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 borohydride de sodium suivie d'une cyclisation en milieu acide.

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

In connection with our studies 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 (I) has been shown to be a useful intermediate (synthon) in the preparation of several heterocyclic indole and oxindole alkaloids.

The recently reported 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. have prepared some 3,4,6,7,12,12b-hevhydroindolo[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) 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 vinylous amide units during sodium borohydride reduction.

RESULTS

Sodium borohydride reduction of 2 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.
Product A, obtained in 30 % yield, was characterized as 3-acetyl-1,4,6,7,12,12b-hexahydroindol[2,3-α]quinalzine (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-ter-butoxylaluminium hydride afforded the diastereoisomeric mixtures of 3-(1-hydroxyethyl)-1,4,6,7,12,12b-hexahydroindol[2,3-α]quinalzines 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 to be identical with the recently described 3-acetyl-1,2,6,7,12,12b-hexahydroindol-[2,3-α]-quinolizine (7).⁷

Product C, obtained in 12 % yield, was characterized as 1-acetyl-3,4,6,7,12,12b-hexahydroindol[2,3-α]quimalzine (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 2,¹⁷ followed by acid-induced cyclization.¹¹ 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 'H 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.
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 in the IR spectra of compounds 1 and 8 indicates that conformation a, which means trans-quinolizinizing juncture of C/D rings, dominates the conformational equilibrium between a, b, and c. 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 conformation a in the conformational equilibrium.

The preponderance of conformation a in the conformational equilibrium of compounds 1 and 8 is also supported by ¹H 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-quinolizinizing juncture).

The structures proposed for compounds 1, 4, 7, and 8 were confirmed by ¹³C NMR spectral analysis. The fully proton-decoupled spectra of 1, 4, 7, and 8, taken in CDCl₃ (I in DMSO-d₆), 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.

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...
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.

CONCLUSIONS

The present reaction constitutes a novel and 
short synthesis of the useful indole and oxindole 
alcohol synthons, 3-acetyl-1,4,6,7,12,12b-hexa-
 hydroidindolo[2,3-a]quinolizine (I).

To our knowledge, this is the first time that 
a 1,2,6,7,12,12b-hexahydroindolo[2,3-a]quinoli-
zine derivative has been prepared by metal 
hydride reduction, and a novelty in the pre-
paration 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-hexahydroidindolo[2,3-a]quinoli-
zine nucleus. Applications of the method to 
the synthesis 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 'H NMR 
spectra were taken either with a Varian T-60 
instrument or with a Jeol JNM FX-100 instru-
ment and the 13C 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 re-
corded 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 deter-
mined on a Kofer micro hot stage and are un-
corrected.

Synthesis of compounds 1, 7 and 4. 3-Acetyl-
1-[2-(3-indoly)-ethyl]pyridinium bromide 2,4,6,7 
(700 mg) was added during 20 min into a 
suspension of NaBH₄ (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 dichlorometh-
ane extracts were added to 30 ml of MeOH 
saturated with dry HCl gas and the resulting 
mixture stirred overnight. Saturated NaHCO₃ 
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 Na₂SO₄, and evaporated under 
vacuum. Crude yield 418 mg (77 %). The 
mixture was fractionated by preparative layer 
chromatography [Merek 60 PF 254 silica gel 
(CHCl₃/acetic; 5/4) (activation 1 h 110 °C)] 
affording three main components A (RF 0.50), 
B (RF 0.53) 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. 205 °C).
IR (KBr): NH 3330 (s), Bohllmann bands 2820 
(m) and 2760 (m), C=O 1655 (s) cm⁻¹. UV 
[EtOH 94 % (log ε) λmax 226 (4.66), 273 (3.92), 
281 (3.93) and 289 (3.87) nm, λmin 252, 276 and 
287 nm. 'H NMR (100 MHz, CDCl₃/DMSO-d₆; 
1/1) δ 2.30 (3 H, s, CH₃CO) 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 
IR, UV, '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=O 1630 (m) 
cm⁻¹. UV [EtOH 94 % (log ε) λmax 225 (4.68), 
272 (3.93), 281 (3.94) and 290 (3.89) nm, λmin 
251, 277 and 287 nm. 'H NMR (100 MHz, 
CDCl₃) δ 2.50 (3 H, s, CH₃CO), 5.15 (1 H, br s; 
H-12b) 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 (I) and 80 mg of LiAlH₄ 
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 
was washed with water, dried over Na₂SO₄, and 
evaporated under vacuum. Crude yield 29 mg 
NMR, MS and TLC were identical with those 
of the sample described earlier (Ref. 7 
compounds 3a and 3b).

1a-Acetyl-1,2,3,4,6,7,12,12b-octahydroindolo-
[2,3-a]quinolizine 8. Catalytic hydrogenation 
(Pd/C 10 %) of compound C (4) in abs. EtOH 
172–173 °C (PrOH) (lit. 171–173 °C). IR 
(KBr): NH 3360 (s), Bohllmann bands 2820 
(m), 2760 (m), C=O 1700 (s), C=O 1620 (w) 
cm⁻¹. 'H NMR (100 MHz, CDCl₃) δ 2.29 (3 H, 
s, CH₃CO), 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 %; Et₃N) of 
2,17 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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REFERENCES


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