Chloroformate Ester-induced Reductive 1,2-Bond Cleavage of Some 1,2,3,4-Tetrahydro-β-carboline Derivatives

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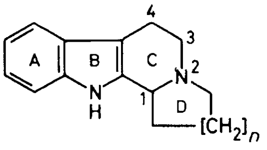
Summary Treatment with a chloroformate ester at −70 °C and subsequent reaction with $NaBH_3CN$ converts 1,2,5,6,11,11b-hexahydro-3*H*-indolo[3,2-*g*]indolizine and derivatives of 1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]-quinolizine cleanly into the corresponding C/D ring-cleaved urethane derivatives; when the order of addition of reagents is reversed in experiments performed at 0 °C, formation of stable substrate–cyanoborane adducts competes with this reaction.

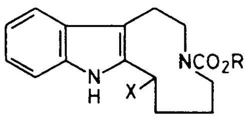
Hydrogenolysis of the 1,2-bond in the tetrahydro-β-carboline nucleus of (**1a**) and (**1b**), or compounds containing one of these ring systems,‡ has been achieved on their *N*(2)-alkyl quaternary salts, either catalytically,[1] or using alkali metal in liquid ammonia,[2–7] or $LiAlH_4$.[3] Attention has also been focussed on 1,2-bond cleavages which concomitantly incorporate functionality at C-1, reactions valuable in indole alkaloid synthesis,[8] of which the very mild *solvolytic* cleavage undergone by *Corynanthe* alkaloids, their derivatives, or analogues, when treated with a chloroformate ester or cyanogen bromide in the presence of ethanol, methanol, or water, is a particularly useful example.[9]



(1)‡

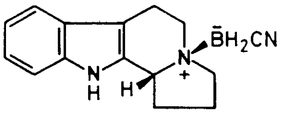
a; *n* = 1

b; *n* = 2



(2)

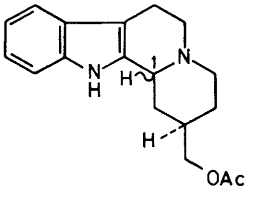
a; X = R′O (R′ = H, Me, Et),
R = Et, Ph
b; X = H, R = Et
c; X = H, R = Ph
d; X = H, R = CH_2Ph



(3)

In connection with a total synthesis of (±)-ϵ_2-dihydromavacurine[10] it was necessary to develop a reaction which combined features of the *hydrogenolytic* and *solvolytic* cleavage reactions, and I now communicate how the range of nucleophiles able to participate in the latter has been extended to include 'hydride.'

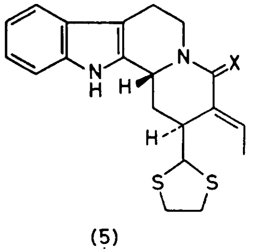
The amine (**1a**)[11] was found to undergo the *solvolytic* C/D ring opening with chloroformate esters ($ClCO_2R$) readily to give the urethanes (**2a**).[12] When $NaBH_3CN$ replaced the hydroxylic reagent (R′OH) in a tetrahydrofuran (THF) solution of (**1a**) prior to the addition (at 0 °C) of $ClCO_2Et$, the reductively cleaved urethane (**2b**) (m.p. 126–127 °C, from $EtOH–H_2O$) was obtained in a 58% yield, but consumption of (**1a**) by conversion into its cyanoborane adduct (**3**) (38%) was highly competitive.§ Similar results were obtained with $ClCO_2Ph$ and $ClCO_2CH_2Ph$. It was found, however, that treatment of (**1a**) with $ClCO_2R$ at −70 °C for 1 h and then



(4)

a; C-1-H-α

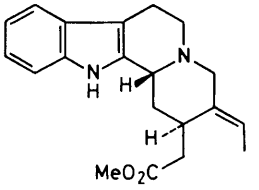
b; C-1-H-β



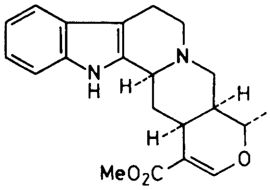
(5)

a; X = H_2

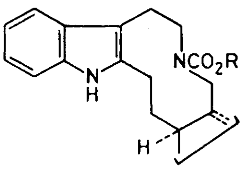
b; X = O



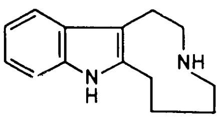
(6)



(7)



(8) R = Ph



(9)

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‡ The ring systems and their states of hydrogenation are those described in the Summary. However, the numbering of the common β-carboline nucleus is used for convenience henceforth in this paper and is given in structure (**1**).

§ When $LiBH_4$ replaced the $NaBH_3CN$ in this experiment, the corresponding (**1a**)–borane adduct was formed to the exclusion of reductive cleavage.

addition of the reducing agent effected clean reductive ring opening with complete suppression of the formation of (**3**) (Table; entries A and B). Derivatives of (**1b**) reacted analogously: thus, the substrates (**4**),[9] (**5a**),[10] (**6**),[13] and (**7**) (tetrahydroalstonine) were converted using $ClCO_2Ph$ into the corresponding urethanes of partial structure (**8**) (Table; entries C—G).

TABLE. Reactions of some tetrahydro-β-carboline derivatives with $ClCO_2R$ and $NaBH_3CN$.

Entry	Substrate[a]	Cleaved product	% isolated yield[b]	M.p./°C[b]
A	(**1a**)	(**2c**)	83	164—165 (Et_2O–petrol)
B	(**1a**)	(**2d**)	82	168 (Et_2O–petrol)
C	(**4a**)	(**8a**)[c]	81	209—210 (EtOAc–petrol)
D	(**4b**)	(**8a**)[c]	85	
E	(**5a**)	(**8b**)[c]	>71[d]	amorphous
F	(**6**)	(**8c**)[c]	76	amorphous
G	(**7**)	(**8d**)[c]	89	amorphous

[a] Racemic, except for (**7**) (naturally derived tetrahydroalstonine). [b] Yields refer to analytically pure material for crystalline products. Compounds (**8b**—**8d**) gave satisfactory accurate mass measurements for M^+ in the mass spectra. [c] Partial structure; remainder of structure is as in substrate. [d] Quoted yield is over the two steps of Bu^i_2AlH reduction and reductive cleavage from (**5b**) (ref. 10).

A molar excess of $ClCO_2R$ and 1·5 mol. equiv. of $NaBH_3CN$ were employed in the experiments using the more reactive substrates (**1a**) and (**4b**), but a larger excess (arbitrarily 10-fold) of $ClCO_2R$ (and, correspondingly, 7 mol. equiv. of $NaBH_3CN$) was required to obtain high yields in the other cases. After the addition of reducing agent (in THF solution), the reaction mixture was allowed to warm to ambient temperature overnight and the products were purified chromatographically after work-up with NaOH solution.

The synthetic potential of this novel reaction is demonstrated in the preparation of the amine (**9**), a compound reported[6] to have diuretic activity and previously obtainable only with difficulty,[6,14] which was formed in essentially quantitative yield by hydrogenolysis of (**2d**) over Pd–C.

The incorporation of deuteride (using $NaBD_3CN$) in (**8a**) from each of the amines (**4**) has been shown by chemical correlation to proceed with stereospecific inversion of configuration.[15]

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