EASY PREPARATION OF INDOLOQUINOLIZIDINE ENAMINES

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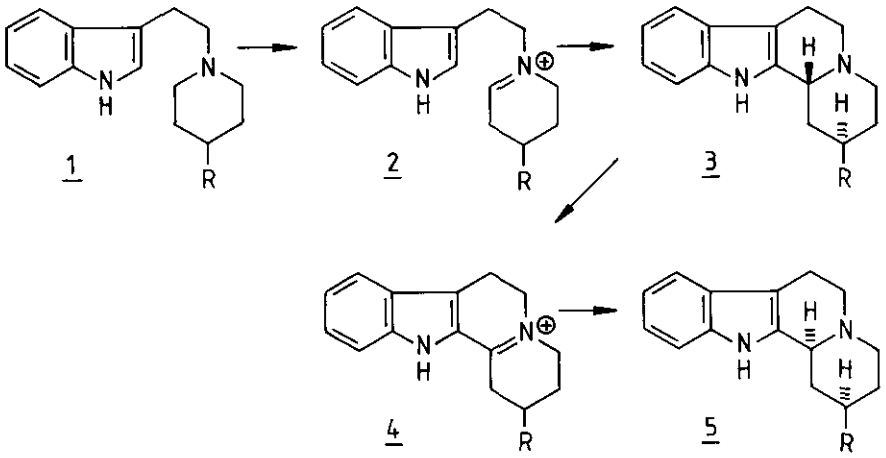
Abstract - A new and efficient synthesis of indoloquinolizidine enamines, including the highly valuable Wenkert's enamine (9a), is described. The behaviour of enamines (9a) and (9b) under reductive conditions was investigated.

We recently became interested[1] in the stereochemistry of some 2-substituted indoloquinolizidine (= indolo[2,3-a]quinolizidine) derivatives prepared from 4-substituted 1-[2-(3-indolyl)ethyl]piperidines by mercuric acetate oxidation[2-5] [1. 10 eq. $Hg(OAc)_2$, 5% aq. AcOH, 100°C, 1 h; 2. H_2S] followed by $NaBH_4$ treatment (hereafter called the "classical procedure"). In that connection we equally applied the modified oxidation conditions of Fujii et al.[6,7] [33% aq. EtOH, 3 eq. $Hg(OAc)_2$, 3 eq. disodium edetate (EDTA-2Na), 3 h reflux]. To our surprise, the stereochemistry of the major product prepared by the Fujii oxidation method followed by $NaBH_4$ treatment (hereafter called the "Fujii procedure") was different from that obtained by the classical procedure.

Considering these apparently contradictory results, we reasoned that in the classical procedure the main product was formed by the initial oxidation of the piperidine derivative (1) to the corresponding iminium salt (2) followed by cyclization to the tetracyclic indoloquinolizidine derivative (3). Only

a small amount of the indoloquinolizidine derivative (3) was further oxidized to the iminium salt (4) which was then reduced by $NaBH_4$ to compound (5) (Scheme 1).

In the Fujii procedure, most, if not all, of the initially formed indoloquinolizidine derivative (3) was oxidized to the iminium salt (4), which was then reduced by $NaBH_4$ to compound (5) (Scheme 1).



Scheme 1

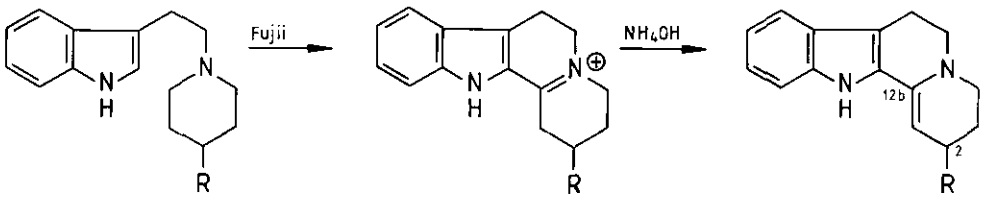
As iminium salts of type (4) are easily converted by base to the corresponding enamines, it seemed to us that the Fujii oxidation method might be ideally suited for an easy preparation of indoloquinolizidine enamines, which have proven to be useful intermediates in the synthesis of various indole alkaloids and their derivatives (vide infra). In this paper we describe the results obtained.

RESULTS AND DISCUSSION

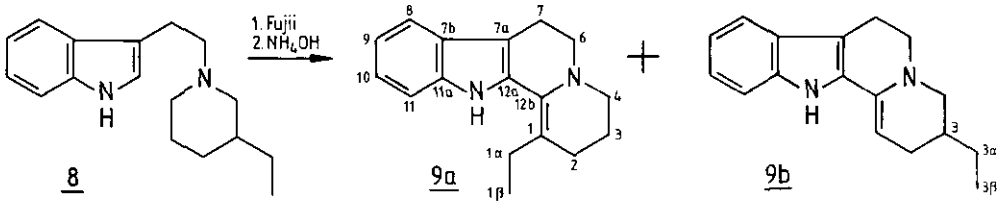
We started our investigation using the unsubstituted piperidine derivative (6a).[5,8,9] The Fujii oxidation method (cf. Experimental), followed by

basification of the reaction mixture with aqueous ammonia, afforded the indoloquinolizidine enamine (7a) in almost quantitative yield.[10-13] Similarly, oxidation of the 4-methylpiperidine derivative (6b)[9] (symmetrically substituted piperidine ring) led to the corresponding indoloquinolizidine enamine (7b) in practically quantitative yield (Scheme 2).

We then turned our attention to the 3-ethylpiperidine derivative (8)[5,14,15] (unsymmetrically substituted piperidine ring). The Fujii oxidation method, followed by basification, led to a reaction mixture containing two major products. The separation of the components by flash chromatography on silica gel afforded indoloquinolizidine enamines (9a)[12,16-19] (Wenkert's enamine) and 9b[19,20] in about 1:3 ratio (Scheme 3).



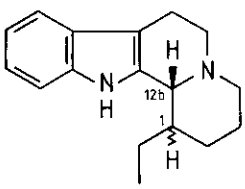
Scheme 2

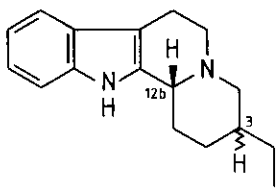


Scheme 3

In order to study the behaviour of the indoloquinolizidine enamines (9a) and (9b) under reductive conditions, they were treated both with H_2/PtO_2 (using basic conditions to avoid the iminium ion formation) and with $NaBH_4$.

Catalytic reduction and $NaBH_4$ treatment of the indoloquinolizidine enamine (9a) both yielded the indoloquinolizidine derivative (10a)[14] [C(1)H-C(12b)H cis]. The isomeric indoloquinolizidine derivative (11a) [C(1)H-C(12b)H trans] was detected in trace amounts.[21] In contrast to these results, the catalytic reduction of the indoloquinolizidine enamine (9b) led to an approximatively 1:1 mixture of indoloquinolizidine derivatives (10b)[14] [C(3)H-C(12b)H cis] and (11b)[14] [C(3)H-C(12b)H trans] in quantitative yield, whereas the $NaBH_4$ treatment afforded almost exclusively indoloquinolizidine derivative (11b).





10a C(1)H-C(12b)H cis
11a C(1)H-C(12b)H trans

10b C(3)H-C(12b)H cis
11b C(3)H-C(12b)H trans

CONCLUSIONS

A new and efficient synthesis of indoloquinolizidine enamines has thus been developed. The procedure gives the enamines in high yields in one step from the corresponding piperidine derivatives, which in turn are easily prepared from tryptophyl bromide and appropriately substituted pyridine derivatives in two steps (salt formation and reduction). In our opinion, the present procedure is the méthode de choix in the preparation of indoloquinolizidine enamines deriving from symmetrically substituted piperidines. Because of its shortness and simplicity, the procedure is also highly useful for the synthesis of indoloquinolizidine enamines having a substituent in the 1-

or 3-position [deriving from 3-substituted piperidines (unsymmetrical substitution), e.g., for the highly valuable Wenkert's enamine (9a) and its regioisomer (9b)], despite the necessary separation step (vide supra).

Choosing the appropriate reduction method (vide supra) permits an easy transformation of enamines (9a) and (9b) to the corresponding indoloquinolizidines (10a) and (11b) [possessing the C(1)H-C(12b)H cis and C(3)H-C(12b)H trans relationship, respectively] in nearly exclusive manner.

EXPERIMENTAL

Ir spectra were recorded with a Perkin-Elmer 700 spectrophotometer. Absorption bands are expressed in reciprocal centimetres (cm^{-1}) using polystyrene calibration. ^{1}H and ^{13}C Nmr spectra were recorded in $CHCl_3$ with a JEOL JNM-FX 60 spectrometer working at 59.80 MHz (^{1}H Nmr) and 15.04 MHz (^{13}C Nmr). Chemical shift data are given in ppm downfield from TMS. Abbreviations s, d, t, m, br and def are used to designate singlet, doublet, triplet, multiplet, broad and deformed, respectively. Mass spectrometry was done on a JEOL DX 303/DA 5000 instrument.

Preparation of enamines (7a) and (7b): Piperidine derivative (6a)[5,8,9] or (6b)[9] (1 mmol) was dissolved in EtOH (15 ml). A solution containing EDTA disodium salt dihydrate (3 mmol) and mercuric acetate (3 mmol) in H_2O (30 ml) was added and the resulting mixture was heated gently under reflux for 3 h. After cooling, CH_2Cl_2 was added, and then dilute aqueous ammonia until the pH reached 11. The phases were separated and the aqueous layer was extracted three times with CH_2Cl_2. After the combined extracts were dried rapidly with K_2CO_3, filtered and condensed, they yielded compound (7a) or (7b).

Compound 7a: Yield 94%. Amorphous material (Lit.,[10] mp 161-164°C). Analytical data were identical with those described earlier.[12]

Compound 7b: Yield 97%. Viscous oil. Ir: 1650 (C=C-N). ^{1}H Nmr: 1.04 (3H, d, J = 6.6 Hz, -CH_3), 4.80 (1H, d, J = 2.9 Hz, H-1), 6.86-7.48 (4H, m, H-8, 9, 10, 11), 8.14 (1H, br s, NH). ^{13}C Nmr: 21.4 (C-7), 22.9 (C-2α) 27.5 (C-2), 30.9 (C-3), 49.5 (C-4), 51.2 (C-6), 101.4 (C-1), 110.2 (C-7a), 110.7 (C-11), 118.3 (C-8), 119.2 (C-9), 122.3 (C-10), 127.1 (C-7b), 130.2 (C-12a), 134.8 (C-12b), 135.7 (C-11a). Ms: 238 (M^+), 223 (100 %); exact mass: 238.1491 (calcd for $C_{16}H_{18}N_2$: 238.1470).

Preparation of enamines (9a) and (9b): 3-Ethylpiperidine derivative (8) (0.256 g, 1.00 mmol) was treated with 4 eq. of 1:1 $Hg(OAc)_2$-EDTA in 33% aq. EtOH for 3 h at reflux and worked up as described above. Flash chromatography [EtOAc-triethylamine (TEA), 100:2] yielded compounds (9b) and (9a) (in that order).

Compound 9a: Yield 22%. Amorphous material. Analytical data were identical with those described earlier.[12]

Compound 9b: Yield 56%. Viscous oil (Lit.,[20] oil). Ir: 1640 (C=C-N). ^{1}H Nmr: 0.91 (3H, def, -CH_3), 4.79 (1H, br s, H-1), 6.92-7.47 (4H, m, H-8, 9, 10, 11), 8.01 (1H, br s, NH). ^{13}C Nmr: 11.3 (C-3β), 21.2 (C-7), 27.0 (C-3α), 28.7 (C-2), 34.4 (C-3), 51.2 (C-6), 56.2 (C-4), 94.2 (C-1), 109.7 (C-7a), 110.6 (C-11), 118.2 (C-8), 119.1 (C-9), 122.0 (C-10), 127.0 (C-7b), 130.2 (C-12a), 136.2 (C-12b), 136.6 (C-11a). Ms: 252 (M^+), 251, 237, 224, 223 (100%), 209, 195; exact mass 252.1612 (calcd for $C_{17}H_{20}N_2$: 252.1626). (cf. ref. 20).

Preparation of compound (10a) by catalytic reduction: Enamine (9a) (36 mg, 0.14 mmol) was dissolved in EtOAc (5 ml), a few drops of TEA were added, and the solution was degassed (3 x N_2). PtO_2 (15 mg) was added and the mixture was vigorously stirred overnight under hydrogen atmosphere. Normal work-up gave compound (10a) (containing traces of compound 11a[21]).

Compound (10a): Yield 97%. Amorphous material.[22] Analytical data were identical with those reported earlier.[14]

Preparation of compounds (10b) and (11b) by catalytic reduction: Enamine (9b) (99 mg, 0.39 mmol) was hydrogenated with PtO_2 in EtOAc using the procedure described above. Normal work-up gave a ca. 1:1 mixture of compounds (10b) and (11b) in quantitative yield. The products were separated by flash chromatography on silica gel (first CH_2Cl_2-MeOH, 98:2; then CH_2Cl_2-MeOH-TEA, 95:4:1).

Compound (10b): Yield 52%. Viscous oil (Lit.,[23] viscous oil). Analytical data were identical with those reported earlier.[14]

Compound 11b: Yield 45%. mp 159-161°C (EtOH) (Lit., 157°C,[20] 159-161°C,[23] 160-161°C[24]). Analytical data were identical with those reported earlier.[14]

Preparation of compound (10a) by $NaBH_4$ reduction: Enamine (9a) (56 mg, 0.22 mmol) was dissolved in MeOH (10 ml) and the solution was stirred at 0°C under Ar. Excess $NaBH_4$ was added in small portions and the mixture was stirred at 0°C for 0.5 h and then at room temperature for 2 h. The mixture was treated with acetic acid and condensed. The residue was dissolved in CH_2Cl_2 and the solution was shaken with aq. Na_2CO_3; the layers were separated and the aqueous layer was extracted with CH_2Cl_2; after the combined extracts were dried (Na_2SO_4), filtered and condensed, they yielded compound 10a (containing traces of compound 11a[21]).

Compound 10a: Yield 97%. Amorphous material.[22] Analytical data were identical with those described earlier.[14]

Preparation of compound (11b) by $NaBH_4$ reduction: Enamine (9b) (42 mg, 0.16 mmol) was reduced with excess $NaBH_4$ in MeOH using the procedure described above. Practically pure compound (11b) was obtained.

Compound (11b). Yield 98%. mp 159-161°C (EtOH) (Lit., 157°C,[20] 159-161°C,[23] 160-161°C[24]). Analytical data were identical with those reported earlier.[14]

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