Communications to the Editor

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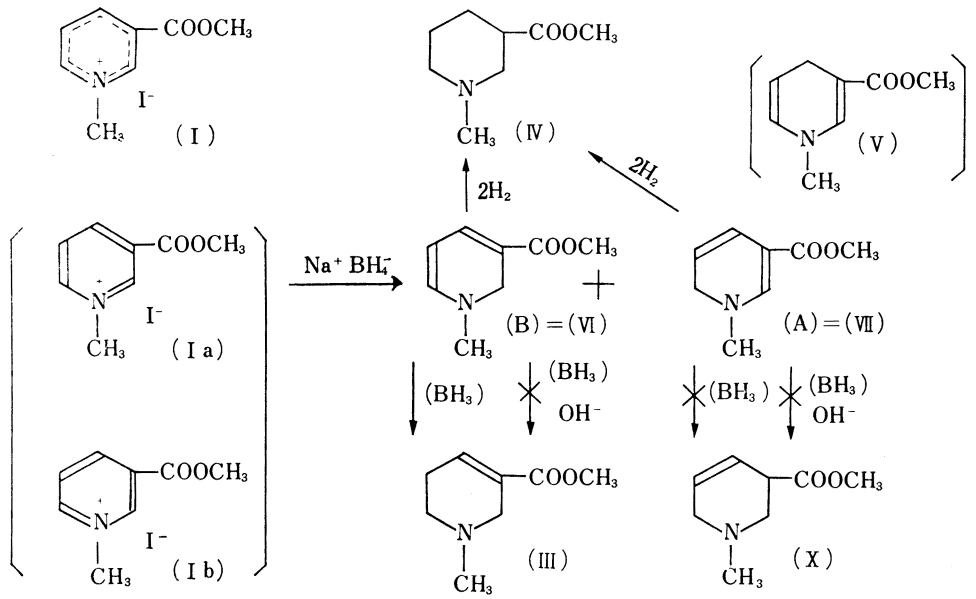
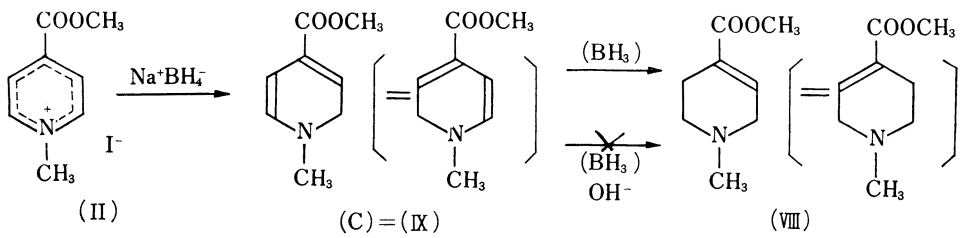
Reduction of 1-Methyl-3- and -4-methyoxycarbonyl Pyridinium Iodide with Sodium Borohydride

In connection with the work[1] on a synthesis of arecoline analogs, the reduction mechanism of 1-methyl-3- (I) and -4-methoxycarbonyl pyridinium iodide (II) with sodium borohydride was studied.

The reaction of (I) with 1.05 mole of $NaBH_4$ in MeOH gave methyl 1,2,5,6-tetrahydro-1-methylnicotinate (arecoline)[1] (III) (yield 34%) and dihydropyridine derivative (A) (yield 28%), unstable yellow oil, b.$p_{4.5}$ 105~112°, UV $\lambda_{max}^{H_2O}$ mμ (log ε): 263 (3.76), 362 (3.84) (*Anal.* Calcd. for $C_8H_{11}O_2N$: C, 62.73; H, 7.24; N, 9.14. Found: C, 62.55; H, 7.73; N, 8.56.), which afforded methyl 1-methylnipecotate (IV), b. p_{16} 86°, on catalytic reduction (PtO_2) with 2 moles of hydrogen. The total yield of the products ((III)+(A)) increased in parallel





1) T. Tsukamoto, N. Kinoshita, A. Andō: Yakugaku Zasshi, to be published in Vol. 82, No. 9 (1962).

with the amount (up to 1 mole) of $NaBH_4$ employed, but the ratio of the yields of (III) and (A) was always almost constant (7:5).

When (I) was reduced with $NaBH_4$ in 0.8*N* NaOH-MeOH (NaOH : 2 mole) solution, (III) was not produced at all and approximately equal amounts of (A) and another dihydropyridine derivative (B), unstable yellow oil, b.$p_{0.1}$ 88~90°, UV $\lambda_{max}^{H_2O}$ mμ (log ε) : 432 (3.76), (*Anal.* Calcd. for $C_8H_{11}O_2N$: N, 9.14. Found : N, 8.81), were obtained, and the latter was reduced catalytically (PtO_2) with 2 moles of hydrogen to (IV). The yield of the mixture, (A)+(B), reached at the maximum when 0.25 mole of $NaBH_4$ was used, however, the ratio of the yields of (A) and (B) was independent of the amount of $NaBH_4$ used.

The significant differences of the UV spectra of (A) and (B) from that of methyl 1,4-dihydro-1-methylnicotinate*[1] (V), yellowish oil, b.$p_{0.2}$ 84°, UV $\lambda_{max}^{H_2O}$ mμ (log ε) : 363 (3.86), indicated that either one of (A) or (B), was 1,2-dihydro derivative (VI) and the other 1,6-dihydro compound (VII). In 1951 Panouse[4] reported that the reduction of (I) with KBH_4 in dilute aqueous alkali solution afforded (III) and 1,2-dihydro compound (VI). However, since (VI) has the longest chromophore among the three possible dihydropyridinine derivatives ((V), (VI), (VII)), (VI)) was assigned to (B), showing the UV absorption maximum at the longest wave length among the three, (A), (B) and (V), and therefore (A) was regarded to have a structure of (VII).*[2]

The reaction of (II) with $NaBH_4$ (1.05 mole) in MeOH gave methyl 1,2,5,6-tetrahydroisonicotinate[1] (VIII) (yield 85%) without producing any dihydro compound and the yield of (VIII) was observed highest when 1 mole of $NaBH_4$ was used. A decrease of the amount of reagent produced less (VIII), recovering more (II). On the contrary, in 0.8*N* NaOH-MeOH (NaOH : 2 mole) solution (II) did not provide (VIII). A very unstable (purification being unsuccessful) pale yellow oil (C), UV $\lambda_{max}^{H_2O}$ mμ : 250~270, 310~330, IR : $\nu_{C=C}$ 1667 cm^{-1}; $\nu_{C=C}$ 1646 cm^{-1}; $\nu_{C=C}$ 1633 cm^{-1}; $\nu_{C=O}$ 1724 cm^{-1} (all in liquid), was the sole product. By analogy with the reduction of (I) and taking account of the spectral data, (C) was presumed to be the 1,2-dihydro (=1,6-dihydro) compound (IX).

The above results lead to the following presumptions in the reaction.

1. In the first step of the reduction by $NaBH_4$ in either MeOH or NaOH-MeOH solution, the nucleophilic attack of the BH_4 anion was taken place on the pyridinium cation to give 1,2- and 1,6-dihydro compounds.
2. In MeOH, the successive reduction of enamine double bond in the dihydro compounds with electrophilic BH_3, formed at the first stage, will occur secondly, giving the corresponding tetrahydro compounds. Thus (II) was converted solely to (VIII). Possible reason for the formation of both (III) and (VII) from (I) was interpreted by the reduction of one of the Kekule's structures (Ia) to 1,2-dihydro compound (VI), followed by the BH_3 reduction, giving the 1,2,5,6-tetrahydro compound (III), while 1,6-dihydro compound (VII) from another Kekule's structure (Ib) was not reduced further to 1,2,3,6-tetrahydro derivative (X), probably because of the presence of the methoxycarbonyl group at the terminal of the enamine.

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*1 Obtained by the $Na_2S_2O_4$ reduction of (I) in aq. Na_2CO_3 solution in the same way as in the preparations of 1-methyl-1,4-dihydronicotinamide[2] (XI) and 1-methyl-1,4-dihydronicotinonitrile[3] (XII), the structures of which were unequivocally verified. The UV spectrum was quite similar to those of (XI), λ_{max} mμ (ε) : 355 (6680), and (XII), λ_{max}^{EtOH} mμ (ε) : 340 (5600).

*2 1-Methyl-1,6-dihydronicotinonitrile[3] was reported to provide UV λ_{max}^{EtOH} mμ (ε) : 240 (5400), 349 (4950) and 1-(2,6-dichlorobenzyl)-4,6-dimethyl-1,2-dihydronicotinamide[5] was shown to have UV λ_{max}^{MeOH} mμ (ε) : 392 (4720).

2) R. F. Hutton, F. H. Westheimer : Tetrahedron, **3**, 73 (1958).
3) K. Schenker, *et al.* : Helv. Chim. Acta, **42**, 1960 (1959).
4) J. J. Panouse : Compt. rend., **233**, 260, 1200 (1951).
5) K. Wallenfels, H. Schüly : Ann., **621**, 215 (1959).

3. In NaOH-MeOH solution, however, BH_3 formed at the first stage being captured by NaOH, reduction of enamine with BH_3, was prevented at the second stage of the reaction and the dihydro compounds remained unchanged.

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Gas Chromatography of the Morphine Alkaloids and the Related Compounds

The microanalytical separation of the comparatively high molecular weight compounds such as steroids and alkaloids by gas chromatography has been very rapidly developed.[1~8]

In the present studies, the gas chromatographic analyses of forty three compounds, including the morphine alkaloids, sinomenine and its derivatives, were carried out in order to obtain the correlation between their structures and their retention times.

The compounds listed in the table gave single sharp peaks, consistent with the absence of decomposition, except for 8,14-dihydroxydihydrocodeinone (XXVIII).*1 The relative retention times were calculated based on that of codeine (XIV) as a reference and the characteristics in the structure were illustrated comparing with dihydrodesoxycodeine D (II).

The retention times were increased as shown in the following cases: 1) opening of C_4~C_5 ether bridge, (II)~(IV), (VI)~(XX), (XXI)~(XXXVII), (XXX)~(XLII); 2) hydroxylation at C_{14}, (I)~(IX), (II)~(VI), (IV)~(XX), (XI)~(XXVI), (XIV)~(XXVII), (XVII)~(XXXII), (XXI)~(XXX), (XXXVII)~(XLII); 3) N-demethylation, (XIV)~(XIX), (XXX)~(XL); 4) acetylation of 14-hydroxy, (VI)~(X), (XXIX)~(XXXI), (XXX)~(XXXVI); 5) oxidation of the axial type hydroxy at C_6-position into the carbonyl,*2 (XI)~(XXI), (XVI)~(XXIV), (XXVI)~(XXX). The retention times were decreased as observed in the following cases: 1) removal of the hydroxy or carbonyl group from C_6-position and the phenolic group from C_4-position, (III) or (XIV)~(I), (XI) or (XXI) or (XVII)~(II), (XXVI) or (XXX) or (XXXII)~(VI), (XXVII) or (XXIX)~(IX), (XXXVII)-(VII) (XXXVI)~(X); 2) methylation or ethylation of C_3- or C_4-phenolic group, (XXXVII)~(XXIV), (XLIII)~(XLI), (XXII)~(XVIII) or (XIV).

*1 This showed also a single sharp peak with the same retention time as that of 14-hydroxycodeinone (XXIX) and it is expected that this compound is dehydrated into (XXIX) in the flash heating step.

1) W.J.A. VandenHeuvel, C.C. Sweeley, E.C. Horning: J. Am. Chem. Soc., **82**, 3481 (1960).
2) *Idem*: Biochem. Biophys. Research Comm., **3**, 33 (1960).
3) C. Chen, C.D. Lantz: *Ibid.*, **3**, 451 (1960).
4) E.O.A. Haahti, W.J.A. VandenHeuvel, E.C. Horning: J. Org. Chem., **26**, 626 (1961).
5) W.J.A. VandenHeuvel, E.O.A. Haahti, E.C. Horning: J. Am. Chem. Soc., **83**, 1513 (1961).
6) S.R. Lipsky, R.A. Landowne: Anal. Chem., **33**, 818 (1961).
7) H.A. Lloyd, H.M. Fales, P.E. Highet, W.J.A. VandenHeuvel, W.C. Wildman: J. Am. Chem. Soc., **82**, 3791 (1960).
8) K. Tsuda, K. Sakai, N. Ikekawa: This Bulletin, **9**, 835 (1961).