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Regiochemistry in the synthesis of 2,3,8,8a-tetrahydro-7*H*-oxazolo[3,2-*a*]pyridines

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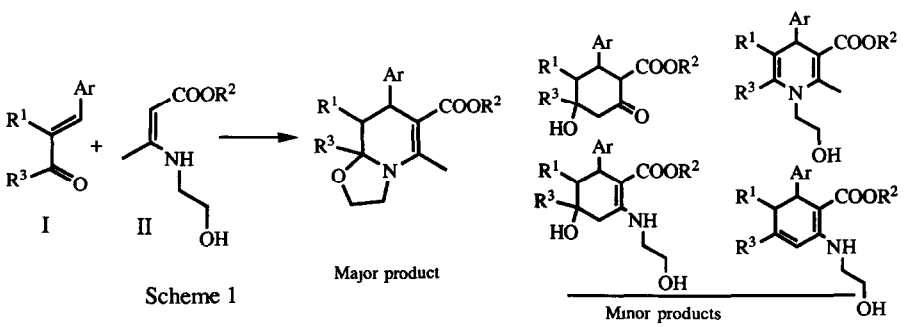
Abstract. The regiochemistry of the reaction between *N*-hydroxyethyl-enamines and α,β-unsaturated carbonyls and carboxylic esters is discussed. The structure of the 2,3,8,8a-tetrahydro-7*H*-oxazolo[3,2-*a*]pyridines obtained by this methodology depends on the substituents at the β-position of the α,β-unsaturated reagent.

Introduction

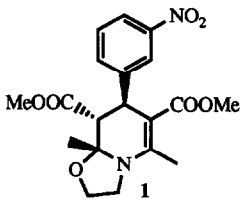
In the first paper of this series we described the synthesis of several 2,3,8,8a-tetrahydro-7*H*-oxazolo[3,2-*a*]pyridine derivatives[1]. The formation of the fused heterocyclic system was achieved by reaction between α,β-unsaturated carbonyl compounds and *N*-hydroxyethyl-enamines (Scheme 1). Although other minor products were detected, such as dihydropyridines and cyclohexane derivatives, the main reaction products were compounds with the 2,3,8,8a-tetrahydro-7*H*-oxazolo[3,2-*a*]pyridine skeleton. As they displayed an interesting long-lasting antihypertensive activity, we prepared several derivatives by variation of substituents R^1, R^2 and R^3. Surprisingly, we obtained unexpected products, which must derive from a different regiochemical pathway of the reaction [2]. In this paper we report the results of the new study and we propose an alternative mechanism to explain these variations.



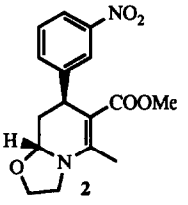
Scheme 1

Methods and results

The tetrahydro-oxazolopyridine **1** had been prepared from the corresponding Knoevenagel precursor derived from methyl acetylacetate (I; R^1=COOMe, R^3=Me) and the *N*-hydroxyethyl-enamine carrying a methyl ester function (II; R^2=Me). Structure **1** was established by spectroscopic methods, but we have now realized that the ^{13}C NMR signals for methoxyl groups were erroneously assigned. In that case, it was only possible to obtain one regioisomer, because the same structure is formed whether the oxygen of the oxazolidine moiety is attached to the Knoevenagel residue or to the enamine residue. The structures of further derivatives were assigned by comparison of their spectroscopic data with those of compound **1**.



1



2

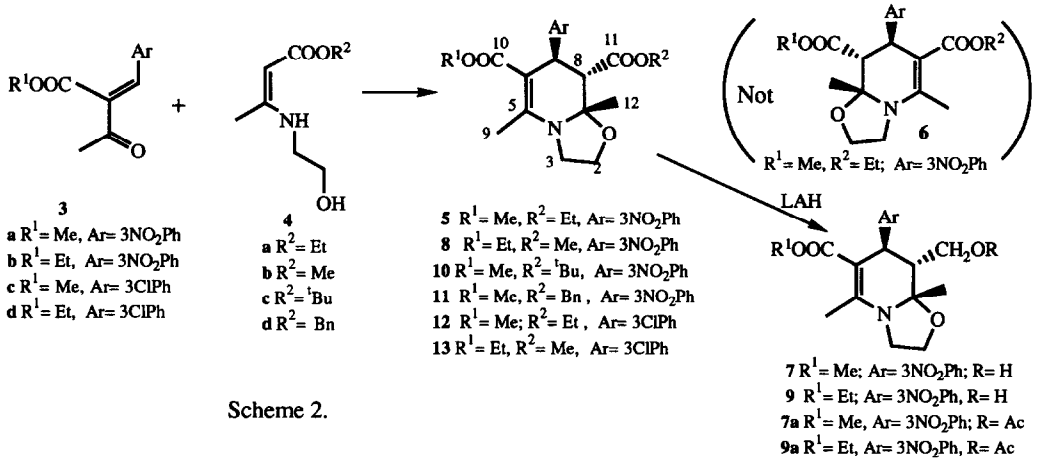
When the α,β-unsaturated reagent was the conjugate aldehyde cinnamaldehyde (I; R^1=R^3=H), compound **2** was formed. The regiochemistry of the reaction implied the attack of the oxygen to the α,β-unsaturated carbonyl moiety. In our previous paper, all these results were explained, by a common mechanism.[1]

During the synthesis of other oxazolopyridines and their LAH reduction products (Scheme 2), we observed that several compounds seemed to derive from a different regiochemistry of the cycloaddition reaction. In order to clarify these results, we have now prepared new products, by the reaction of Knoevenagel compounds **3** with enamines **4**. For example, when **3a** (R^1=Me) reacts with **4a** (R^2=Et) in refluxing methanol, the main reaction product is **5** (R^1=Me, R^2=Et) instead of the expected **6**. One-bond and long-range heteronuclear H/C correlations (Table 1) clearly supported structure **5**. Among others, the connectivities between H-8 and the non-conjugated carboxylic carbon (C-11) and between the methoxyl protons and the conjugated one (C-10) were definitive. LAH reduction of **5** confirmed the proposed structure, because the hydroxy-ester **7** maintained the methyl ester moiety. The coupling observed between H-8 and those protons of the hydroxymethyl grouping formed, was in accordance with the selective reduction of the non-conjugated carboxylic ester. Furthermore, when the reaction was carried out with **3b** (R^1=Et) and **4b** (R^2=Me) the regioisomer **8** was produced, thus confirming the reaction outcome with the oxygen attached to the enamine residue. Reduction of **8** resulted in the conversion of the non-conjugated methyl carboxylate into the hydroxymethyl group, yielding compound **9**. Reduction of **1** also produced **7** and this allowed us to correct the assignment of ^{13}C NMR signals for methoxyl carbons.

Table 1. Selected long-range H/C correlations for compound **5**.

H	7	8	9	12	OMe
C	6, 8, 8a, 11	7, 8a, 11, 12	5, 6	8, 8a	10

Similar results were obtained in the synthesis and reduction of compounds **10-13**. So, the oxazolopyridines are always formed on the carbons from the enamine reagent, and the double bond is conjugated to the carboxylic ester from the Knoevenagel reagent. The relative stereochemistries for all those products were the same as we deduced in the previous paper.[1]



3
a R^1= Me, Ar= $3NO_2Ph$
b R^1= Et, Ar= $3NO_2Ph$
c R^1= Me, Ar= 3ClPh
d R^1= Et, Ar= 3ClPh

4
a R^2= Et
b R^2= Me
c R^2= ^{t}Bu
d R^2= Bn

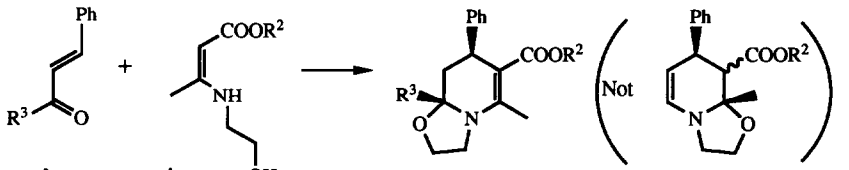
5 R^1= Me, R^2= Et, Ar= $3NO_2Ph$
8 R^1= Et, R^2= Me, Ar= $3NO_2Ph$
10 R^1= Me, R^2= ^{t}Bu, Ar= $3NO_2Ph$
11 R^1= Me, R^2= Bn, Ar= $3NO_2Ph$
12 R^1= Me; R^2= Et, Ar= 3ClPh
13 R^1= Et, R^2= Me, Ar= 3ClPh

7 R^1= Me; Ar= $3NO_2Ph$; R= H
9 R^1= Et; Ar= $3NO_2Ph$, R= H
7a R^1= Me, Ar= $3NO_2Ph$; R= Ac
9a R^1= Et, Ar= $3NO_2Ph$, R= Ac

Scheme 2.

Next we turned to the reaction between enamines and cinnamaldehyde (**14**). There was not doubt about the structure of compound **2**, obtained from enamine **4b**, because the other possible product **15** has olefinic protons. When the reduction of **2** under the same conditions was attempted, unreacted material was recovered, thus confirming the proposed structure with the opposite regiochemistry from that observed in products **5**, **8** and **10-13**. The same results were obtained with enamines **4a-c-d** whose reaction products **16-18** were not reduced.

To check the behaviour of other α,β-unsaturated carbonyl compounds with *N*-hydroxyethyl-enamines, we used 4-phenylbut-3-en-2-one **19** (Scheme 3). In this case compounds **20** and **21** were isolated, whose structures also derive from the linkage between the oxygen and the α,β-unsaturated carbonyl residue. None of these products suffered reduction by LAH. The relative stereochemistries of **20** and **21** were established as a consequence of the shielding of the methyl on C-8a, which must lie parallel to the aromatic ring.



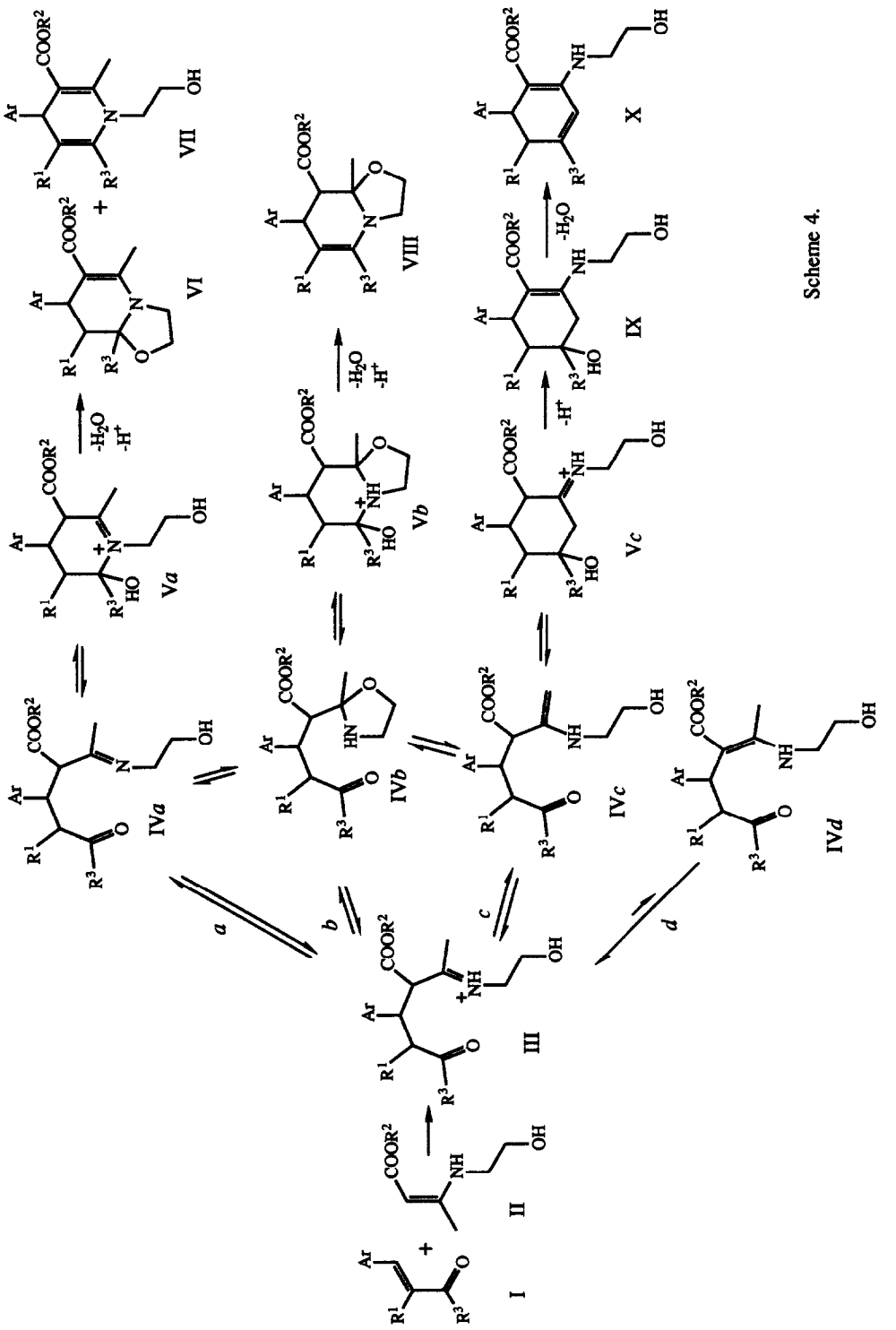
14 R^3= H
19 R^3= Me

4
b R^2= Me
a R^2= Et
c R^2= tBu
d R^2= Bn

2 R^2= Me, R^3= H
16 R^2= Et, R^3= H
17 R^2= tBu, R^3= H
18 R^2= Bn, R^3= H
20 R^2= Me, R^3= Me
21 R^2= Et, R^3= Me

15

Scheme 3.



Scheme 4.

As a result, it is clear that a different regiochemistry of the reaction is induced depending on the structure of the unsaturated carbonyl reagent . The main difference among these reagents is the presence or absence of an electron withdrawing group corresponding to the R^1 substituent (I: R^1= ester group, **3a-d**; or R^1= H, **14** and **19**). To explain the regiochemical outcome of the reaction we propose the mechanism depicted in Scheme 4.

The Michael addition has been recognized as the rate-determining step in the Hanztsch synthesis [3-6]. This is also the rate-limiting stage, because it is not possible to detect other intermediates between the reagents and the final products. Another fact that was previously proven[1], is the impossibility of transforming *N*-hydroxyethyl-dihydropyridines into the oxazolopyridine system, under the reaction conditions. Taking into account the Michael addition as the initial limiting step and the dehydratation as the final step, the differences must lye on the intermediate stages. Unfortunately, it is not possible to detect the intermediates involved in the reaction, because they must evolve rapidly.

In spite of the lack of other data, it is possible to propose these intermediates in the light of the structure of final products (Scheme 4). Thus, the dehydrated-deprotonated compounds VI-X would arise from type V intermediates. Between these and the common Michael adduct III, initially formed from the reagents, some possibilities could be proposed for the intermediates IV, depending on the route *a-d* followed towards the ending products.

Although the conjugate enamine is favoured in the starting material, it is not the case in the type IV*d* intermediate because it must be destabilized by the presence of four substituents on the double bond [7,8]. Imine IV*a* and enamine IV*c* are other possibilities for the intermediates, together representing an example of the well-documented imine-enamine equilibrium [9]. IV*a* and *c* are reasonable intermediates to oxazolopyridines VI, with the oxygen bonded to the Knoevenagel moiety, to dihydropyridines VII and to the minor cyclohexene derivatives IX and X (Scheme 4).

The oxazolopyridines, with the oxygen bonded to the enamine moiety, must derive from an alternative reaction pathway. Consequently, our proposal is that the intermediate oxazoline IV*b*, through the formation of the aminal V*b*, will lead to the oxazolines VIII. Path *b* is a feasible explanation if we take into account the easy formation of pyrrolidine enamines of acetylacetates, which is comparable to the conversion of IV*b* into VIII. In addition, the imine-oxazoline (IV*a*-IV*b*) equilibrium is well known [10], and it can be produced during the reaction.

As compounds produced by methanol addition are not observed, the last step V to VI-X is not reversible. For this reason, intermediates IV*a-d* and V*a-c* could participate in an equilibrium mixture from which the obtained products are formed. One explanation for the different regiochemistry observed as a function of the R^1 substituent is the stabilization gained by conjugation in the transition state from V*b* to VIII, which will favour the formation of these oxazolines when the substituent is an alcoxycarbonyl group (R^1=COOR). If there is no substituent (R^1=H), such stabilization is only gained through path V*a* to VI, by conjugation of the ester group (-$COOR^2$) with the double bond being formed.

Trials directed towards the synthesis of other types of 2,3,8,8a-tetrahydro-7*H*-oxazolo[3,2-*a*]pyridines, in order to gain a deeper knowledge of the mechanism, failed. Thus enamines from cyclohexane-1,3-dione did not react at room temperature and produced complex mixtures from which cyclohexane derivatives were mainly only obtained, when the reaction was carried out under reflux. N-trisubstituted enamines mainly produced cyclohexane derivatives, at has been observed in similar reactions [11]. When the α,β-unsaturated system was the less reactive arylmethyllidene malonate, the reaction did not work under standard (r.t. or reflux) conditions.

These results indicate that this synthesis of oxazolo[3,2-*a*]pyridines is limited to N-hydroxy-ethylenamines from β-ketoesters and α,β-unsaturated ketones or aldehydes. With these reagents the heterocyclic system is obtained in medium to high yields (better results are obtained when the reaction is carried out at room temperature, because minor products are produced in smaller amounts). A number of other 2,3,8,8a-tetrahydro-7*H*-oxazolo[3,2-*a*]pyridines with different aryl (phenyl, 2-nitrophenyl, etc) and heteroaryl (2-pyrrolyl, 2-thienyl, 2-furyl, 2-pyridyl) substituents at C-7 have been easily produced by this method, but no further evidence about the mechanism was deduced.

EXPERIMENTAL

General experimental information..

Mps were determined on a Buchi 510 instrument and are uncorrected. UV spectra were recorded in ethanol on a Hitachi 100-60 spectrometer. IR spectra were obtained in KBr disks in a Beckman Acculab VIII spectrophotometer. ^{1}H NMR (200.13 MHz) and ^{13}C NMR (50.3 MHz) spectra were measured in a Bruker WP 200 SY instrument, in deuterochloroform solutions and tetramethylsilane as internal standard, unless otherwise stated. δ values are expressed in ppm and J values in Hz. Mass spectra were determined by the electron impact method on a VG-TS-250 mass spectrometer. Column chromatography was performed over silica gel Merck 60 (0.063-0.2 mm). For flash chromatography, an Eyela EF-10 apparatus was used, with 3-85 mL/min flow rate, over silica gel Merk 60 (0.040-0.063 mm). TLC was performed on precoated silica gel polyesther plates (0.25 mm thickness) with fluorescent indicator UV254 (Polychrom SI F_{254}). Microanalyses were obtained in a Perkin-Elmer 2400 CHN elemental analyzer.

Preparation of 2,3,8,8a-tetrahydro-7H-oxazolo[3,2-a]pyridines.

A solution of the Knoevenagel adduct (20 mmol) and enamine (20 mmol) in MeOH (50 ml), was refluxed for 6 hours or was allowed to stand at room temperature for 20 hours. The solvent was removed and the oxazolo[3,2-a]pyridines were isolated in 43-60% yield by flash chromathography (Hex/EtOAc) and/or crystallization.

Methyl 7-(3-nitrophenyl)-5,8a-dimethyl-8-ethoxycarbonyl-2,3,8,8a-tetrahydro-7H-oxazolo[3,2-a]pyridin-6-carboxylate (**5**) (45%). M.p.118°C (MeOH). IR ($CHCl_3$): 1735, 1680, 1560 cm^{-1}. ^{1}H NMR (DMSO): 0.81 (s, 3H, C_{8a}-Me), 1.30 (t, J=7.1 Hz, 3H, -CH_2-CH_3), 2.60 (s, 3H, C_5-Me), 3.34 (s, 1H, H_8), 3.46 (s, 3H, OMe), 3.6-3.8 (m, 2H, H_3), 4.0-4.2 (m, 2H, H_2), 4.10 (q, J=7.1 Hz, 2H, -CH_2-CH_3), 4.45 (s, 1H, H_7), 7.44 (t, J=7.9 Hz, 1H, $H_{5'}$), 7.61 (d, J=7.8 Hz, 1H, $H_{6'}$), 8.03 (da, J=7.9 Hz, 1H, $H_{4'}$), 8.12 (s, 1H, $H_{2'}$). MS *m/z* (%): 404 (21, M^+), 373 (20), 359 (18), 345 (82), 331 (100), 194 (20), 128 (25). Anal. cal. for $C_{20}H_{24}O_7N_2$: C 59.30, H 5.98, N 6.92 %, found: C 59.07, H 5.80, N 6.78 %.

Ethyl 7-(3-nitrophenyl)-5,8a-dimethyl-8-methoxycarbonyl-2,3,8,8a-tetrahydro-7H-oxazolo[3,2-a]pyridin-6-carboxylate (**8**) (50%). IR: 1750, 1680, 1580 cm^{-1}. ^1H NMR: 0.84 (s, 3H, C_{8a}-Me), 0.90 (t, J=7.1 Hz, 3H, $-CH_2-\mathbf{CH_3}$), 2.61 (s, 3H, C_5-Me), 3.37 (s, 1H, H_8), 3.73 (s, 3H, OMe), 3.70 (m, 2H, H_3), 4.10 (m 2H, H_2), 4.09 (q, J=7.1 Hz, 2H, $-\mathbf{CH_2}-CH_3$), 4.45 (s, 1H, H_7), 7.45 (t, J=7.8 Hz, 1H, $H_{5'}$), 7.61 (d, J=7.7 Hz, 1H, $H_{6'}$), 8.06 (d, J=7.8 Hz, 1H, $H_{4'}$), 8.13 (s, 1H, $H_{2'}$).

Methyl 7-(3-nitrophenyl)-5,8a-dimethyl-8-tert-butoxycarbonyl-2,3,8,8a-tetrahydro-7H-oxazolo[3,2-a]pyridin-6-carboxylate (**10**) (54%). M.p. 142-143°C(MeOH/ether). IR: 1740, 1660, 1590 cm^{-1}.^1H NMR: 0.81 (s, 3H, C_{8a}-Me), 1.47 (s, 9H, $(CH_3)_3C$), 2.60 (s, 3H, C_5-Me), 3.22 (s, 1H, H_8), 3.43 (s, 3H, OMe), 3.6-3.7 (m, 2H, H_3), 4.0-4.1 (m, 2H, H_2), 4.42 (s, 1H, H_7), 7.47 (t, J=7.8 Hz, 1H, $H_{5'}$), 7.64 (d, 1H, J=7.8 Hz, 1H, $H_{6'}$), 8.04 (d, 1H, J=9.4 Hz, $H_{4'}$), 8.12 (s, 1H, $H_{2'}$). MS *m/z* (%): 433 (10, M^++1), 376 (78), 331 (82), 194 (25), 115 (15), 86 (22). Anal. cal. for $C_{22}H_{28}O_7N_2$: C 61.11, H 6.48, N 6.48 % found C 61.18, H 6.51, N 6.28 %.

Ethyl 7-(3-chlorophenyl)-5,8a-dimethyl-8-methoxycarbonyl-2,3,8,8a-tetrahydro-7H-oxazolo[3,2-a]pyridin-6-carboxylate (**13**). (45%). M.p. 142°C (MeOH). IR: 1740, 1710, 1600, cm^{-1}. ^1H NMR: 0.89 (s, 3H, C_{8a}-Me), 0.97 (t, J=7.2 Hz, 2H, $-CH_2-\mathbf{CH_3}$), 2.57 (s, 3H, C_5-Me), 3.35 (s, 1H, H_8), 3.6-3.8 (m, 2H, H_3), 3.70 (s, 3H, OMe), 4.05 (m, 2H, H_2), 3.90 (q, J=7.2 Hz, 2H, $-\mathbf{CH_2}-CH_3$), 4.35 (s, 1H, H_7), 7.1-7.4 (m, $4H_{arom.}$). MS *m/z* (%): 364 (18, M^+ -Et), 318 (9), 291 (35), 245 (100), 211 (18), 165 (32), 115 (21), 69 (12).

Ethyl 7-phenyl-5-methyl-2,3,8,8a-tetrahydro-7H-oxazolo[3,2-a]pyridin-6-carboxylate (**16**) (50%). M.p. 79-80°C (MeOH). IR: 1690, 1580, cm^{-1}. ^1H NMR: 1.01 (t, J=7.0 Hz, $-CH_2-\mathbf{CH_3}$), 1.67 (ddd, J_1=11.9, J_2=10.4, J_3=5.5 Hz, 1H, $H_{8\beta}$), 2.25 (ddd, J_1=11.9, J_2=3.6, J_3=2.5 Hz, 1H, $H_{8\alpha}$), 2.57 (s, 3H, C_5-Me), 3.54 (m, 2H, H_3), 3.78 (ddd, J_1=9.5, J_2=8.8, J_3=6.7 Hz, 1H, H_2), 3.90 (q, J=7.0 Hz, $-\mathbf{CH_2}-CH_3$), 4.13 (ddd, J_1=8.9, J_2=5.3, J_3=3.2 Hz, 1H, H_2), 4.21 (d, J=4.1 Hz, 1H, H_7), 4.39 (dd, J_1=10.4, J_2= 3.6 Hz, 1H, H_{8a}), 7.0-7.2 (m, $5H_{arom.}$). ^{13}C NMR: 14.2 ($-CH_2-\mathbf{CH_3}$), 17.8 (C_9), 33.4 (C_8), 38.0 (C_7), 46.2 (C_3), 58.5 ($-\mathbf{CH_2}-CH_3$), 65.4 (C_2), 84.3 (C_{8a}), 95.4 (C_6), 125.6 ($C_{4'}$), 127.3 ($C_{5'}$), 127.3 ($C_{3'}$), 127.4 ($C_{2'}$), 127.9 ($C_{6'}$), 146.2 ($C_{1'}$), 152.3 (C_5), 168.0 (C_{10}). MS *m/z* (%): 287 (82, M^+), 258 (50), 242 (20), 214 (100), 182 (5), 128 (21), 103 (8), 91 (10). Anal. cal. for $C_{17}H_{21}O_3N$: C 71.08, H 7.30, N 4.87 %, found: C 71.16, H 7.25, N 4.99 %.

Tert-butyl 7-phenyl-5-methyl-2,3,8,8a-tetrahydro-7H-oxazolo[3,2-a]pyridin-6-carboxylate (**17**) (60%). M.p. 120-121°C (MeOH). IR: 1690, 1580 cm^{-1}. ^1H NMR: 1.20 (s, 9H, $(CH_3)_3C$), 1.68 (ddd, J_1=11.7, J_2=10.3, J_3=5.8 Hz, 1H, $H_{8\beta}$), 2.23 (ddd, J_1=11.9, J_2=3.3, J_3=2.3 Hz, 1H, $H_{8\alpha}$), 2.55 (s, 3H, C_5-Me), 3.53 (m, 2H, H_3), 3.84 (ddd, J_1=9.5, J_2=8.9, J_3=,6.8 Hz, 1H, H_2), 4.17 (ddd, J_1=9.5 J_2=5.1, J_3=2.5 Hz, 1H, H_2), 4.20 (m, 1H, H_7), 4.41 (dd, J_1=10.4, J_2=3.5 Hz, 1H, H_{8a}), 7.1-7.2 (m, $5H_{arom.}$). ^{13}C NMR: 17.8 (C_9), 28.3 ($(\mathbf{CH_3})_3C$), 33.8 (C_8), 38.8 (C_7), 46.7 (C_3), 65.6 (C_2), 78.1 ($(CH_3)_3\mathbf{C}$), 84.4 (C_{8a}), 97.5 (C_6), 125.7 ($C_{4'}$), 127.6 ($C_{5'}$), 127.7 ($C_{3'}$), 128.0 ($C_{2'}$), 128.0 ($C_{6'}$), 147.1 ($C_{1'}$), 151.5 (C_5), 168.3 (C_{10}). MS *m/z* (%): 315 (28, M^+), 259 (59), 242 (100), 214 (29), 182 (43), 128 (20), 115 (12), 69 (15). Anal. cal. for $C_{19}H_{25}O_3N$: C 72.38, H 7.93, N 4.44 %, found: C 72.22, H 7.53, N 4.52 % .

Benzyl 7-phenyl 5-methyl-2,3,8,8a-tetrahydro-7H-oxazolo[3,2-a]pyridin-6-carboxylate (**18**) (60%). M.p. 118°C (MeOH/ether). IR: 1680, 1565 cm^{-1}. ^1H NMR: 1.69 (ddd, J_1=11.9, J_2=10.6, J_3=5.7 Hz, 1H, $H_{8\beta}$), 2.27 (ddd, J_1=12.0, J_2=3.6, J_3=2.5 Hz, 1H, $H_{8\alpha}$), 2.60 (s, 3H, C_5-Me), 3.54 (m, 2H, H_3), 3.82 (ddd, J_1=9.0 , J_2=8.9 , J_3= 6.1, Hz, 1H, H_2), 4.15 (ddd, J_1=8.9, J_2=6.2, J_3=2.9 Hz, 1H, H_2), 4.28 (d, J=5.2 Hz, 1H, H_7), 4.40 (dd, J_1=10.4, J_2=3.6 Hz, 1H, H_{8a}), 4.90 (d, J=13.0 Hz, 1H, **H**CHPh), 5.05 (d, J=13.0 Hz, 1H, HC**H**Ph), 7.1-7.3 (m, $10H_{arom.}$). ^{13}C NMR: 18.0 (C_9), 33.7 (C_8), 38.1 (C_7), 46.3 (C_3), 64.5 (CH_2Ph), 65.5 (C_2), 84.4 (C_{8a}), 95.0 (C_6), 125.9 ($C_{4'}$), 127.1($C_{5'}$), 127.1 ($C_{3'}$), 127.7 (3C, Bn), 128.1 ($C_{2'}$), 128.2 ($C_{6'}$), 128.2 (2C, Bn), 137.5 ($C_{1''}$, Bn). 146.1 ($C_{1'}$), 153.2 (C_5), 168.1 (C_{10}). MS *m/z* (%): 349 (75, M^+), 272 (18), 258 (92), 242 (18), 214 (78), 144 (10), 128 (22), 115 (12), 91 (100), 65 (15). Anal. cal. for $C_{22}H_{23}O_3N$: C 75.64, H 6.59, N 4.01%, found: C 75.46, H 6.36, N 3.99 %.

Methyl 7-phenyl-5,8a-dimethyl-2,3,8,8a-tetrahydro-7H-oxazolo[3,2-a] pyridin-6-carboxylate (**20**) (45 %). M.p. 130°C (MeOH/eter). IR ($CHCl_3$): 1680, 1600, 1570 cm^{-1}. ^1H NMR: 0.73 (s, 3H, C_{8a}-Me), 1.94 (dd, J_1=13.1 J_2=7.3 Hz, 1H, $H_{8\beta}$), 2.47 (dd, J_1=12.7, J_2=1.8 Hz, 1H, $H_{8\alpha}$), 2.54 (s, 3H, C_5-Me), 3.44 (3H, s,

OMe), 3.58 (t, J=6.9 Hz, 2H, H_3), 3.90 (t, J=6.9 Hz, 2H, H_2), 4.30 (d, J=7.3 Hz, H_7), 7.0-7.2 (m, $5H_{arom.}$). ^{13}C NMR: 18.5 (C_9), 24.0 (C_{11}), 37.0 (C_7), 39.5 (C_8), 46.3 (C_3), 50.3 (OMe), 62.3 (C_2), 90.6 (C_{8a}), 95.7 (C_6), 125.4 ($C_{4'}$), 127.4 ($C_{5'}$), 127.4 ($C_{3'}$), 127.8 ($C_{2'}$), 127.8 ($C_{6'}$), 145.6 ($C_{1'}$), 151.2 (C_5), 169.5 (C_{10}). MS m/z (%): 287 (30), 272 (55), 256 (10), 228 (32), 196 (29), 138 (42), 115 (380), 69 (100). Anal. calc for $C_{17}H_{21}O_3N$: C 71.05, H 7.36, N 4.87 %, found: C 70.75, H 7.57, N 4.64 %.

Ethyl 7-phenyl-5,8a-dimethyl-2,3,8,8a-tetrahydro-7H-oxazolo[3,2-a] pyridin-6-carboxylate (**21**) (43%) IR ($CHCl_3$): 1690, 1600, 1580 cm^{-1}. ^1H NMR: 0.77 (s, 3H, C_{8a}-Me), 0.91 (t, J=7.1 Hz, 3H, -CH_2-CH_3), 1.95 (dd, J_1=12.7, J_2=7.3 Hz, 1H, $H_{8\beta}$), 2.46 (dd, 1H, J_1=12.7, J_2=1.4 Hz, 1H, $H_{8\alpha}$), 2.54 (s, 3H, C_5-Me), 3.56 (t, J=7.1 Hz, 2H, H_3), 3.90 (q, J_1=7.1 Hz, -$\mathbf{CH_2}$-CH_3), 4.01 (t, J=7.1 Hz, 2H, H_2), 7,1-7.3 (m, $5H_{arom.}$). ^{13}C NMR: 14.2 (-CH_2-$\mathbf{CH_3}$), 18.5 (C_9), 24.2 (C_{11}), 37.3 (C_7), 39.7 (C_8), 46.3 (C_3), 58.8 (-$\mathbf{CH_2}$-CH_3), 62.3 (C_2), 90.7 (C_{8a}), 95.5 (C_6), 125.4 ($C_{4'}$), 126.7 ($C_{5'}$), 127.7 ($C_{3'}$), 127.9 ($C_{2'}$), 128.1 ($C_{6'}$), 145.4 ($C_{1'}$), 152.0 (C_5), 169.5 (C_{10}).

Table 2 ^{13}C NMR Chemical shifts for oxazolopyridines **1, 5, 7-13.**

C	1	*5	7	8	9	10	11	12	13
2	63.0	63.2	64.3	63.3	64.5	63.2	63.0	63.2	63.2
3	46.7	47.0	46.3	47.0	46.3	47.0	46.8	47.0	47.0
5	153.4	153.8	152.0	153.5	152.0	153.5	153.6	153.0	153.0
6	92.1	92.6	92.8	92.7	92.9	92.9	92.6	93.4	93.6
7	41.0	41.2	41.0	41.4	41.3	41.7	41.1	41.1	41.1
8	52.2	52.6	49.6	52.6	49.8	53.8	52.9	52.7	52.6
8a	89.0	90.2	92.1	90.1	92.0	90.4	90.0	90.3	90.1
9	18.4	18.7	18.3	18.7	18.3	18.8	18.6	18.6	18.5
10	168.6	169.0	168.9	169.0	168.0	169.2	166.8	169.3	168.7
11	170.6	171.7	62.5	171.0	62.7	170.0	170.2	170.9	171.3
12	25.5	25.8	25.1	25.8	25.2	25.9	25.7	25.7	25.6
R^1	**Me**	**Me**	**Me**	**Et**	**Et**	**Me**	**Me**	**Me**	**Et**
	50.2	50.6	50.6	14.2	14.2	50.6	50.4	50.5	14.0
				59.1	59.1				59.0
R^2	**Me**	**Et**	-	**Me**	-	**t_{Bu}**	**Bn**	**Et**	**Me**
	52.2	14.2		51.8		28.1	66.3	14.2	51.3
		60.6				80.8	128.1(3)	60.4	
							135.8		
							128.4(2)		
Ar	**3-NO_2Ph**	**3-NO_2Ph**	**3-NO_2Ph**	**3-NO_2Ph**	**3-NO_2Ph**	**3-NO_2Ph**	**3-NO_2Ph**	**3-ClPh**	**3-ClPh**
1'	147.2	147.1	148.3	147.6	148.5	147.8	147.3	147.2	147.2
2'	122.2	122.6	122.4	122.6	122.6	122.6	122.5	126.3	126.1
3'	148.2	148.5	148.3	148.5	148.5	148.4	148.4	134.2	135.5
4'	121.0	121.0	120.8	121.3	120.9	121.3	121.2	125.9	125.9
5'	128.9	129.1	128.9	129.1	128.9	129.1	129.1	129.4	129.3
6'	133.6	133.9	133.7	133.6	133.9	133.9	133.8	127.8	127.5

Solvent $CDCl_3$. *DMSO-d_6. TMS as intenal standard.

General procedure of reductions with $LiAlH_4$

Lithium aluminum hydride (5 mmol) was added to a solution of the oxazolopyridine (1 mmol) in anhydrous ether (10 ml) under Argon. The mixture was stirred for 3 hours at room temperature. The reaction was monitored by TLC, and upon completion, ethyl acetate was added. The solvent was removed and the products were isolated in 42-52 % yield after flash chromathographic purification over silica gel (EtOAc) and crystallization.

Acetylation of 8-hydroxymethyl-2,3,8,8a-tetrahydro-7H-oxazolo[3,2-a]pyridines

200 mg of hydroxymethyloxazolopyridines in anhydrous pyridine (0.5 ml) was allowed to react with acetic anhydride (0.5 ml) at room temperature. After usual work-up the acetates were isolated in quantitative yield.

Methyl 8-Hydroxymethyl-7-(3-nitrophenyl)-5,8a-dimethyl-2,3,8,8a-tetrahydro-7H-oxazolo[3,2-a]pyridine-6-carboxylate (**7**). IR ($CHCl_3$): 3420, 1680, 1550 cm^{-1}. ^1H NMR: 0.79 (s, 3H, C_{8a}-Me), 2.66 (dd, J_1=8.5, J_2=4.0 Hz, 1H, H_8), 2.60 (s, 3H, C_5-Me), 3.45 (m, 1H, H_{11}), 3.47 (s, 3H, OMe), 3.73 (m, 2H, H_3), 3.76 (m, 1H, H_{11}), 4.05 (m, 2H, H_2), 4.30 (s, 1H, H_7), 7.40 (dd, J=7.9 Hz, 1H, $H_{5'}$), 7.60 (d, J=7.8 Hz, 1H, $H_{6'}$), 8.02 (da, J=7.9 Hz, 1H, $H_{4'}$), 8.09 (s, 1H, $H_{2'}$). MS *m/z* (%): 362 (20, M^+), 345 (38), 331 (68), 303 (60), 273 (20), 257 (12), 194 (35), 115 (50), 86 (45).

Methyl 8-Acetoxymethyl 7-(3-nitrophenyl)-5,8a-dimethyl-2,3,8,8a-tetrahydro-7H-oxazolo[3,2-a]pyridine-6-carboxylate (**7a**). M.p.=144°C (Ether). IR: 1750, 1690, 1570 cm^{-1}. ^1H NMR: 0.78 (s, 3H, C_{8a}-Me), 2.16 (s, 3H, CH_3CO), 2.76 (dd, J_1=10.0, J_2=4.0 Hz,1H, H_8), 3.48 (s, 3H, OMe), 3.57 (dd, J_1=10.0, J_2=10.0 Hz, 1H, H_{11}), 3.63 (dd, J_1=6.0, J_2=6.0 Hz, 2H, H_3), 4.06 (dd, J_1=6.0, J_2=6.0 Hz, 2H, H_2), 4.42 (s, 1H, H_7), 4.48 (dd, J_1=10.0, J_2=4.0 Hz, 1H, H_{11}), 7.43 (dd, J=7.8 Hz, 1H, $H_{5'}$), 7.56 (d, J=7.7 Hz, 1H, $H_{6'}$), 8.0 (d, J=7.9 Hz, 1H, $H_{4'}$), 8.08 (s, 1H, $H_{2'}$). ^{13}C NMR: 18.5 (C_9), 21.1 (**CH_3**CO), 25.1 (C_{12}), 40.3 (C_7), 46.2 (C_3), 46.7 (C_8), 50.6 (OMe), 62.9 (C_{11}), 63.2 (C_2), 90.7 (C_{8a}), 91.6 (C_6), 120.9 ($C_{4'}$), 122.5 ($C_{2'}$), 128.9 ($C_{5'}$), 133.9 ($C_{6'}$), 148.3 ($C_{1'}$), 148.3 ($C_{3'}$), 152.2 (C_5), 168.1 (C_{10}), 171.0 (**CH_3**CO).

Ethyl 8-Hydroxymethyl-7-(3-nitrophenyl)-5,8a-dimethyl-2,3,8,8a-tetrahydro-7H-oxazolo[3,2-a]pyridine-6-carboxylate (**9**). (42%). IR ($CHCl_3$): 3490, 1680, 1570 cm^{-1}. ^1H NMR: 0.81 (s, 3H, C_{8a}-Me), 0.95 (t, J=7.1 Hz, 3H, -CH_2-**CH_3**), 2.59 (s, 3H, C_5-Me), 2.66 (dd, J_1=8.9, J_2=4.6 Hz, 1H, H_8), 3.46 (m, 1H, H_{11}), 3.73 (m, 1H, H_{11}), 3.76 (s, 2H, H_3), 4.06 (m, 2H, H_2), 4.09 (q, J=7.1 Hz, 2H, -**CH_2**-CH_3), 4.26 (s, 1H, H_7), 7.42 (t, J=7.9 Hz, 1H, $H_{5'}$), 7.62 (d, J=7.9 Hz, 1H, $H_{6'}$), 8.03 (d, J=7.8 Hz, 1H, $H_{4'}$), 8.10 (s, 1H, $H_{2'}$).

Ethyl 8-Acetoxymethyl 7-(3-nitrophenyl)-5,8a-dimethyl-2,3,8,8a-tetrahydro-7H-oxazolo[3,2-a]pyridine-6-carboxylate (**9a**). IR ($CHCl_3$): 1740, 1690, 1510 cm^{-1}. ^1H NMR: 0.80 (s, 3H, C_{8a}-Me), 0.94 (t, J=7.0 Hz, 3H, -CH_2-**CH_3**), 2.18 (s, 3H, -CH_3CO), 2.57 (s, 3H, C_5-Me), 2.75 (dd, J_1=10.8, J_2=4.0 Hz, 1H, H_8), 3.55 (dd, J_1=10.8 , J_2=10.8 Hz, 1H, H_{11}), 3.63 (s, 2H, H_3), 3.96 (q, J=7.0 Hz, 2H, -**CH_2**-CH_3), 4.07 (m, 2H, H_2), 4.44 (s, 1H, H_7), 4.46 (dd, J_1=10.8, J_2=4.0 Hz, 1H, H_{11}), 7.43 (t, J=7.8 Hz, 1H, $H_{5'}$), 7.57 (d, J=7.7 Hz, 1H, $H_{6'}$), 8.05 (d, J=7.9 Hz, $H_{4'}$), 8.10 (s, 1H, $H_{2'}$). ^{13}C NMR: 14.3 (-CH_2-**CH_3**), 18.5 (C_9), 21.1 (**CH_3**CO), 25.2 (C_{12}), 40.4 (C_7), 46.3 (C_3), 46.7 (C_8), 59.1 (-**CH_2**-CH_3), 62.9 (C_{11}), 63.3 (C_2), 90.8 (C_{8a}), 91.9 (C_6), 120.9 ($C_{4'}$), 122.6 ($C_{2'}$), 128.9 ($C_{5'}$), 134.0 ($C_{6'}$), 148.4 ($C_{3'}$), 148.4 ($C_{1'}$), 152.0 (C_5), 168.6 (C_{10}), 171.2 (**CH_3**CO).

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