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AMIDOALKYLATION IN ORGANIC SYNTHESIS.1. TOTAL SYNTHESIS OF ISORETRONECANOL AND TRACHELANTHAMIDINE

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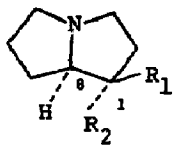
Abstract: The title compounds are prepared in five steps from N-2-bromo ethyl succinimide.

While many physiologically active alkaloids attack the central nervous system, the pyrrolizidine alkaloids exhibit selective toxic action on the liver. This toxicity is associated with the metabolic conversion of the pyrrolizidine nucleus to a pyrrole.[2] Isoretronecanol (1) and trachelanthamidine (2) are representatives of this alkaloid class.



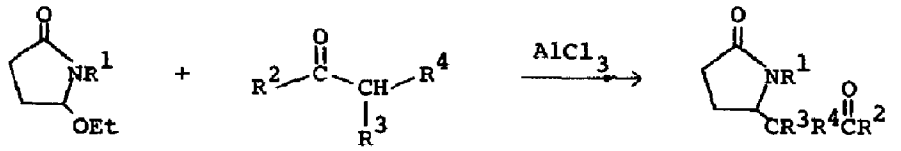
1 $R_1 = CH_2OH$, $R_2 = H$

2 $R_1 = H$, $R_2 = CH_2OH$

A number of imaginative syntheses of 1 and 2 have been reported and are collated in recent reviews.[3] We wish to communicate the most direct and operationally convenient synthesis of 1 and 2 yet reported. The synthetic approach has as its key step the formation of the C1-C8 bond. This is accomplished by an amidoalkylation reaction[4] of 4[5] with either dimethylmalonate or ethyl acetoacetate. Although no amidoalkylation reactions of ω-alkoxy lactams and activated methylene compounds have been previously reported, several examples of amidoalkylation reactions with methylol derivatives of lactams and imides are known.[4] Interestingly, no enamides were isolated under our reaction condition. In an effort to extend the amidoalkylation approach to other members

of the pyrrolizidine alkaloids, a variety of active methylene compounds were tried. The results are shown in Table I.

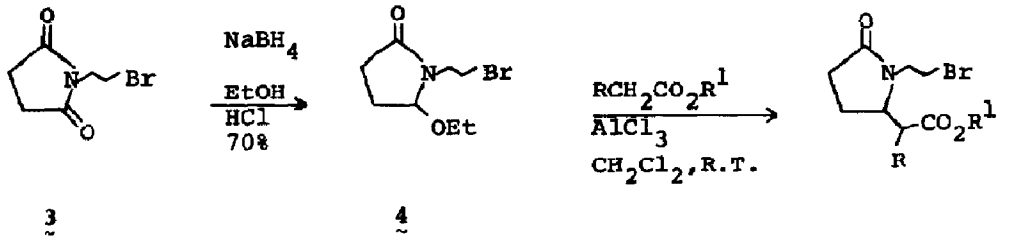
Table I - Amidoalkylation Results



R^1	R^2	R^3	R^4	Yield (%)
H	OCH_3	H	CO_2CH_3	60.5
H	OEt	CH_2CO_2Et	CO_2Et	55
H	OEt	$CH_2CH_2O_2C$		70.5
CH_2CH_2Br	OCH_3	H	NO_2	67
CH_2CH_2Br	OEt	CO_2Et	CO_2Et	51.6
$CH_2CH{=}CH_2$	OCH_3	H	CO_2CH_3	63
CH_2CH_2Br	CH_3	H	$p\text{-}CH_3C_6H_5SO_2$	0
H	OEt	H	$p\text{-}CH_3C_6H_5SO_2$	0
H	OEt	H	CO_2CH_2Ph	52.5

Unfortunately, both β-ketosulfones and β-carboethoxy sulfones failed to yield amidoalkylation products. This failure might be ascribed to the extremely low enol content of both compounds. Pyrolysis of the sulfone moiety would have served to introduce unsaturation at carbons 1 and 2 which is found in more complex pyrrolizidine alkaloids.

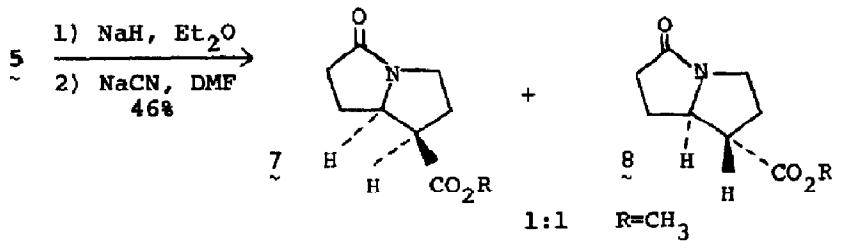
The formation of 1 and 2 from 5 and 6 is accomplished by intramolecular alkylation, decarboxylation and reduction. In the case of amide diester 5 this sequence involves cyclization with sodium hydride in ether at ambient temperature followed by decarbomethoxylation with sodium cyanide in DMF[6] and reduction with lithium aluminum hydride.[8] The isomeric amide esters produced by the decarbomethoxylation step could be easily separated by column chromatography on silica gel. Amide ester 6 could be transformed into a 1:4 mixture of 7[7] and 8[9] by reaction with excess sodium ethoxide in ethanol at ambient temperature for 24 hours. The reduction of 8 with lithium aluminum hydride

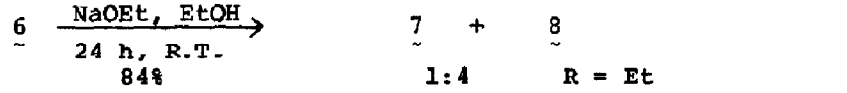


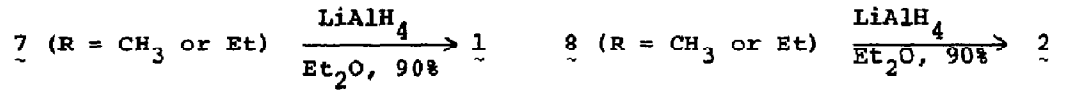
3 4

55% 5 R = CO_2CH_3, R^1 = CH_3

54% 6 R = $COCH_3$, R^1 = Et







provided 2 in 90% yield. The amino alcohol 2 readily formed a picrate with melting point 168-171°C (lit.[10] 172-173°C). Reduction of 7 afforded 1 in 90% yield.

A synthesis that involved similar dissections is a recent contribution by Speckamp and coworkers.[11] The Speckamp synthesis utilizes a clever intramolecular amidoalkylation of an alkene to form the C1-C8 bond. This efficient approach, although somewhat longer than our route, should also be sufficiently flexible to permit the synthesis of a variety of analogs. Related syntheses which create the pyrrolizidine ring system by annelation onto a functionalized pyrrolidine ring include the elegant nitrone strategy of Tufariello,[12] the thiolactam strategy of Pinnick[13] and the N-formyl-L-proline chemistry of

Albonico.[14] The latter approach affords a better overall yield of 1 than our scheme, but does not appear to be applicable to the synthesis of more complex pyrrolizidine alkaloids. Experiments designed to extend the above route to other alkaloid systems are presently in progress.

Acknowledgment

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References and Notes

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5. NMR(δ) 1.22(t, 3H, J=6.5Hz), 1.85-2.80(m, 4H), 3.53(q, 2H, J=6.5Hz), 3.4-4.0(m, 4H), 5.05-5.17(m, 1H). CMR($CDCl_3$) 14.7, 24.3, 28.0, 28.6, 42.1, 61.2, 89.2, 174.3.
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7. Endoester: CMR($CDCl_3$) 22.2, 30.1, 33.7, 41.0, 45.1, 51.6, 63.0, 172.7, 175.3. See footnote 9 for CMR of exo ethyl ester.
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9. NMR(δ) 1.3(t, 3H, J=7Hz), 1.5-2.7(m, 7H), 2.7-4.2(m, 3H), 4.18(q, 2H, J=7Hz). CMR($CDCl_3$) 13.7, 25.3, 30.1, 33.7, 40.3, 49.0, 60.3, 63.7, 171.4, 174.2.
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