NITROGEN ASSISTED ACETAL RING CLEAVAGE. PART II[‡]. PREPARATION OF SYNTHONS FOR EBURNAMINE-VINCAMINE ALKALOIDS

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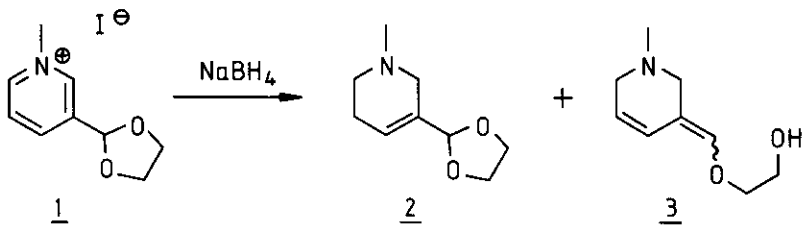
Abstract - The cleavage of cyclic 3-substituted tetrahydropyridine acetals under the modified Polonovski reaction conditions is described. The method was applied to the preparation of a 1-formylindolo[2.3-a]quinolizidine derivative.

In our earlier communication[1] we described a nitrogen assisted cyclic acetal ring opening during the sodium borohydride reduction of 3-substituted pyridinium acetals. Salt 1, for example, yields the enol ether 3 (cis-trans isomers) in addition to the normal reduction product 2 (Scheme 1).



1 2 3

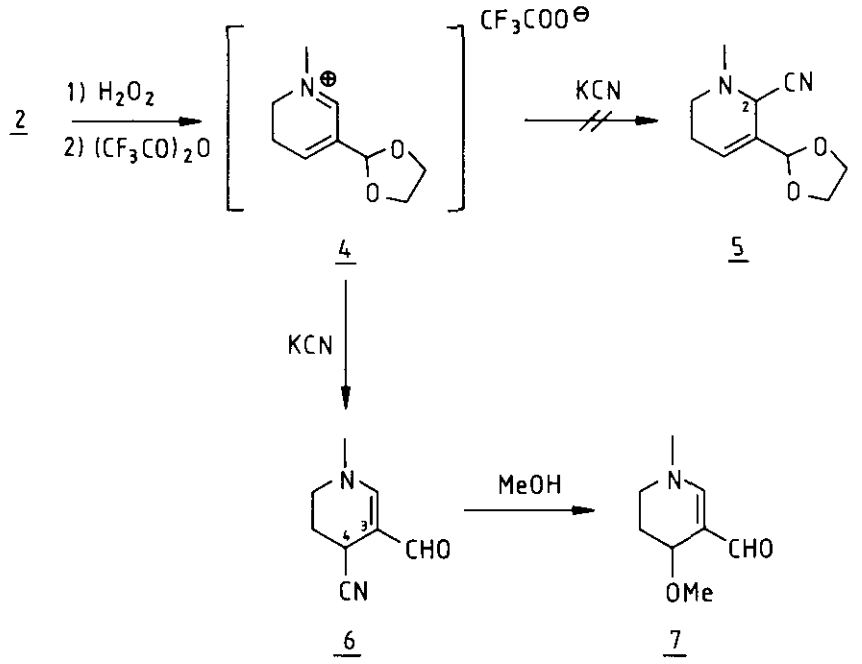
Scheme 1

In this paper we report the behaviour of tetrahydropyridines of type 2 under the modified Polonovski reaction[2] conditions. We found that the acetal group is easily cleaved and thus aldehydes and ketones, which otherwise are susceptible to unwanted side reactions under these conditions, can be utilised for synthetic purposes. These results are applied to the preparation of synthons for indole alkaloid synthesis.

[‡]For Part I, see Ref. 1.

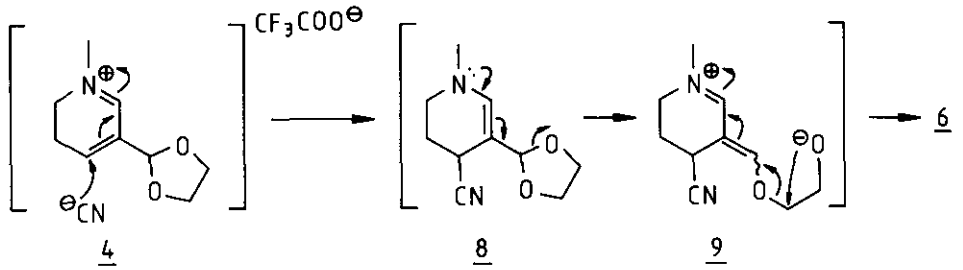
RESULTS AND DISCUSSION

Our attempts to prepare an α-aminonitrile from 2 in the usual manner[3] failed to give the expected product 5, and gave instead the enamine aldehyde (= vinylogous amide) 6[4] with the cyano group in the 4-position.[5] Furthermore, during the column chromatography (silica gel, CH_2Cl_2/MeOH), compound 6 was partly transformed (60%) to a 4-methoxy derivative 7[6] (Scheme 2).



Scheme 2

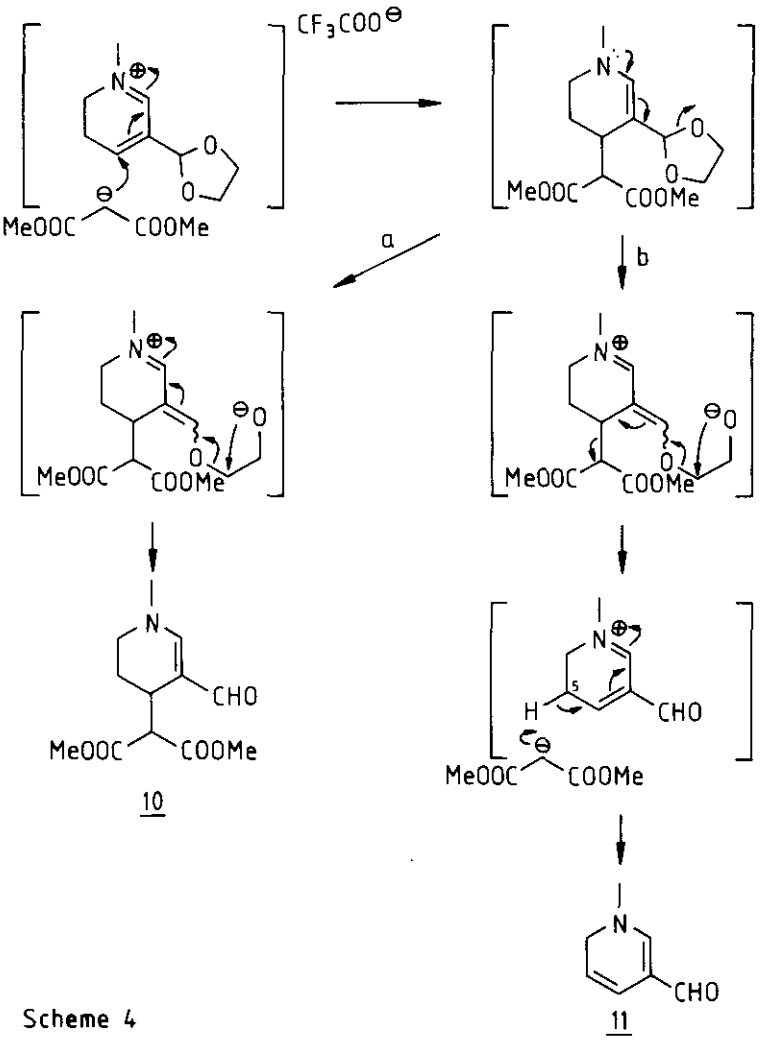
The attack of the cyano group at the 4-position instead of at the 2-position of the iminium species 4 is probably explained by steric reasons. In the cleavage of the acetal group, however, the nitrogen electron pair plays the key role (as in the formation of compound 3 in the $NaBH_4$ reduction of 1[1]). The mechanism for the formation of 6 may be presented as follows (Scheme 3):



Scheme 3

The enamine acetal intermediate 8 is not isolable, because the acetal ring is immediately opened by the effect of the nitrogen lone pair. As there are no hydride ions present to reduce the *iminium species 9, the reaction proceeds to the aldehyde level.*

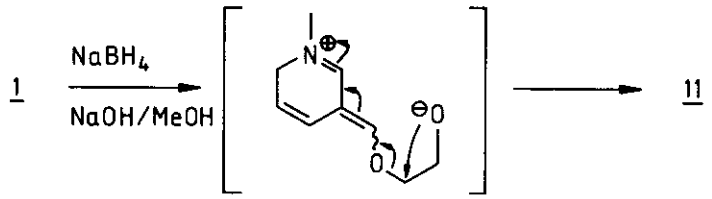
The unexpected formation of 6 (though in low yield) led us to examine the reaction of 4 with other nucleophiles such as malonate anion.[7] And indeed, small amounts of malonate adduct 10[8] were isolated when the iminium species 4 was gently heated with sodium dimethylmalonate in dimethoxyethane (Scheme 4, route a).



Scheme 4

Heating and strongly basic conditions provided the basis for a side reaction, i.e. cleavage of the group introduced at the 4-position and subsequent proton abstraction from the 5-position to *produce a 1,6-dihydropyridylaldehyde 11 (Scheme 4, route b).* The formation of the 1,6-dihydropyridyl aldehyde 11 can also be formulated as a direct proton abstraction from the 5-position of the iminium species 4, followed by the acetal ring cleavage. With sodium methoxide as a nucleophile and/or base the yield of dihydropyridine 11 was about 40%.[9]

The relatively stable compound 11 was also formed (in addition to 2 and 3) in the $NaBH_4$ reduction of 1 (via the iminium enol ether intermediate 12), when the reaction was performed in alkaline conditions (Scheme 5).[10]



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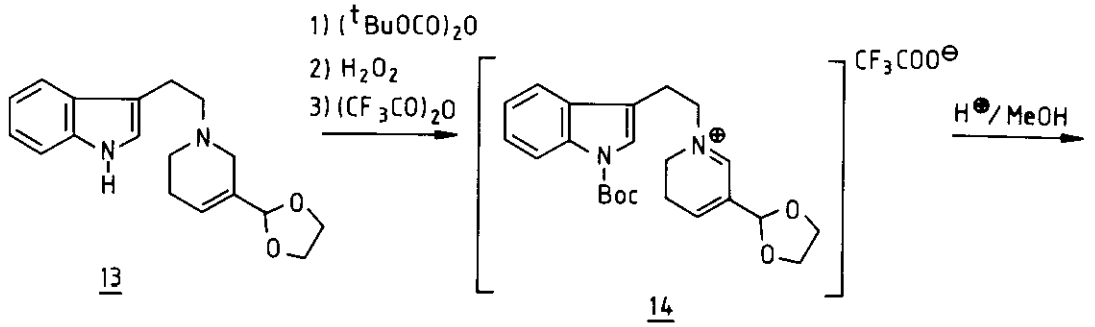
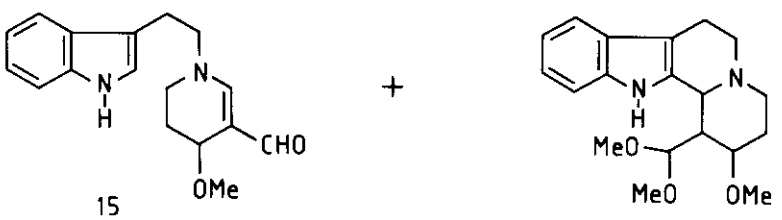
Scheme 5

The facile cleavage of the acetal group was utilised for the preparation of synthons which would lead to eburnamine-vincamine type indole alkaloids. The indole derivative 13[1] was converted to the iminium species 14, which was then subjected to acid induced cyclisation (Scheme 6).



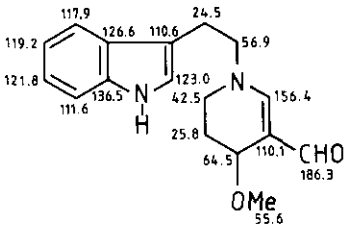
13 14



15 16

Scheme 6

When cyclisation of 14 was performed in methanolic hydrochloric acid and the reaction was stopped prematurely, the expected enamine aldehyde 15[11] was isolated as an intermediate. Its cyclisation product 16[12], in which reacetalisation had occurred, had also been formed in small amounts.



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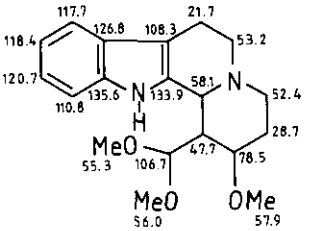

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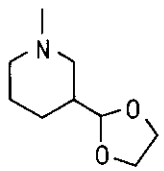
Fig. 1

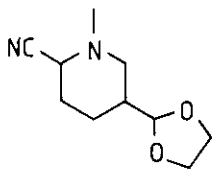
1-Formylindolo[2.3-a]quinolizidines are desired synthons for the preparation of indole alkaloids of eburnamine-vincamine type.[13] Their synthesis is, however, often rather tedious. According to our observations, the normal Wenkert procedure (catalytic hydrogenation of appropriate pyridinium salts, followed by acid induced cyclisation), which has been used successfully for the synthesis of 1-acetylindolo[2.3-a]quinolizidines,[14] turned out to be less satisfactory in the aldehyde case. The present method seems to provide an alternative to overcome these difficulties. The applications of the procedure to the synthesis of indole alkaloids are in progress.

REFERENCES AND NOTES

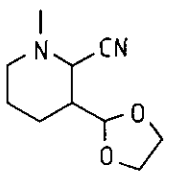
1. M. Lounasmaa and A. Tolvanen, Heterocycles, 1986, 24, 651.
2. M. Lounasmaa and A. Koskinen, Heterocycles, 1984, 22, 1591.
3. A. Koskinen and M. Lounasmaa, Tetrahedron, 1983, 39, 1627.
4. Trapping of the iminium intermediate derived from the piperidine acetal A with cyanide ion has been shown to produce the α-aminonitriles B and C normally (3:1, total yield 80%): see R. Jokela, T.Tamminen and M. Lounasmaa, Heterocycles, 1985, 23, 1735.



A



B



C

5. Compound 6: Yellow oil, yield 20%. IR (ν cm^{-1}, $CHCl_3$): 2280 (w), 1620 (s). ^1H NMR (δ, $CDCl_3$): 8.94 (1H, s), 7.01 (1H, s), 3.00 (3H, s). ^{13}C NMR (δ, $CDCl_3$): 186.0 (d), 156.6 (d), 118.8 (s), 110.4 (s), 47.0 (t), 43.2 (q), 34.5 (d), 23.4 (t). EIMS (70 eV, m/z): 150 (M^+, 60), 124 (52), 122 (100); exact mass: 150.0765 (calc. for $C_8H_{10}N_2O$: 150.0793).

6. Compound 7: Yellow oil, yield 60% (see text). IR (ν cm^{-1}, $CHCl_3$): 1600 (s). ^1H NMR (δ, $CDCl_3$): 8.95 (1H, s), 6.98 (1H, s), 4.39 (1H, m), 3.35 (3H, s), 3.15 (3H, s). ^{13}C NMR (δ, $CDCl_3$): 186.3 (d), 156.6 (d), 110.6 (s), 64.1 (d), 55.8 (q), 44.3 (t), 43.4 (q), 25.8 (t). EIMS (70 eV, m/z): 155 (M^+, 35), 124 (100), 122 (71); exact mass: 155.0947 (calc. for $C_8H_{13}NO_2$: 155.0947).
7. For alkylation of 1,2,5,6-tetrahydropyridine derived α-aminonitriles with nucleophiles see R.F. Chapman, N.I.J. Phillips and R.S. Ward, Tetrahedron, 1985, 41, 5229, and references cited therein.
8. Compound 10: Pale yellow oil, yield 15%. IR (ν cm^{-1}, $CHCl_3$): 1730 (s), 1600 (s). ^1H NMR (δ, $CDCl_3$): 8.83 (1H, s), 6.92 (1H, s), 3.71 (3H, s), 3.69 (3H, s), 3.08 (3H, s). ^{13}C NMR (δ, $CDCl_3$): 186.1 (d), 169.0 (s, 2C), 155.9 (d), 109.8 (s), 53.8 (d), 52.5 (q), 52.1 (q), 45.7 (t), 43.2 (q), 28.0 (d), 23.5 (t). EIMS (70 eV, m/z): 255 (M^+, 11), 240 (28), 124 (100); exact mass: 255.1102 (calc. for $C_{12}H_{17}NO_5$: 255.1107).
9. Compound 11: Reddish brown viscous oil, yield 40%. IR (ν cm^{-1}, $CHCl_3$): 1650 (s), 1590 (s). ^1H NMR (δ, $CDCl_3$): 8.70 (1H, s), 6.81 (1H, s), 6.40 (1H, dd, J = 10.0 and 1.7 Hz), 5.16 (1H, dt, J = 10.0 and 2.6 Hz), 4.24 (2H, AB q, J = 2.6 and 1.7 Hz), 2.95 (3H, s). ^{13}C NMR (δ, $CDCl_3$): 182.7 (d), 156.0 (d), 118.9 (d), 112.3 (d), 109.3 (s), 51.8 (t), 43.1 (q). EIMS (70 eV, m/z): 123 (M^+, 52), 122 (100); exact mass: 123.0679 (calc. for C_7H_9NO: 123.0684).
10. In 1.25 M NaOH (aq MeOH) the yield of 11 was 25%.
11. Compound 15: Brown oil, yield 35% (reaction not completed, see text). IR (ν cm^{-1}, $CHCl_3$): 3300 (m), 2930 (m), 1595 (s). ^1H NMR (δ, $CDCl_3$): 9.02 (1H, br s), 8.70 (1H, s), 6.83 (1H, d), 6.62 (1H, s), 4.36 (1H, m), 3.32 (3H, s). ^{13}C NMR (δ, $CDCl_3$): see Fig. 1. EIMS (70 eV, m/z): 284 (M^+, 1), 252 (76), 144 (90), 143 (65), 130 (100); exact mass: 284.1515 (calc. for $C_{17}H_{20}N_2O_2$: 284.1525).
12. Compound 16: Yellowish brown oil, yield 10% (reaction not completed, see text). IR (ν cm^{-1}, $CHCl_3$): 3300 (m), 2950 (m), 1650 (m). ^1H NMR (δ, $CDCl_3$): 9.82 (1H, br s), 4.81 (1H, br s), 3.81 (1H, m), 3.61 (3H, s), 3.42 (3H, s), 3.38 (3H, s). ^{13}C NMR (δ, $CDCl_3$): see Fig. 1. EIMS (70 eV, m/z): 330 (M^+, 90), 329 (32), 299 (75), 298 (45), 75 (100); exact mass: 330.1937 (calc. for $C_{19}H_{26}N_2O_3$: 330.1944).
13. W. Oppolzer, H. Hauth, P. Pfäffli and R. Wenger, Helv. Chim. Acta, 1977, 60, 1801.
14. E. Wenkert, Pure Appl. Chem., 1981, 53, 1271; E. Wenkert, Heterocycles, 1984, 21, 325.

Received, 27th January, 1986