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STEREOCHEMICAL COURSE OF THE MODIFIED POLONOVSKI REACTION AND MERCURIC ACETATE OXIDATION IN THE PREPARATION OF 2-SUBSTITUTED 1,2,3,4,6,7,12,12b-OCTAHYDROINDOLO[2,3-a]QUINOLIZINES

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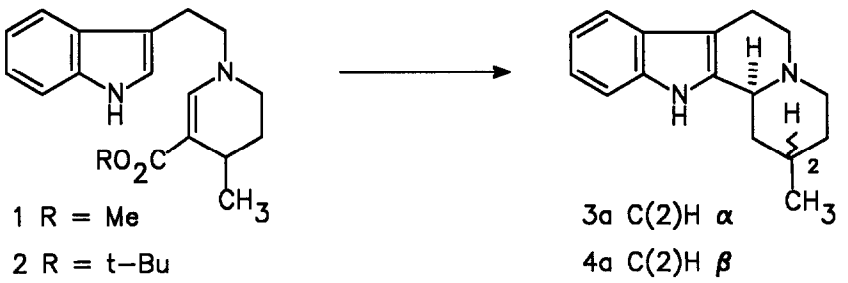
Abstract: H_2O_2 oxidation of C(4) monosubstituted 1-[2-(3-indolyl)ethyl]-piperidines 7a, 7b and 7c followed by the modified Polonovski reaction yielded exclusively indolo[2,3-a]quinolizidines 4a, 4b and 4c possessing the C(12b)H-C(2)H trans-relationship. The same piperidines, when subjected to the Fujii modification of the mercuric acetate oxidation followed by $NaBH_4$ reduction (the Fujii procedure), gave nearly exclusively indolo[2,3-a]quinolizidines 3a, 3b and 3c possessing the C(12b)H-C(2)H cis-relationship. The "classical" mercuric acetate oxidation of 4-methyl-1-[2-(3-indolyl)ethyl]-piperidine 7a yielded predominantly indolo[2,3-a]quinolizidine 4a, possessing the C(12b)H-C(2)H trans-relationship, together with the other isomer, 3a, in amounts depending on the work-up procedure (with or without $NaBH_4$-reduction).

A few years ago, Wenkert et al.[1] criticized the conclusions presented by our laboratory regarding the general stereochemical outcome of the alkaline decarboalkoxylative cyclization of substituted 1-[2-(3-indolyl)ethyl]-3-methoxycarbonyl-1,4,5,6-tetrahydropyridines[2-5]. Reinvestigating the decarboalkoxylative cyclization of methylester 1 under basic conditions and that of t-butylester 2 under acidic conditions, they obtained 8:1 and 4:1 mixtures of products 3a and 4a, respectively (Scheme 1). The major product, 3a, possessed the C(12b)H-C(2)H cis-stereochemistry, the same as the product 3a obtained earlier in our laboratory.[3]

In an effort to rationalize their results, Wenkert et al. stated that, because there is only one small substituent in the piperidine ring (besides the N-tryptophyl unit), the intermediate N-alkyl-4-methyl-1-piperideinium ion assumes energetically similar half-chair 5 and half-boat 6 conformations (Fig. 1) and cyclization of the latter form yields the major product 3a. Now, if what they say is true, similar cis-selectivity should be observed in



Scheme 1

the modified Polonovski reaction[6-10], provided, of course, that both reactions pass through the same iminium (=immonium) ion intermediate. The cis-selectivity should be present also in the "classical" mercuric acetate oxidation procedure of 4-methyl-1-[2-(3-indolyl)ethyl]-piperidine 7a (observable when the procedure is performed without the $NaBH_4$-treatment) (vide infra).

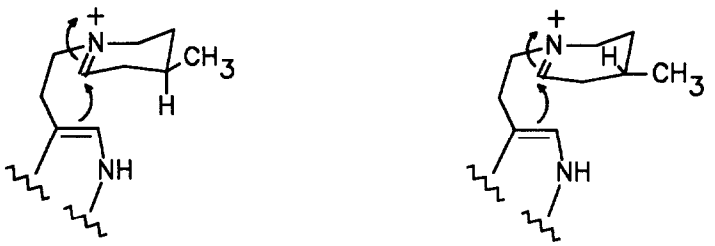


Fig 1.

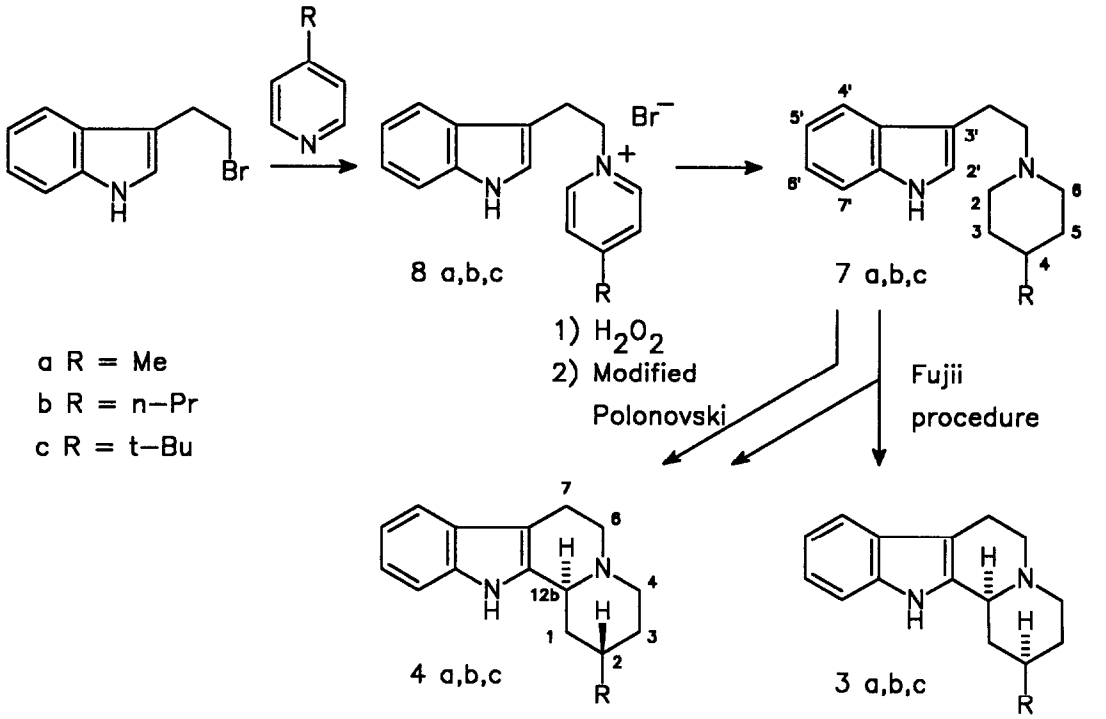
To clarify the mechanistic similarities and/or differences in these reactions, we studied the cyclization of 4-methyl-, 4-n-propyl- and 4-tert-butyl-1-[2-(3-indolyl)ethyl]-piperidines 7a, 7b and 7c under the conditions of the modified Polonovski reaction (via the corresponding N-oxides)[11,12] and under the conditions of the "classical" mercuric acetate oxidation procedure[13-16] and its modern version described by Fujii et al.[17,18] In this paper we present the results obtained.

RESULTS AND DISCUSSION

The piperidines 7a, 7b and 7c were prepared from tryptophyl bromide[19] and the corresponding pyridine derivatives via salts 8a, 8b and 8c (Scheme 2).

Catalytic transfer hydrogenation[20,21], which proceeds faster and employs a cheaper catalyst (Pd/C) than the traditional method (H_2, PtO_2), was applied for the reduction of the salts 8a, 8b and 8c. A reaction time of 1-2 hr provided the best results; prolonged heating led to increased amounts of 3-ethylindole in the product mixtures (vide infra).

In the H_2O_2 oxidation of the piperidines 7a, 7b and 7c followed by the modified Polonovski reaction {carried out under the conditions of Chevolot et al.[11,12] [1. H_2O_2; 2. $(CF_3CO)_2O$; 3. 1 M HCl, 70°C]}, the only identifiable product (compound 4a, 4b or 4c) possessed the C(12b)H-C(2)H trans-stereochemistry regardless of the size of the C-2 substituent (methyl, n-propyl or tert-butyl) (Scheme 2). Our results thus confirm those of Chevolot et al.[11,12], and at the same time argue against the explanation put forth by Wenkert et al. (vide supra). Furthermore, no C(12b)H epimerization was observed when the 2-methyl compound 3a was subjected to the conditions of the modified Polonovski reaction (2 hr) or refluxed with HCl/MeOH (6 hr). However, on prolonged heating of compound 3a in refluxing acetic acid (four days, under argon) a roughly 3:1 mixture of 3a and 4a was produced.



Scheme 2

Turning our attention to the mercuric acetate oxidation of piperidines 7a, 7b and 7c, we first applied the modified oxidation conditions of Fujii et al.[17,18] (33% aq EtOH, 3 eq $Hg(OAc)_2$, 3 eq EDTA, 3 hr reflux) followed by $NaBH_4$ reduction (the Fujii procedure). The major isomer to form was the C(12b)H-C(2)H cis-product (compounds 3a, 3b and 3c, respectively) (Scheme 2). Oxidation of the 4-methyl piperidine 7a and reductive treatment with $NaBD_4$ instead of $NaBH_4$ gave the cis-isomer with deuterium incorporation to C-12b (compound 3a-12b-d_1). The product mixture also contained a small amount of the trans-isomer 4a with some deuterium incorporation. Presumably, in the Fujii procedure, the initially formed tetracyclic amine(s) was/were reoxidized, producing a new iminium ion which was then reduced with $NaBH_4$ (or $NaBD_4$) to yield nearly exclusively the cis-product. The Fujii oxidation has allowed us to develop a simple method for the preparation of indoloquinolizidine enamines.[22]

Finally, the "classical procedure" [1. 10 eq $Hg(OAc)_2$, 5% aq AcOH, 100°C, 1 hr; 2. H_2S; 3. $NaBH_4$] was applied to the 4-methyl piperidine 7a, yielding a roughly 3:1 mixture of trans- and cis-isomers 4a and 3a in 60% yield. When the procedure was performed without $NaBH_4$-treatment the product ratio was about 6:1 in favour of the trans-product 4a, but the yield was only 37%.

CONCLUSIONS

The H_2O_2 oxidation of C(4) monosubstituted 1-[2-(3-indolyl)ethyl]-piperidines 7a, 7b and 7c followed by the modified Polonovski reaction yielded exclusively the indolo[2,3-a]quinolizidines 4a, 4b and 4c, respectively, all possessing the C(12b)H-C(2)H trans-relationship. The same piperidine derivatives, when subjected to the Fujii procedure (vide supra), gave nearly exclusively the indolo[2,3-a]quinolizidines 3a, 3b and 3c, respectively, all possessing the C(12b)H-C(2)H cis-relationship. In contrast, the "classical" mercuric acetate oxidation procedure applied to 4-methyl-1-[2-(3-indolyl)ethyl]-piperidine 7a yielded primarily indolo[2,3-a]quinolizidine 4a possessing the C(12b)H-C(2)H trans-relationship, together with variable amounts of the C(12b)H-C(2)H cis isomer 3a, depending on the work-up procedure (with or without $NaBH_4$-reduction). Thus the stereochemical relationship C(12b)H-C(2)H can be selected cis or trans at will[23] simply by choosing the proper reaction conditions: the Fujii procedure or the H_2O_2/modified Polonovski reaction route, respectively.

Our results show that the explanation offered by Wenkert et al[1]. for the preponderant formation of 2-methyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-

a]quinolizine 3a [(12b)H-C(2)H cis] in the decarboalkoxylative cyclization of tetrahydropyridines 1 and 2 is an oversimplification and that other factors need to be taken into consideration in predicting the C(12b)H-C(2)H relationships of the formed indolo[2,3-a]quinolizidines.

EXPERIMENTAL

^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ with a JEOL JNM-FX 60 spectrometer working at 59.80 MHz (^1H 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. Flash chromatography was performed using silica gel 60 Merck 9385.

Catalytic transfer hydrogenation of salts 8a, 8b and 8c

The salt 8a, 8b or 8c was dissolved in MeOH (100 ml) and the solution was degassed (4xAr) and cooled to avoid the risk of the solvent vapours igniting during catalyst addition. To this solution, 10% Pd/C (3.0-3.2 g) and ammonium formate (6.31 g, 100 mmol) were added and the solution was vigorously refluxed for 1-2 hr (salt 8b 1 hr, salt 8a 1.5 hr and salt 8c 2 hr) and filtered hot. The catalyst was washed with copious amounts of methanol. The solvents were evaporated and the residue was partitioned between 10% aq Na_2CO_3 and CH_2Cl_2 and the aqueous layer was extracted with two more portions of CH_2Cl_2. Drying over Na_2SO_4, filtering and evaporation gave the crude product, which was purified by flash chromatography. The product was first eluted with CH_2Cl_2 to obtain 3-ethylindole, which was invariably present in the crude product. Subsequent elution with CH_2Cl_2-MeOH-triethylamine (TEA) (100:2:1) gave the piperidine derivative 7a, 7b or 7c.

Compound 7a:

Y. 72%. Mp. 111°C (EtOH) (lit. Mp.[23] 110-111°C).

Analytical data were identical with those described earlier.[23]

Compound 7b:

Y. 79%. Mp. 122-123°C (EtOH).

^1H NMR: 6.85 (1H, d, J=2 Hz, H-2), 6.98-7.63 (4H, m, H-4, 5, 6, 7), 8.98 (1H, br s, NH).

^{13}C NMR (see Note 24).

MS: 270 (M^+), 140 (100%), 130; exact mass: 270.2110 (calc. for $C_{18}H_{26}N_2$: 270.2096).

Compound 7c:

Y. 62%. Mp. 157-158°C (MeOH) (lit. Mp. 157°C[11], Mp. 158-159°C[23]).

Analytical data were identical with those described earlier.[11,23]

H_2O_2 oxidation of piperidine derivatives 7a, 7b and 7c followed by the modified Polonovski reaction

The piperidine derivative 7a, 7b or 7c (1 mmol) was dissolved in 1:1 mixture (6 ml) of EtOH and chloroform, 30% aq hydrogen peroxide (0.58 ml) was added and the solution was stirred at 60°C for 24 hr. The excess peroxide was then destroyed by adding 10% Pd/C to the solution and stirring the mixture until oxygen generation ceased. Filtration and evaporation gave the crude N-oxide as a foam, which was dissolved in dry CH_2Cl_2 (15 ml) and stirred under argon at 0°C. Trifluoroacetic anhydride (0.8 ml, 5.7 mmol) was added via syringe over a period of 15 min. Stirring was continued for 1 hr at 0°C and 1 hr at rt. To this mixture 1 M aq HCl (4.5 ml) was added and the two-phase system was heated for 15 min at 70-75°C. Extractive work-up with 10% aq Na_2CO_3 and CH_2Cl_2, drying and evaporation gave the crude product, which was subjected to flash chromatography (EtOAc-triethylamine, 9:1) yielding compound 4a, 4b or 4c.

Compound 4a:

Y. 31%. Amorphous material (lit. Mp. 110-112°C[1], 128-130°C[25], 154-155°C[26]).
Analytical data were identical with those described earlier.[1,25,26]

Compound 4b:

Y. 31%. Amorphous material (lit.[26] amorphous material).
Analytical data were identical with those described earlier.[26]

Compound 4c:

Y. 22%. Amorphous material (lit.[23,27] amorphous material).
Analytical data were identical with those described earlier.[23,27]

Mercuric acetate oxidation of piperidine derivatives 7a, 7b and 7c followed by $NaBH_4$ reduction (Fujii procedure)

The piperidine derivative 7a, 7b or 7c (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 refluxed gently for 3 hr. After cooling, CH_2Cl_2 was added, and then dilute aqueous ammonia until the pH reached 9. $NaBH_4$ (0.378 g, 10 mmol) was added and the reaction mixture was stirred at room temperature for 4 hr. Chloroform was added and the mixture was filtered. Extraction, washing with brine, drying (Na_2SO_4), filtering and evaporation gave the crude product containing two isomers 3a and 4a, 3b and 4b or 3c and 4c. These were separated by flash chromatography (hexane-chloroform-diethylamine/35:25:5).

Compound 3a:
Y. 70%. Mp. 162-164°C (MeOH) (lit. Mp. 165-166°C[3], 165-166°C[23]).
Analytical data were identical with those described earlier.[3,23]
Compound 4a:
Y. 10%. Amorphous material (lit. 110-112°C[1], 128-130°C[25], 154-155°C[26]).
Analytical data were identical with those described earlier.[1,25,26]
Compound 3b:
Y. 86%. Mp. 119-122°C (MeOH) (Melting at ca. 80°C and resolidifying at ca. 100°C) (lit.[26] Mp 80-81°C).
Analytical data were identical with those described earlier.[26]
Compound 4b:
Y. 5%. Amorphous material (lit.[26] amorphous material).
Analytical data were identical with those described earlier.[26]
Compound 3c:
Y. 78%. Mp. 156-157.5°C (hexane-benzene) (lit. Mp. 155-156[23], 157-158°C[27]).
Analytical data were identical with those described earlier.[23,27]
Compound 4c:
Y. 12%. Amorphous material (lit.[23,27] amorphous material).
Analytical data were identical with those described earlier.[23,27]

Mercuric acetate oxidation of piperidine derivative 7a followed by $NaBD_4$ reduction (Fujii procedure)

The piperidine derivative 7a (0.242 g, 1.00 mmol) was treated with 3 eq of 1:1 $Hg(OAc)_2$-EDTA disodium salt dihydrate in 33% aq EtOH for 3 hr under reflux. The reaction mixture was cooled and the pH of the mixture was raised to 9 with aqueous ammonia. $NaBD_4$ (0.419 g, 10 mmol) was added and the reaction mixture was stirred at room temperature for 6 hr. Chloroform was added to the reaction mixture and the mixture was filtered. Extraction, washing with brine, drying (Na_2SO_4), filtering and evaporation gave the crude product, which was purified by flash chromatography (hexane-chloroform-diethylamine/35:25:5) yielding indoloquinolizines 3a-12b-d_1 and 4a (containing small amounts of 4a-12b-d_1 according to MS).
Compound 3a-12b-d_1:
Y. 76%. Mp. 162-164°C (MeOH).
^1H NMR: 0.97 (3H, def, $-CH_3$), 6.95-7.50 (4H, m, H-8, 9, 10, 11), 7.83 (1H, br s, NH).
MS: 241 (M^+, 100%), 240, 239, 226, 212, 198, 185, 171, 170; exact mass 241.1708 (calc. for $C_{16}H_{19}N_2D$: 241.1689).
Compound 4a:
Y. 7%. Amorphous material (lit. 110-112°C[1], 128-130°C[25], 154-155°C[26]).

Analytical data were identical with those described earlier.[1,25,26]

Mercuric acetate oxidation of piperidine derivative 7a followed by $NaBH_4$ reduction (classical procedure)

A solution of piperidine derivative 7a (0.123 g, 0.51 mmol) and mercuric acetate (1.62 g, 5.1 mmol) in 5% aq. AcOH (12 ml) was stirred at 100°C for 1 hr. A stream of H_2S gas was then passed through the mixture for 1 hr at the same temperature. The black mixture was filtered through a Celite pad, which was washed with 1:1 EtOH-aq AcOH. The filtrate was concentrated, 50% aq EtOH was added and the pH was adjusted to 8-9 by the addition of solid $NaHCO_3$. Excess $NaBH_4$ was added in several portions and the reaction mixture was stirred overnight under argon. The pH was then adjusted to 1 with 1 M aq HCl and the mixture was filtered, concentrated and basified with solid K_2CO_3. Extraction with $CHCl_3$, washing with H_2O, drying (K_2CO_3) and concentration gave, in 60% yield, the crude product consisting of a roughly 3:1 mixture of compounds 4a and 3a according to ^{13}C NMR analysis.

Another experiment under the same conditions, but without the $NaBH_4$-treatment, gave after extractive work-up the crude product in 37% yield. According to ^{13}C NMR analysis this consisted of a roughly 6:1 mixture of compounds 4a and 3a.

Acetic acid treatment of compound 3a

Compound 3a (44 mg, 0.18 mmol) was dissolved in acetic acid (12 ml); the solution was degassed (4xAr) and refluxed under argon for 96 hr. Evaporation of the solvent followed by extractive work-up with CH_2Cl_2 and aq. Na_2CO_3, drying and evaporation afforded the crude product (44 mg, 100%), consisting of a roughly 3:1 mixture of compounds 3a and 4a as judged from the ^{13}C NMR spectrum.

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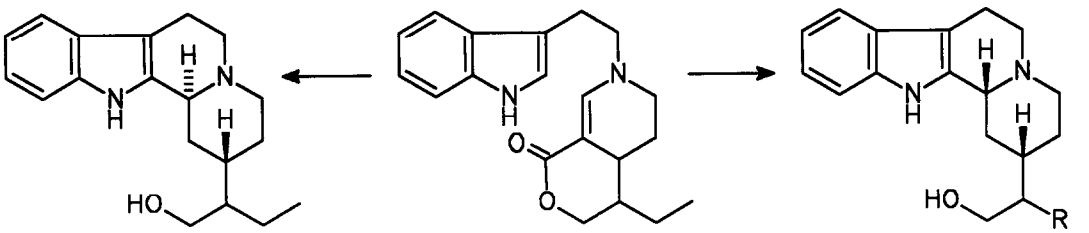
the only clearly detectable dihydroantirhine is dl-3-epi-18,19-dihydroantirhine iii. For further confirmation, we prepared dl-3-epi-18-nor-18,19-dihydroantirhine iv from the appropriate tetrahydropyridine by the same method (Ref. 29).



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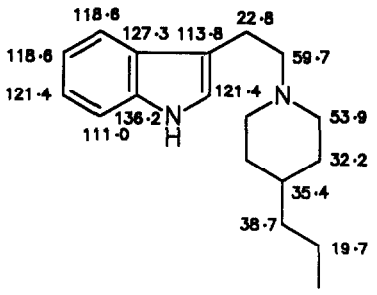
24. ^{13}C NMR spectrum of compound 7b.



7b

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