The Synthesis of a Cocaine Intermediate *via* a Sodium–Liquid Ammonia Carbon–Carbon σ-Bond Cleavage of an Azabicyclic Succinate-type Ester

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A four-step synthesis of the diester (**1**), based on the sodium–liquid ammonia reductive cleavage of the carbon–carbon σ-bond of the bicyclic compound (**2**) is described; since (**1**) has previously been converted into (±)-cocaine (**3**), the overall synthetic pathway constitutes a total synthesis of this alkaloid.

We report a four-step synthetic route to the intermediate (**1**), the key reaction step of the sequence being the reductive cleavage by sodium in liquid ammonia of the carbon–carbon σ-bond in the succinic ester fragment of the *N*-methyl-7-azabicyclo[2.2.1]heptane diesters (**2**). Since (**1**) has previously been converted into (±)-cocaine (**3**),[1] the overall route constitutes a total synthesis of this alkaloid. The overall strategy is based on the reactions outlined in Scheme 1.

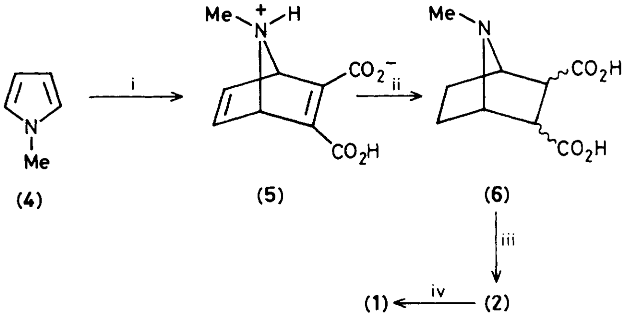
Cycloaddition of *N*-methylpyrrole (**4**) and acetylenedicarboxylic acid in refluxing Et$_2$O following the procedure of Prinzbach *et al.*[2] led to (**5**) in 9% yield. Despite the poor yield, the commercial availability of the starting materials and the simplicity of isolation make this a useful reaction for the preparation of (**5**). Compound (**5**) is of particular interest in that it exists as a zwitterionic mixture of *N*-methyl *syn* and *anti* invertomers.[3]

Although treatment of ethyl pyrrole-1-carboxylate with dimethyl acetylenedicarboxylate led to a high yield of (**8**),[4] in our hands the conversion of the NCO$_2$Et group into the NMe group proved difficult and tedious.

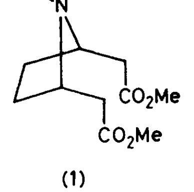
The *syn–anti* diacid mixture (**5**) was hydrogenated with 10% palladium on charcoal as the catalyst to yield the saturated 7-azanorbornane derivatives as a stereoisomeric mixture of diacids (**6**) in 65% yield, m.p. 208—215 °C. The crude diacid mixture (**6**) was refluxed in methanolic HCl and the crude product chromatographed on silica gel (CCl$_4$–Me$_2$CO, 7 : 3, as eluant) to yield a stereoisomeric mixture of diesters (**2**) in 66% yield [^{1}H n.m.r. (CDCl$_3$) δ 1.38 (m), 1.84 (m), 2.23 (s), 2.36 (s), 2.92 (d), 3.48 (m), 3.55 (m), 3.67 (s), 3.70 (s), and 3.72 (s)].

Addition of (**2**) to excess of sodium metal (6—8 equiv.) in distilled liquid ammonia at −78 °C during 5 min followed by quenching with ammonium chloride and chromatography of the crude oil on silica gel (EtOAc as eluant) led to *cis*-2,5-bis(methoxycarbonylmethylene)-1-methylpyrrolidine (**1**) in 50% yield [pale tan oil: ^{1}H n.m.r. (CDCl$_3$) δ 1.51 (m, 2H), 1.98 (m, 2H), 2.25 (m, 5H), 2.66 (m, 4H), and 3.67 (s, 6H)].

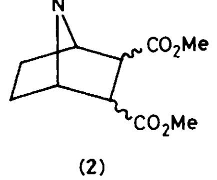
Jung and Rohloff[5] have recently reported that the reductive cleavage of the *trans* dimethyl ester (**2**) by sodium in liquid ammonia (unspecified conditions) led only to trace amounts of (**1**). The difference in yields between this latter report and our work is probably not due to differences in the isomeric compositions of the diesters (**2**) used by the two groups. Gassman and Creary[6] have reported the cleavage of (**9a**) and of (**9b**) by sodium in liquid ammonia to give (**10**). Other examples of the C–C cleavages of vicinal diesters by metals in liquid ammonia have been reported.[7] It might also be noted that dissolving metal reductions (Li or K) of esters in alkylamines can lead to deoxygenation products (alkanes from the alcohol portion) or the parent alcohol. The product which is formed is dependent on the solvent, temperature, metal, and presence of crown ether.[8]



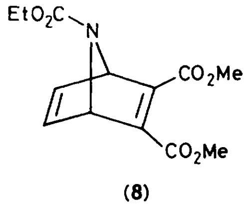
Scheme 1. *Reagents:* i, acetylenedicarboxylic acid, Et$_2$O, reflux, 24 h; ii, H$_2$–Pd on charcoal, 50 lb in^{-2}, 14 h, Parr apparatus; iii, methanolic hydrogen chloride, reflux; iv, Na in liquid ammonia, −78 °C, 5 min, NH$_4$Cl quench.



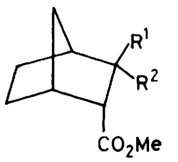
(**1**)



(**2**)

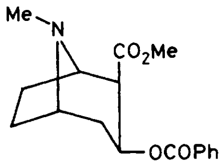


(**8**)

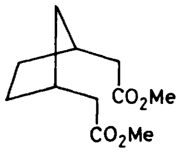


(**9**)

a; R^1 = H, R^2 = CO$_2$Me
b; R^1 = CO$_2$Me, R^2 = H



(**3**)



(**10**)

The factors which favour reductive cleavage of vicinal diesters by alkali metals in liquid ammonia over Bouveault–Blanc reduction, acyloin formation, or possible deoxygenations will be discussed in the full paper.

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