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Versatile Synthesis and Reactivity of Tropanes and Related Azabicycloalkanes

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The four 5-alkenyl-1-pyrroline 1-oxide-5-carboxylic esters **1–4** undergo regioselective intramolecular cycloaddition to give the cycloadducts **5–8**, which can be hydrogenolyzed to generate a range of azabicyclic compounds and unusual cyclic amino esters.

The tropane alkaloid family contains a large array of natural products that share a common 8-azabicyclo[3.2.1]octane skeleton (*1–3*). Some representative examples that exhibit interesting biological activity are cocaine (a local anaesthetic and CNS stimulant) (*4*), atropine (reduces the secretion of saliva) (*5*), and scopolamine (intensely poisonous and sedative in small doses) (*6*). The significant bioactivity displayed by these compounds has maintained a continuing interest in the synthesis of these natural products and of their analogues (*7–9*). The structurally related azabicyclo[4.2.1]nonane, anatoxin-a is a potent neurotoxin found in the blue-green microalga *Anabaena flos-aquae* (*10–12*). Until recently, anatoxin-a was the only known naturally occurring alkaloid possessing the azabicyclo[4.2.1]nonane skeleton (*13*). In addition, it exhibits stereospecific agonistic effects at acetylcholine receptors (*14*). These two factors in particular have aroused synthetic interest in this system which has been recently reviewed (*13*).

The intramolecular cycloaddition of alkenyl-nitrones presents a potentially versatile approach to the synthesis of tropane and related systems, and several examples have already been reported (*15–20*). We now describe an investigation of a series of 5-alkenyl-1-pyrroline 1-oxide-5-carboxylic esters **1–4** (*21*). The allyl pyrroline 1-oxide **1** gave the cycloadduct **5** in 79% yield on heating in toluene for 4 days. The reaction was regiospecific and this mode of addition was anticipated. In the cycloaddition of the homologous butenyl pyrroline 1-oxide **2**, a six-membered transition state is clearly favored over a seven-membered one and leads to cycloadduct **6** as the major product, with a minor amount of cycloadduct **7** being formed. The thermal cycloaddition of the higher homologous pentenyl pyrroline 1-oxide **3** occurs as readily as that of the allyl nitrone **1**, and in this case the less-strained transition state affords a 77% yield of

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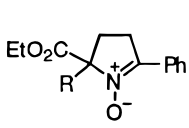
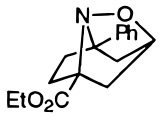
the cycloadduct **8**. The homologous hexenyl nitrone **4** failed to undergo cycloaddition, presumably because both possible transition states are too highly strained.



R
1: $CH_2CH{=}CH_2$
2: $(CH_2)_2CH{=}CH_2$
3: $(CH_2)_3CH{=}CH_2$
4: $(CH_2)_4CH{=}CH_2$



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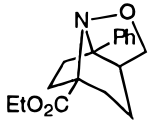

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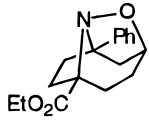

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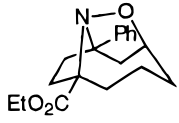

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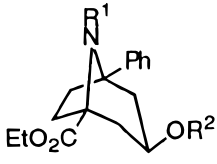
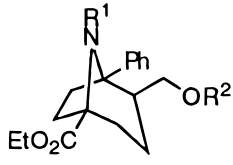
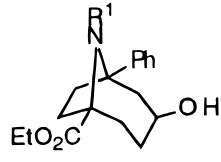
Hydrogenolysis of the cycloadducts **5–8** led to cleavage of the N-O bond in all instances and also the benzylic C-N bond in some. Hydrogenolysis of adduct **5** gave the azabicyclooctane **9** in high yield, but use of high pressure led to the cycloheptane amino ester **10** from either adduct **5** or azabicyclooctane **9**. Methylation of azabicyclooctane **9** gave the homolog **11**, benzoylation of which yielded compound **12**. High pressure hydrogenolysis of cycloadduct **6** was required to generate the azabicyclooctane **13** but further hydrogenolysis of the benzylic C-N bond could not be achieved.



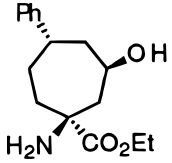
	R^1	R^2
9:	H	H
11:	Me	H
12:	Me	COPh



	R^1	R^2
13:	H	H
14:	Me	H
15:	Me	COPh



	R^1
16:	H
18:	Me



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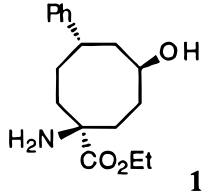

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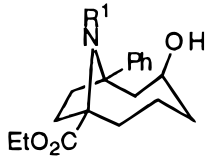

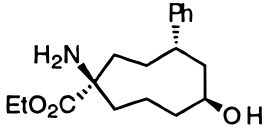

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	R^1
19:	H
21:	Me

Compound **13** was N-methylated to give **14**, and subsequent benzoylation gave **15**. A mixture of the azabicyclononane **16** and the cyclooctane amino ester **17** was obtained from cycloadduct **7**, and compound **16** was methylated to give **18**. The cycloadduct **8** similarly gave a mixture of azabicyclodecane **19** and the cyclononane amino ester **20**, and methylation of **19** gave **21**.

This sequence of reactions thus enables formation of tropane and related homologous azabicycloalkanes. Furthermore, the presence of the phenyl and carboxylic ester substituents offers the possibility of forming some novel cyclic amino esters containing a seven-, eight-, or nine-membered carbocycle. Such compounds could be of use in the synthesis of peptide mimics.

EXPERIMENTAL

*Ethyl 6-phenyl-8-oxa-7-azatricyclo[4.2.1.0^{3,7}]nonane-3-carboxylate **5***

Ethyl 5-allyl-2-phenyl-1-pyrroline-1-oxide-5-carboxylate **1** (300 mg, 1.09 mmol) was heated at reflux in toluene (50 ml) for 4 days, the solvent was removed and the red-brown residue was chromatographed (dichloromethane) to give adduct **5** as colorless crystals (237 mg, 79%), m.p. 98°C. (Found: C, 70.2; H, 7.2; N, 5.1. $C_{16}H_{19}NO_3$ requires C, 70.3; H, 7.0; N, 5.1%.) γ_{max} 209 nm (ε 620). υ_{max} 1720, 1415, 1250 cm^{-1}. ^{1}H NMR spectrum: δ 1.30, t, *J* 7.17Hz, 3H, Me; 1.72, d, *J* 12.03Hz, 1H, H9; 1.94, d, *J* 12.01Hz, 1H, H2; 1.23–2.23, m, 2H, H4 and H5; 2.33–2.52, m, 3H, H4, H5 and H2; 2.65–2.71, m, 1H, H9; 4.21–4.28, q, *J* 7.17Hz, 2H, OCH_2; 4.86–4.90, t, *J* 4.86Hz, 1H, H1; 7.15–7.20, m, 1H, ArH; 7.27–7.32, m, 2H, ArH; 7.49–7.53, m, 2H, ArH. ^{13}C NMR spectrum: δ 14.08, Me; 30.14, CH_2; 34.97, CH_2; 47.23, CH_2; 50.21, CH_2; 62.22, OCH_2; 74.92, C3; 76.32, C6; 81.25, C1; 125.14, 126.24, 128.24, ArH; 147.19, ArC; 173.31, CO. Mass spectrum: 273 (M, 48%), 232 (60), 201 (20), 200 (100), 184 (21), 182 (28), 170 (24), 156 (30), 144 (32), 143 (21), 129 (25), 115 (48), 103 (50), 91 (65), 77 (35).

*Ethyl 6-phenyl-3-oxa-2-azatricyclo[3.3.2.0^{2,6}]decane-1-carboxylate **6** and Ethyl 3-phenyl-8-oxa-7-azatricyclo[4.2.2.0^{3,7}]decane-6-carboxylate **7***

Ethyl 5-(but-3-*en*-1-*yl*)-2-phenyl-1-pyrroline-1-oxide-5-carboxylate **2** (780 mg, 2.72 mmol) in boiling xylene (30 ml) after 2 days similarly gave two major products, which were separated by chromatography (dichloromethane).

(i) Adduct **6** (507 mg, 65%), m.p. 82–84°C (from ethanol/water). (Found: C, 71.3; H, 7.5; N, 4.7. $C_{17}H_{21}NO_3$ requires C, 71.1; H, 7.4; N, 4.9%.) λ_{max} 206 nm (ε 4580). υ_{max} 1715, 1410, 1235, 1175, 885 cm^{-1}. ^{1}H NMR spectrum: δ 1.29, t, *J* 6.93Hz, 3H, Me; 1.67–1.75, m, 2H, H9 and H10; 1.85–1.95, m, 2H, H2 and H3; 2.04–2.15, m, 1H, H9; 2.21–2.31, m, 2H, H10 and H2; 2.36–2.49, m, 1H, H3; 2.59–2.61, m, 1H, H8; 3.53–3.58, m, 1H, H7; 3.89–3.91, d, *J* 6.93Hz, 1H, H7; 4.23, q, *J* 7.2Hz, 2H, OCH_2; 7.14–7.17, m, 1H, ArH; 7.19–7.30, m, 2H, ArH; 7.45–7.52, m, 2H, ArH. ^{13}C NMR spectrum: δ 13.49, Me; 23.45, CH_2; 26.10, CH_2; 27.75, CH_2; 29.57, CH_2; 45.83, CH; 60.83, OCH_2; 71.95, C1; 73.96, C4; 75.45, C6; 124.88, ArH; 126.50, ArH; 128.05, ArH; 144.35, ArC; 173.28, CO. Mass spectrum: 287 (M, 100%), 218 (18).

(ii) Adduct **7** (218 mg, 28%), m.p. 82–84°C. (Found: C, 71.3; H, 7.5, N, 4.7%. $C_{17}H_{21}NO_3$ requires C, 71.1; H, 7.4; N, 4.9%.) λ_{max} 232 nm (ε 5740). υ_{max} 1460,

1375 cm^{-1}. ^1H NMR spectrum: δ 1.26, t, J 7.20Hz, 3H, Me; 1.39–1.50, m, 1H, H2; 1.55–1.62, m, 1H, H9; 1.98–2.37, m, 7H, H9, H10, H4, H5; 2.76–2.83, dd, J_1 7.95 and J_2 12.42Hz, 1H, H2; 4.19, q, J 7.20Hz, 2H, OCH_2; 4.44, t, J 7.95Hz, 1H, H1; 7.15, t, J 5.13Hz, 1H, ArH; 7.21–7.29, m, 2H, ArH; 7.47–7.51, m, 2H, ArH. ^{13}C NMR spectrum: δ 14.08, Me; 21.14, CH_2; 26.33, CH_2; 30.72, CH_2; 35.75, CH_2; 51.00, CH_2; 60.22, OCH_2; 69.03, C6; 74.73, C9; 77.55, C3; 125.37, 126.12, 128.122, ArH; 148.08, ArC; 174.39, 1C, CO. Mass spectrum: 287 (M, 9%), 257 (50, 234 (20), 233 (100), 216 (84), 214 (38), 196 (6), 172 (21), 143 (32), 115 (37), 103 (40), 91 (36), 77 (39), 69 (15).

When the reaction solvent was changed from xylene to toluene, the two regioisomers **6** and **7** were isolated in 84% and 5% yield, respectively.

*Ethyl 1-phenyl-9-oxa-10-azatricyclo[6.2.1.0^{4,10}]undecane-4-carboxylate **8***

Ethyl 5-(pent-4-*en*-1-*yl*)-2-phenyl-1-pyrroline-1-oxide-5-carboxylate **3** (28.8 mg, 0.096 mmol), after reflux for 3 days in toluene (10 ml) gave an oil which was chromatographed (diethyl ether/light petroleum) to give adduct **8** as white needles (22.4 mg, 77%), m.p. 56–57°C. (Found: C, 71.6; H, 7.8; N, 4.4. $C_{18}H_{23}NO_3$ requires C, 71.7; H, 7.7; N, 4.6%.) λ_{max} 217 nm (ε 10420). υ_{max} 1710, 1405, 1240, 1175, 1130, 750, 640 cm^{-1}. ^1H NMR spectrum: δ 1.24, t, J 7.17Hz, 3H, Me; 1.55–1.91, m, 7H, H2, H3, H5, H6, H7; 2.18–2.45, m, 4H, H2, H3, H7, H11; 2.57–2.65, dd, J_1 8.97 and J_2 12.96Hz, 1H, H11; 4.09–4.22, m, 2H, OCH_2; 4.50–4.55, 1H, H8; 7.16, t, J 5.13Hz, 1H, ArH; 7.26, t, J 6.42Hz, 2H, ArH; 7.49, dd, J_1 1.53 and J_2 6.42Hz, 2H, ArH. ^{13}C NMR spectrum: δ 14.18, Me; 18.81, CH_2; 27.65, CH_2; 32.15, CH_2; 32.64, CH_2; 34.97, CH_2; 42.76, CH_2; 60.97, OCH_2; 74.29, C4; 77.21, C8; 79.87, C1; 125.47, 126.32, 128.12, ArH; 147.05, ArC; 175.67, CO. Mass spectrum: 301 (M, 5%), 284 (32), 233 (22), 228 (100), 103 (20), 97 (20), 91 (28), 81 (30), 69 (48), 55 (37), 43 (47).

*Ethyl 3-hydroxy-5-phenyl-8-azabicyclo[3.2.1]octane-1-carboxylate **9***

Method A. Adduct **5** (220 mg, 0.77 mmol) was hydrogenated in absolute ethanol (10 ml) at atmospheric pressure with palladium on charcoal (200 mg, 10%). After 24 h the reaction mixture was filtered and the ethanol removed to leave an oil which was purified using flash chromatography (dichloromethane) to give compound **9** as a colorless oil (181 mg, 82%). ^1H NMR spectrum: δ 1.17, t, 3H, Me; 1.44, m, 2H, H2 and H4; 1.89, m, 2H, H6, H7; 2.11, m, 3H, H2, H4, H6; 2.35, m, 1H, H7; 4.01, m, 1H, C<u>H</u>OH; 4.11, q, 2H, OCH_2; 7.14, m, 1H, ArH; 7.23, m, 2H, ArH; 7.31, m, 2H, ArH. ^{13}C NMR spectrum: δ 14.07, Me; 34.71, CH_2; 36.64, CH_2; 42.76, CH_2; 49.76, CH_2; 61.16, CHOH; 65.23, OCH_2; 66.13, C1; 66.29, C5; 125.10, 126.72, 128.25, ArH; 146.41, ArC; 173.85, CO. Mass spectrum: 276 (M + 1, 5%), 259 (4), 258 (13), 217 (23), 202 (62), 184 (53), 158 (100), 156 (28), 143 (25), 115 (28), 103 (25), 91 (21), 77 (32).

Method B. Adduct **5** (200 mg, 0.73 mmol) was dissolved in ethanol (10 ml). Ammonium formate (100 mg, 1.59 mmol) was added to the solution along with palladium on charcoal (100 mg, 10%). The resulting mixture was heated at reflux for 36 h, the reaction mixture was filtered and the ethanol was evaporated. The residue was partitioned between dichloromethane (10 ml) and water (10 ml). The