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Synthetic Studies in the Alkaloid Field. Part VIII.* The Sodium Borohydride Reduction of 3-Acetyl-1-[2-(3-indolyl)-ethyl]-pyridinium Bromide

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The preparation of three isomeric acetylhexahydroindolo[2,3-*a*]-quinolizines by the sodium borohydride reduction of 3-acetyl-1-[2-(3-indolyl)ethyl]pyridinium bromide, followed by acid-induced cyclization, is described.

On décrit la préparation de trois acétylhexahydroindolo[2,3-*a*]-quinolizines isomères par la réduction du bromure d'acétyl-3 [(indolyl-3)-éthyl-2]-1 pyridinium par le borohydrure de sodium suivie d'une cyclization en milieu acide.

N-Alkylpyridinium salts are reduced by various metal hydrides to dihydro- and/or tetrahydropyridines.[1a–c] Appropriate hydropyridines prepared from 1-[2-(3-indolyl)ethyl]pyridinium salts can be converted by acid-induced cyclization to the corresponding tetracyclic compounds, indolo[2,3-*a*]quinolizines. Wenkert, for example, has used the method in one of his flavopereirine syntheses..[1c]

In connection with our studies [2–7] concerning the preparation of indole alkaloid models we became interested in the easy preparation of isomeric acetylhexahydroindolo[2,3-*a*]quinolizines, of which 3-acetyl-1,4,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizine (*1*) has been shown to be a useful intermediate (synthon) in the preparation of several heterocyclic indole and oxindole alkaloids.[8–12]

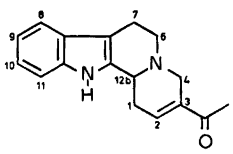
The recently reported [13,14] reduction of 1-substituted pyridinium salts possessing an electron-withdrawing group at position 3 to the corresponding 1,2-, 1,4- and 1,6-dihydropyridines, encouraged us to study its possible application to the synthesis of acetylhexahydroindolo[2,3-*a*]quinolizines. The reduction, combined with acid-induced cyclization, seemed to be ideally suited for the easy preparation of several acetylhexahydroindolo[2,3-*a*]quinolizines, provided that simultaneous reduction of the acetyl group could be avoided. The possible formation of the intermediate 3-acetyl-1,6-dihydropyridine *3* was of special interest because it would permit the preparation of 1-acetyl-3,4,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizine (*4*), difficult to achieve by other methods. Recently Potier *et al.*[15] have prepared some 3,4,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizine derivatives by the modified Polonovski reaction.

The sodium borohydride reduction of 3-acetyl-1-[2-(3-indolyl)-ethyl]pyridinium bromide (*2*)[7,17] in alkaline medium, followed by acid treatment, was selected as the method to be tested. We expected that the 3-acetyl group would survive the reaction owing to the low reactivity of vinylogous amide units during sodium borohydride reduction.

RESULTS

Sodium borohydride reduction of *2* [7,17] in 1 % NaOH-MeOH at −70 °C, followed by acid treatment, afforded a mixture of three main products (A, B and C), which were separated by preparative layer chromatography.

* Part VII. Lounasmaa, M. and Jokela, R. *Tetrahedron. In press.*



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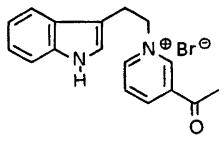

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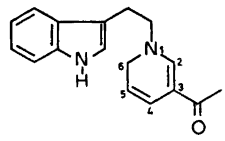

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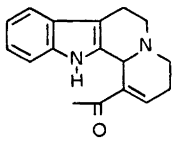

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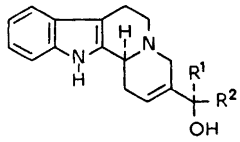
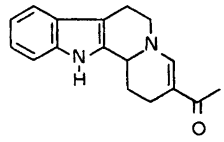


5 R^1 = Me ; R^2 = H

6 R^1 = H ; R^2 = Me



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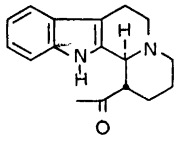

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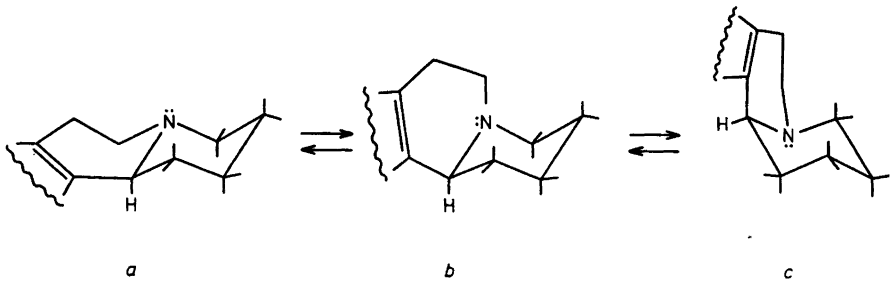
Product A, obtained in 30 % yield, was characterized as 3-acetyl-1,4,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizine (*1*). The double bond in the D ring was fixed at the 2,3-position owing to the intense peak at *m/e* 170 in the mass spectrum of product A (retro Diels-Alder process). The presence of the C=O stretching vibration at 1655 cm^{-1} (α,β-unsaturated ketone) in the IR spectrum indicates that the acetyl group is at C-3 and not at C-1, the only plausible alternative. Moreover, the physical and spectral data found for product A are very similar to those indicated for *1* prepared by a different method.[8]

Reduction of product A with lithium tri-*t*-butoxyaluminium hydride afforded the diastereoisomeric mixtures of 3-(1-hydroxyethyl)-1,4,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizines *5* and *6* in nearly quantitative yield. Thus a new short synthesis (*cf.* Refs. 7 and 16) of this useful indole alkaloid synthon, the diastereoisomeric mixtures of *5* and *6*, was available. Moreover, the transformation of product A to the diastereoisomeric mixtures of *5* and *6* furnishes supplementary evidence of the presence of the acetyl group at C-3 in product A.

Product B, obtained in 7 % yield, turned out be identical with the recently described 3-acetyl-1,2,6,7,12,12b-hexahydroindolo-[2,3-*a*]-quinolizine (*7*).[7]

Product C, obtained in 12 % yield, was characterized as 1-acetyl-3,4,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizine (*4*). Catalytic hydrogenation of product C afforded in nearly quantitative yield a sample of *8*, which proved to be identical with *8* obtained by catalytic hydrogenation of *2* [7,17] followed by acid-induced cyclization.[17] This confirms the presence of the acetyl group at C-1. The double bond in the D ring of compound C was fixed at the 1,2-position on the basis of several experimental findings. First, owing to the strong deshielding effect of the double bond, the ^1H NMR signal of the H-12b appears at δ 5.15. Secondly, the absence of an intense peak at *m/e* 170 in the mass spectrum of product C eliminates the only plausible alternative structure, the 2,3-double bond isomer. The 2,3-double bond isomer is also excluded by the presence of the C=O stretching vibration at 1640 cm^{-1} (α,β-unsaturated ketone) in the IR spectrum.

Compound *8* can exist in a conformational equilibrium by nitrogen inversion and *cis*-decalin type ring interconversion (Scheme 1; only one enantiomer is illustrated). Ring C is assumed to be in the half chair conformation



a *b* *c*

Scheme 1.

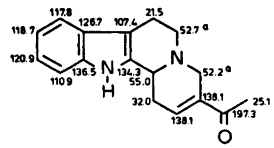
and only the chair forms of ring D are considered. A similar conformational analysis can be presented for compounds *1*, *4* and *7*, considering ring D to be in different half chair forms.

The presence of the so-called Bohlmann bands [18] in the IR spectra of compounds *1* and *8* indicates that conformation *a*, which means *trans*-quinolizine juncture of C/D rings, dominates the conformational equilibrium between *a*, *b*, and *c* (Scheme 1). On the other hand, the absence of the Bohlmann bands in the IR spectrum of compound *4* suggests the preponderance of conformation *c* (the contribution of conformer *b* is considered to be negligible). A similar conclusion reached on the basis of the absence of the Bohlmann bands in the IR spectrum of compound *7* would be less valid because C-4 is trigonal. On the contrary, a study of the nonbonded interactions of each conformer of compound 7, made with the aid of Dreiding models, indicates the preponderance of conformer *a* in the conformational equilibrium.

The preponderance of conformation *a* in the conformational equilibrium of compounds *1* and *8* is also supported by ^{1}H NMR spectroscopy. The absence of any signal downfield from δ 3.9 that could be assigned to the H-12b is characteristic of conformation *a* (*trans*-quinolizine juncture).[19–21]

The structures proposed for compounds *1*, *4*, *7*, and *8* were confirmed by ^{13}C NMR spectral analysis. The fully proton-decoupled spectra of *1*, *4*, *7*, and *8*, taken in $CDCl_3$ (*1* in DMSO-d_6), showed the chemical shifts depicted on the formulas. The proper shift assignments were confirmed by single-frequency, off-resonance decoupled (sford) spectra and by comparison with earlier shift assignments.[4–6,22,23]

The chemical shifts found for C-7 and C-4 of compound *4* (17.0 and 41.9 ppm, respectively) support the strong contribution of conformer *c* to the conformational equilibrium. A study of the nonbonded interactions of conformer *a* of compound *4*, made with the aid of Dreiding models, reveals a strong interaction between



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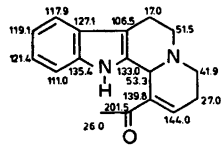

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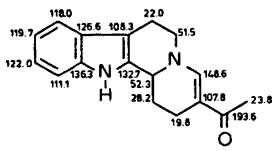

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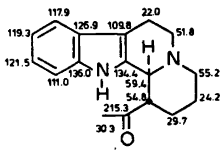

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the C-1 functional group and the N-12 hydrogen and/or lone electron pair. The surprisingly low shift value found for C-4 reflects, in addition to the involvement with C-7, the influence of an endocyclic homoallyl effect.[22]

CONCLUSIONS

The present reaction constitutes a novel and short synthesis of the useful indole and oxindole alkaloid synthon, 3-acetyl-1,4-6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizine (*1*).

To our knowledge, this is the first time that a 1,2,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizine derivative has been prepared by metal hydride reduction, and a novelty in the preparation of vallesiachotamine models has thus been achieved.

Although the yield of compound C is relatively low (12 %), its formation is of unusual interest because the present method is one of the very few procedures permitting the preparation of the 3,4,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizine nucleus. Applications of the method to the syntheses of alkaloids of eburnamine type can be predicted.

EXPERIMENTAL

The IR spectra were measured on a Perkin-Elmer 457 apparatus and the UV spectra on a Beckman ACTA M IV apparatus. The ^{1}H NMR spectra were taken either with a Varian T-60 instrument or with a Jeol JNM FX-100 instrument and the ^{13}C NMR spectra with a Jeol JNM FX-100 instrument operating at 25.20 MHz in the Fourier transform mode. TMS was used as internal standard. The mass spectra were recorded on an Hitachi-Perkin-Elmer RMU-6E Mass Spectrometer at 75 eV using direct sample insertion into the ion source, whose temp. was 150 – 160 °C. The melting points were determined on a Kofler micro hot stage and are uncorrected.

Synthesis of compounds 1, 7 and 4. 3-Acetyl-1-[2-(3-indolyl)-ethyl]pyridinium bromide *2*[7,17] (700 mg) was added during 20 min into a suspension of $NaBH_4$ (200 mg) in 20 ml of 1 % NaOH-MeOH at – 70 °C under nitrogen. After 45 min 200 ml of water was added and the resulting mixture extracted several times with dichloromethane. The combined dichloromethane extracts were added to 30 ml of MeOH saturated with dry HCl gas and the resulting mixture stirred overnight. Saturated $NaHCO_3$ solution was added, the dichloromethane layer separated and the water phase extracted several times with dichloromethane. The combined dichloromethane fractions were washed with water, dried over Na_2SO_4, and evaporated under vacuum. Crude yield 418 mg (77 %). The mixture was fractionated by preparative layer chromatography [Merck 60 PF 254 silica gel ($CHCl_3$/acetone; 5/4) (activation 1 h 110 °C)] affording three main components A (R_F 0.50), B (R_F 0.33) and C (*Rf* 0.13).

3-Acetyl-1,4,6,7,12,12b-hexahydroindolo[2,3-a]-quinolizine 1. Compound A. Yield 162 mg (30 %). M.p. 213 – 214.5 °C (MeOH) (lit.[8] 205 °C). IR (KBr): NH 3330 (s), Bohlmann bands 2820 (m) and 2760 (m), C=O 1655 (s) cm^{-1}. UV [EtOH 94 % (log ε)] λ_{max} 226 (4.66), 273 (3.92), 281 (3.93) and 289 (3.87) nm. λ_{min} 252, 276 and 287 nm. ^{1}H NMR (100 MHz, $CDCl_3$/DMSO-d_6; 1/1) δ 2.30 (3 H, s, CH_3CO) and 10.40 (1 H, br s, NH). MS [IP 75 eV; *m/e* (% rel. int.)]: 266 (100, M), 265 (32), 170 (98), 169 (90).

3-Acetyl-1,2,6,7,12,12b-hexahydroindolo[2,3-a]-quinolizine 7. Compound B. Yield 38 mg (7 %). M.p. 130 – 134/170 – 180 °C (MeOH). IR, UV, ^{1}H NMR, MS and TLC were identical with those of the sample described earlier (Ref. 7 compound *7*).

1-Acetyl-3,4,6,7,12,12b-hexahydroindolo[2,3-a]-quinolizine 4. Compound C. Yield 65 mg (12 %). M.p. 164 – 165.5 °C (MeOH). IR (KBr): NH 3370 (s), C=O 1640 (s), C=C 1630 (m) cm^{-1}. UV [EtOH 94 % (log ε)] λ_{max} 225 (4.68), 272 (3.93), 281 (3.94) and 290 (3.89) nm. λ_{min} 251, 277 and 287 nm. ^{1}H NMR (100 MHz, $CDCl_3$) δ 2.50 (3 H, s, CH_3CO), 5.15 (1 H, br s; H-12*b*) and 8.30 (1 H, br s, NH). MS [IP 75 eV, *m/e* (% rel. int.)]: 266 (100, M), 265 (38), 251 (38), 223 (62).

3-(1-Hydroxyethyl)-1,4,6,7,12,12b-hexahydro-indolo[2,3-a]quinolizines 5 *and* 6. A mixture of 32 mg of compound A (*1*) and 80 mg of LiAl(*t*-BuO)$_3$H in dry THF was stirred overnight under nitrogen. Water was added and the THF evaporated under vacuum. The residue was extracted several times with dichloromethane. The combined dichloromethane extracts were washed with water, dried over Na_2SO_4, and evaporated under vacuum. Crude yield 29 mg (90 %). M.p. 210 – 215 °C (MeOH). IR, ^{1}H NMR, MS and TLC were identical with those of the sample described earlier (Ref. 7 compounds *3a* and *3b*).

1α-Acetyl-1,2,3,4,6,7,12,12bα-octahydroindolo-[2,3-a]quinolizine 8. Catalytic hydrogenation (Pd/C 10 %) of compound C (*4*) in abs. EtOH yielded *8* in nearly quantitative yield. M.p. 172 – 173 °C (PrOH) (lit.[17] 171 – 173 °C). IR (KBr): NH 3360 (s), Bohlmann bands 2820 (m), 2760 (m), C=O 1700 (s), C=C 1620 (w) cm^{-1}. ^{1}H NMR (100 MHz, $CDCl_3$) δ 2.29 (3 H, s, CH_3CO), 3.86 (1 H, d, *J* 10 Hz, H-12b) and 7.84 (1 H, br s, NH). MS [IP 75 eV; *m/e* (% rel. int.)]: 268 (100, M), 267 (75), 225 (36), 197 (80), 184 (12), 170 (52), 169 (54).

Catalytic hydrogenation (Pd/C 10 %; Et_3N) of *2*,[7,17] followed by acid-induced cyclization,

yielded a sample of *8*, which proved to be identical (mixed m.p., IR, ^{1}H NMR, MS and TLC) with *8* described above.

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