing quantities of ether in petrol produced the pure 10 as a pair of diastereomeric racemates (2.36 g; 63%) and recovered starting material (0.43 g; 15%); ν_{max} 700, 755, 940, 1055, 1140, 1376, 1410, 1448, 1587, 1711, 2890 and 2950 cm^{-1}. The PMR spectrum clearly indicates a pair of diastereomers, δ (CCl_4) 1.19 and 1.30 (two d, J = 3.5 Hz, 3H, CH_3), 1.49–1.70 (m, 4H, CH_2CH_2), 2.30–2.75 (m, 2H, $-CH_2CO-$), 3.45–3.73 (two t, J = 3.5 Hz, H, proton *α* to sulphoxide and keto groups), 3.70–3.97 (m, 4H, OCH_2CH_2O), 4.64–4.83 (m, H, acetal proton), and 7.40–7.67 (m, 5H, aromatic protons); (Found: C, 60.65; H, 6.70; S, 10.90. $C_{15}H_{20}SO_4$ requires: C, 60.78; H, 6.80; S, 10.82%).

6-(1,3-Dioxolan-2-yl)hex-1-en-3-one 5b. The keto-sulphoxide 10 (4.5 g; 15.2 mmol) was dissolved in anhyd CCl_4 (150 ml) and refluxed under dry N_2 for 20 hr. The soln was concentrated to an oil (4.15 g) which was chromatographed over silica gel with increasing quantities of ether in petrol to afford 5b (646 mg; 25%) as a tlc homogeneous, but labile[1] oil; ν_{max} 1030, 1135, 1408, 1612, 1668, 2850 and 2920 cm^{-1}; δ (CCl_4) 1.60–1.78 (m, 4H, CH_2CH_2), 2.48–2.70 (m, 2H, CH_2CO), 3.68–4.00 (m, 4H, OCH_2CH_2O), 4.79 (t, H, acetal proton); 5.60–6.30 (ABX, 3H, $-CH_2-CH-CO-$); (Found: M − 1, 169.0853. $C_9H_{14}O_3$ requires: M − 1, 169.0864).

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†The PMR spectra of the annulation products 7a–d all appeared as superpositions of two partially resolved spectra because these compounds are each formed as a pair of diastereomeric racemates.

‡The annulation products 7a–d were all obtained in a state of good purity and were used directly in the following step of the overall synthesis. They were sensitive to chromatography over silica gel and alumina and to distillation and so could not be obtained in an analytically pure form.

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