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2,3,8,8a-TETRAHYDRO-7*H*-OXAZOLO[3,2-*a*]PYRIDINE: A NEW HETEROCYCLIC SYSTEM[1]

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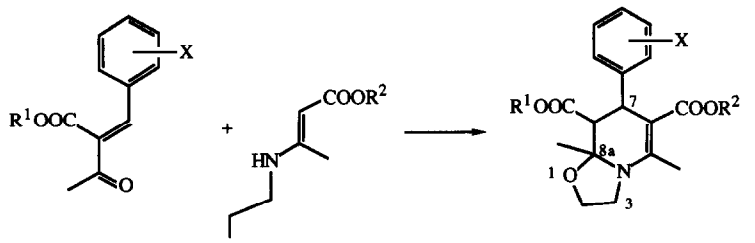
Abstract. Compounds with the previously unreported skeleton of 2,3,8,8a-tetrahydro-7*H*-oxazolo [3,2-*a*]pyridine were prepared by reactions between α,ß-unsaturated ketones or aldehydes and N-hydroxyethyl-enamines of acetoacetate esters. Other compounds like 1,4-dihydropyridines, aminocyclohexene and cyclohexadiene derivatives were also formed as minor products.

Introduction

During the course of our research on the preparation of new products with Ca^{2+} antagonist and/or antihypertensive activity that will permit activity levels over longer times, a series of 2,3,8,8a-tetrahydro-7*H*-oxazolo[3,2-*a*]pyridines was prepared. Strictly speaking, it does not appear that substances with this skeleton have been reported previously. However, reports have been made on the formation of products with an analogous skeleton of oxazolo[3,2-*a*]isoquinoline by reacting isoquinoline derivatives with ethylene oxide in acetic acid medium [2] or by cyclization of N-substituted isoquinolines [3]. None of the compounds prepared by us showed appreciable activity as calcium antagonists in assays on *Tenia coli* from guinea pig, although they did show antihypertensive activity and relevant bradicardic effects in some cases.

Methods and Results

The oxazolo[3,2-*a*]pyridines were prepared by reaction of α,ß-unsaturated ketones (**1**) with N-hydroxyethylenamines of ß-ketoesters (**2**), affording a mixture of several products, among which the major one proved to be the oxazolopyridine in all cases.



1a X = *m*-NO_2, R^1= Me **2a** R^2= Me **3a** X = *m*-NO_2, R^1=R^2= Me

The reaction between **1a** and **2a** was carried out under prolonged refluxing in methanol, isolating from the reaction medium a solid **3a** mp=170-172°C (MeOH) in 46% yield. The constitution of **3a** was established from the following facts: its mass spectrum and elemental analysis were in agreement with a molecular formula of $C_{19}H_{22}O_7N_2$, which corresponded to the sum of formulas of the reagents with the loss of one molecule of water. The IR spectrum exhibited bands of saturated (1745 cm^{-1}) and unsaturated (1690 cm^1) ester groups and, at the same time, the absence of bands assignable to OH or NH groups.

On comparing the ^{13}C NMR spectrum of **3a** with those of the reagents, it may be seen that the disubstituted aromatic ring, the two methyl esters, the methyl group of the enamine fragment (18.4 ppm), the two methylenes (-OCH_2CH_2N-) and two nonprotonated olefinic carbon atoms persisted in the new molecule. The modified signals corresponded to a nonprotonated sp^3 carbon atom which must be functionalized (89.9 ppm), two methines (52.2 and 41.0 ppm) and a methyl group (25.5 ppm). In the ^1H NMR spectrum the two methines appeared as singlets at 4.46 and 3.34 ppm and the methyl group at 0.83 ppm.

Taking these data into account, the bicyclic structure **3a** was proposed for this compound. To confirm its constitution, direct and long range heteronuclear 2D-NMR correlations were carried out (Table 1), observing that the experimental connectivities found for protons 7 and 8 with the neighbouring carbon atoms were in agreement only with structure **3a**.

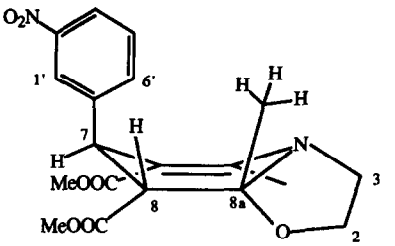
Table 1. Connectivity data from direct and long-range heteronuclear $^1H/^{13}C$ NMR correlations for compound **3a**

H	δ(ppm)	Attached C δ(ppm)	long-range connected C to that H_i
7	4.46	41.0	6, 8, 8a, 9, 1'
8	3.34	52.2	7, 8a, 9, Me-C_{8a}, CO(170.6 ppm)
Me-C_5	2.62	18.4	5, 6
Me-C_{8a}	0.83	25.5	8, 8a

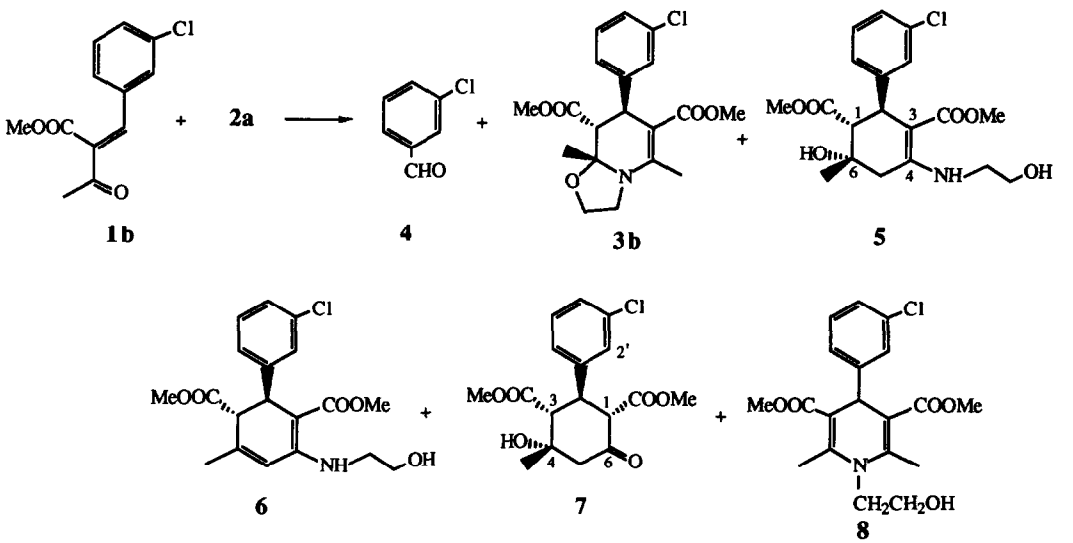
The relative stereochemistry of compound **3a** was established taking into consideration the NOE's observed on irradiation of protons 7 and 8 and Me-C_{8a} (Table 2) and the absence of coupling between protons 7 and 8 in the ^1H NMR spectrum, implying a dihedral angle of approximately 90° between them. The proposed conformation also accounts for the shielding of the methyl C_{8a} by the benzene ring and it is close to that of nifedipine and other 1,4-dihydropyridines [4].

Table 2. NOE differences observed for **3a**

{H}	Detected NOEs
7	8, 1', 6'
8	7, 1', 6', Me-C_{8a}
Me-C_{8a}	2, 3, 8, 1', 6'



A complete structural study of the secondary compounds was carried out using **1b** and **2a** as starting substances, since in this case they appeared at higher proportions in the reaction mixture with respect to the oxazolopyridine **3b**. The reaction was also carried out under methanol reflux conditions, isolating **3b** (37%), **4** (6.2%), **5** (20%), **6** (12%), **7** (17%) and **8** (3.1%) as reaction products.



Scheme 1

Compound **4** was identified as 3-chlorobenzaldehyde by comparison with authentic samples.

Compound **5** was separated by direct crystallization of the reaction product, mp=177-179°C (MeOH). Its EIMS and elemental analysis were in agreement with the formula $C_{19}H_{22}O_6ClN$. The IR spectrum showed an intense band in the zone of the N-H and/or O-H absorption and two bands corresponding to saturated and conjugated ester groups (1735 and 1650 cm^{-1} respectively).

In the ^1H and ^{13}C NMR spectra of **5** the most significant variations with respect to the starting compounds were the presence of a single methyl group (excepting the two methoxyl groups) that could be geminal to an oxygenated function (1.17 ppm) and the appearance of a methylene group as an AB system, with signals centred at 2.51 and 2,63 ppm, and of two methine doublets (2.46 and 4.09 ppm) coupled each other

(J=10.6 Hz).The rest of the signals corresponded to the aromatic system and the -OCH_2CH_2N- grouping, present in the starting enamine. With these data, the molecular constitution shown in the Scheme 1 was proposed for compound **5.**

The relative stereochemistry of **5** was deduced from the NOE effect observed between the Me-C_6 and H_1, and the value of 10.6 Hz for the coupling constant between H_1 and H_2 in the proton spectrum.

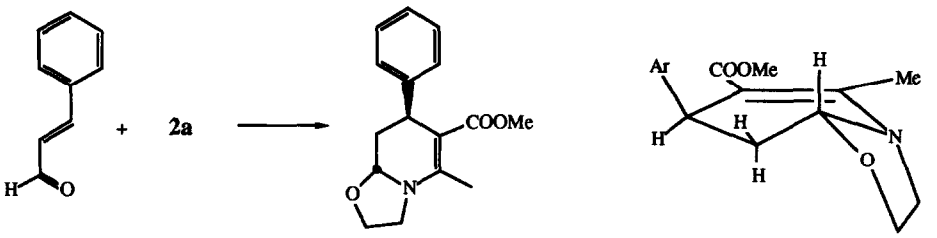
The EIMS of compound **6** displayed a molecular ion M^+ at *m/z* 379, in agreement with the molecular formula $C_{19}H_{20}O_5ClN$. Comparison of its spectroscopic data with those of **5** showed that in **6** one molecule of water must have been eliminated from the tertiary alcohol present in **5** since in its ^1H and ^{13}C spectra there was a signal of one methyl group on a double bond (1.83; 24.3 ppm), an olefinic methine (6.29; 117.9 ppm) and an additional non-protonated sp^2 carbon atom (142.6 ppm) which owing to its deshielding must have been within a conjugated system , the oxygenated carbon signal at 67.5ppm having disappeared. The UV spectrum showed a bathochromic shift from 297 nm in **5** to 348 nm in **6**, which agrees with the presence of the homoannular diene. The relative *trans*-configuration between the phenyl and methoxycarbonyl groups persists with respect to compound **5**, since H_1 and H_2 are not coupled in the ^1H NMR spectrum , which indicated a dihedral angle close to 90° between them.

Compound **7** was a solid of mp=164-166°C (MeOH) and molecular formula $C_{17}H_{19}O_6Cl$, corresponding to the loss of the ethanolamine fragment with respect to the starting compounds. In its ^{13}C NMR spectrum showed three absorptions due to carbonyl groups, corresponding to two ester groups (170.8; 168.6 ppm) and a ketone group (202.8 ppm), in agreement with the absorption in the IR at 1740 and 1720 cm^{-1}; among others, signals are also seen of three aliphatic methines (43.7, 56.1 and 61.5 ppm), an unprotonated oxygenated carbon atom (72.6 ppm) and a methylene (43.7 ppm). Joint analysis of the ^1H and ^{13}C NMR spectra was consistent with a cyclohexanone in which the following groupings would be present: two methoxycarbonyl groups, the aromatic ring and a methyl group geminal to a hydroxyl group. The geminal protons to the ester functions and the aromatic ring are coupled between each other with coupling constant values (12.6 and 12.2 Hz respectively) concordant with a relative *trans*-diaxial situation; accordingly, the relative stereochemistry shown in Scheme 1 was proposed for compound **7**. As a confirmation of its structure, the hydroxy ketone **7** was obtained from the enamine **5** when this compound was treated with Ac_2O/pyridine [5].

Compound **8** was purified in the form of acetate and corresponds to the expected N-hydroxyethyl-dihydropyridine.

Attempting to check the validity of this type of reaction for the preparation of other oxazolo[3,2-*a*]pyridines, assays without optimization were made with other Knoevanagel adducts obtained from 2- and 3-chlorobenzaldehyde, furfuraldehyde, 2-thienylcarbaldehyde, 2-pyrrolylcarbaldehyde and enamines of other esters (ethyl, *tert*-butyl, benzyl) of acetoacetic acid, achieving yields between 25 and 37% of the corresponding oxazolopyridine derivatives (**3c-3h**).

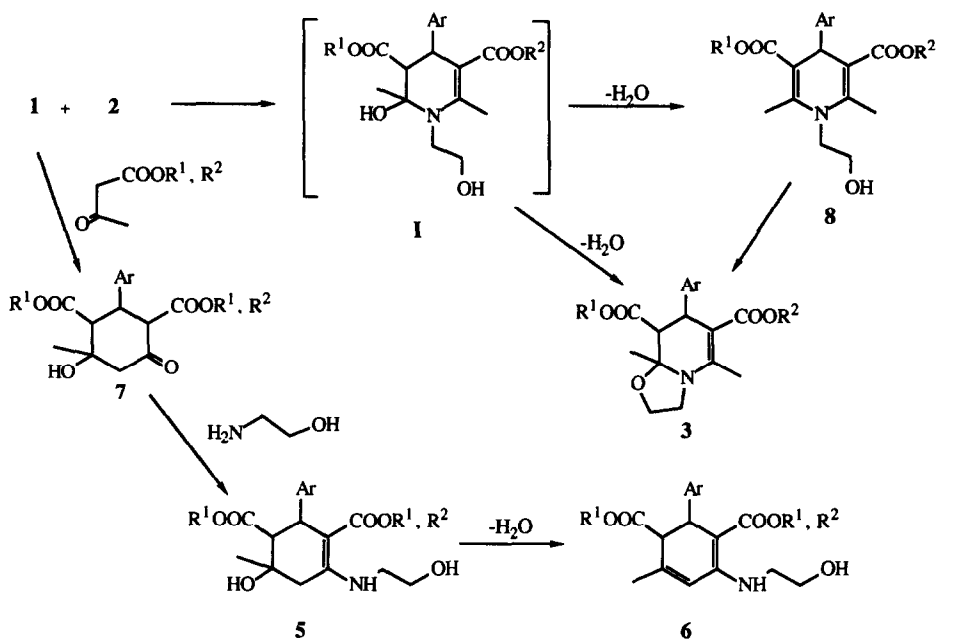
It was also observed that the reaction occurs in a similar fashion using simpler conjugated carbonyl systems as reagents. Thus, the reaction between cinamaldehyde and the enamine **2a** led to **3i**: mp=116-118°C (MeOH) in 43% yield. For this compound, the relative stereochemistry was established on the basis of couplings between protons 7, 8 and 8a in its ^1H NMR spectrum (see experimental part).



3i

The formation of oxazolo[3,2-*a*]pyridines through this reaction could be accounted for in terms of the removal of water from intermediate **I** (Scheme 2) as it is proposed in the formation of 1,4-dihydropyridines[6]. Another possible route would be the Michael addition of the primary hydroxyl group on position 2 of the already formed 1,4-dihydropyridine **8**, as has been proposed by Singh and Kumar [7] in the formation of another oxazoline system. However, in our case, the second possibility can be ruled out by virtue of the fact that compound **8**, which is one of the secondary products, did not evolve towards the oxazolopyridine **3** under the prevailing reaction conditions.

The formation of the minor products could be explained by a Michael reaction between the Knoevanagel adduct and the ß-ketoester resulting from the degradation of the Knoevenagel adduct and the enamine originating the hydroxy-ketone **7**, which by condensation with ethanolamine, would afford **5**, and followed of dehydration would lead to **6**.



Scheme 2

Table 3: ^{13}C Chemical shifts for oxazolopyridines 3a-3i

C	3a	3b	*3c	3d	3e	3f	3g	3h	3i
2	63,0	62,7	63,2	63,2	63,0	63.1	63.3	63.1	65.4
3	46,7	46,3	47,0	46,7	46,8	46.8	47.0	47.0	46.3
5	153,4	152,6	153,0	152,2	153,6	152.0	152.1	152.8	152.8
6	92,1	91,9	93,4	96,5	92,6	92.7	95.6	93.0	95.1
7	41,0	40,1	41,1	38,1	41,1	35.8	37.2	35.1	37.9
8	52,2	51,8	52,7	52,8	52,9	47.5	52.9	51.4	33.5
8a	89,9	89,4	90,3	90,0	90,0	90.1	90.3	90.4	84.5
9	18.4	18.1	18.6	18.3	18.6	18.2	18.5	18.6	17.9
10	168.6	168.2	169.3	167.8	166.8	169.2	169.4	169.8	169.0
11	170.6	170.4	170.9	172.0	170.2	170.9	171.1	171.3	
12	25.5	25.2	25.7	26.4	25.7	23.9	25.1	24.3	
COOMe	50.2	50.0	50.5	51.7	50.4	51.4	50.7	50.8	
COOR	Me	Me	Et	*t*-Bu	Bn	Me	Me	Me	Me
	52.2	51.3	60.4	78.6	66.3	50.4	51.6	51.6	50.3
			14.2	27.9(3)	128.1(3)				
					135.8				
					128.4(2)				
Ar	3-NO_2-Ph	3-Cl-Ph	3-Cl-Ph	2-NO_2-Ph	3-NO_2-Ph	2-furyl	2-thienyl	2-pyrrolyl	phenyl
1'	147.2	147.2	147.2	140.5	147.3	156.3			146.2
2'	122.2	125.9	126.3	149.3	122.5		150.4	136.0	128.1
3'	148.2	132.9	134.2	125.1	148.4	140.5	126.4	115.7	127.5
4'	121.0	125.9	125.9	127.3	121.2	110.3	124.0	108.7	125.9
5'	128.9	129.9	129 4	132.2	129.1	106.1	123.4	105.3	127.5
6'	133.6	127.0	127.8	131.1	133.8				128.2

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

EXPERIMENTAL.

General experimental information. Mps were determined in capillaries on a Buchi 510 instrument and are uncorrected. UV spectra were recorder in EtOH on a Hitachi 100-60 spectrometer. IR spectra were obtained in KBr disks on a Beckman Acculab VIII spectrophotometer. Unless otherwise stated ^1H NMR: (200.13 MHz) and ^{13}C NMR: (50.3 MHz) spectra were measured in $CDCl_3$ or DMSO-d_6 with TMS as internal standard on a Bruker WP 200 SY. δ values are expressed in ppm. EIMS (70 ev) run on a VG-TS-250 mass spectrometer.

Preparation of enamines (2)
The enamines were prepared by addition of ethanolamine (10 mmoles) to the alkyl acetoacetate (10 mmoles) with stirring. The reaction mixture was allowed to stand at room temperature for 24 h and it was extracted with CH_2Cl_2, washed with water, dried and evaporated to give the enamines 2 in 95-98% yield.

General procedure of preparation of 2,3,7,8-tetrahydro-7H-oxazolo[3,2-a]pyridines (3)
A solution of the Knoevenagel adduct 1 (5.0 g, 21 mmoles) and enamine 2 (3,19 g, 21 mmoles) in MeOH (25 ml) was refluxed for 24 h. The solvent was removed and the oxazolo[3,2-*a*]pyridines were isolated by crystallization from the reaction product or after chromatographic purification over silica gel and later crystallization.

Dimethyl 7-(3-nitrophenyl)-5,8a-dimethyl-2,3,7,8-tetrahydro-7*H*-oxazolo[3,2-*a*]pyridin-6,8-dicarboxylate (3a) (46%). M.p.169-171°C (MeOH). IR: 1745, 1690, 1570 cm^{-1}. ^1H NMR: 0.83 (*s*, 3H, C_{8a}-Me), 2.63 (*s*, 3H, C_5-Me), 3.34 (*s*, 1H, H_8), 3.44 (*s*, 3H,C_6-COOMe), 3.73 (*s*, 3H, C_8-COOMe), 3.80 (*m*, 2H, H_3), 4.02 (*m*, 2H, H_2), 4.46 (*s*, 1H, H_7), 7.47 (*dd*, J_1=8.2, J_2=7.8 Hz, 1H, $H_{5'}$), 7.64 (*d*, J=7.8 Hz, 1H, $H_{6'}$), 8.04 (*d*, J=8.2 Hz, 1H, H_4), 8.12 (*s*, 1H, $H_{2'}$). MS *m/z* (%): 390 (8, M^+), 375 (5), 359 (15), 331(100). Anal. cal. for $C_{19}H_{22}O_7N_2$: C 58.46, H 5.64 , N 7.18 %, found: C 58.45, H 5.43, N 7.05 %.

Dimethyl 7-(3-chlorophenyl)-5,8a-dimethyl-2,3,7,8-tetrahydro-7*H*-oxazolo[3,2-*a*]pyridin-6,8-dicarboxylate (**3b**) (37%). M.p.124-126°C (MeOH). IR: 1740, 1690, 1585 cm^{-1}. ^1H NMR: 0.82 (*s*, 3H, C_{8a}-Me) , 2.55 (*s*, 3H, C_5-Me) 3.34 (*s*, 1H, H_8), 3.40 (*s*, 3H,C_6-COOMe), 3.70 (*m*, 2H, H_3), 3.72 (*s*, 3H, C_8-COOMe), 4.05 (*m*, 2H, H_2), 4.30 (*s*, 1H, H_7), 7.10-7.40 (*m*, $4H_{arom}$). MS *m/z* (%): 379 (11, M^+), 364 (5), 348 (17), 320(100). Anal. cal. for $C_{19}H_{22}O_5NCl$: C 60.0, H 5.82 , N 3.63 %, found: C 60.0, H 5.79, N 3.69 %.

Ethyl 7-(3-chlorophenyl)-5,8a-dimethyl-8-methoxicarbonyl-2,3,7,8-tetrahydro-7*H*-oxazolo[3,2-*a*]pyridin-6-carboxylate (**3c**) (35%). M.p.131-133°C (MeOH). IR: 1730, 1675, 1575 cm^{-1}. ^1H NMR: 0.84(*s*, 3H, C_{8a}-Me) , 1.28 (*t*, J=7.2 Hz, 2H, -CH_2**CH_3**), 2.57 (*s*, 3H, C_5-Me), 3.33 (*s*, 1H, H_8), 3.70 (*m*, 2H, H_3), 3.75 (*s*, 3H, C_8-COOMe), 4.05 (*m*, 2H, H_2), 4.15 (*q*, J=7.2 Hz, 3H, -**CH_2**CH_3), 4.35 (*s*, 1H, H_7), 7.10-7.40 (*m*, $4H_{arom}$). MS *m/z* (%): 393 (6, M^+), 362(9), 334(41), 320(100).

Tert-butyl 7-(2-nitrophenyl)-5,8a-dimethyl-8-methoxycarbonyl-2,3,7,8-tetrahydro7*H*-oxazolo[3,2-*a*]pyridin-6-carboxylate (**3d**) (29%). M.p. 214-216°C (MeOH). IR: 1730, 1670, 1575 cm^{-1}. ^1H NMR: 1.05 (*s*, 3H, C_{8a}-Me), 1.05 (*s*, 9H, C_8-C(Me)$_3$), 2.56 (*s*, 3H, C_5-Me), 3.28 (*s*, 1H, H_8), 3.70 (*m*, 2H, H_3), 3.76 (*s*, 3H, C_6-COOMe), 4.05 (*m*, 2H, H_2), 4.82 (*s*, 1H, H_7), 7.30-7.60 (*m*, $3H_{arom}$), 7.95(*d*, J=8.1Hz, 1H, $H_{3'}$). MS *m/z* (%): 433 (10, M^++1), 416(30), 360(21), 332(42), 316(100).

Benzyl 7-(2-nitrophenyl)-5,8a-dimethyl-8-methoxycarbonyl-2,3,7,8-tetrahydro-7*H*-oxazolo[3,2-*a*]pyridin-8-carboxylate (**3e**) (29%). M.p.126-128°C (ether). IR: 1730, 1685, 1555, 1525 cm^{-1}. ^1H NMR: 0.81 (*s*, 3H, C_{8a}-Me), 2.55 (*s*, 3H, C_5-Me), 3.43 (*s*, 1H, H_8), 3.70 (*m*, 2H, H_3), 3.66 (*s*, 3H, C_6-COOMe), 3.90 (*m*, 2H, H_2), 4.50 (*s*, 1H, H_7), 5.15(*d*, J=5.8Hz, 1H, -**HC**HPh), 5.17(*d*, J=5.8 Hz, 1H, -**HC**HPh), 7.20-7.40(*m*, 5H, -CH_2**Ph**), 7.30-7.50 (*m*, $2H_{arom}$), 8.02(*d*, J=7.8Hz, 1H, $H_{4'}$), 8.11(*s*, 1H, $H_{2'}$). MS *m/z* (%) 466 (9, M^+), 435 (10), 408 (22), 375 (22), 331 (100).

Dimethyl 7-(2-furyl)-5,8a-dimethyl-2,3,7,8-tetrahydro-7*H*-oxazolo[3,2-*a*]pyridin-6,8-dicarboxylate (**3f**) (37%). M.p.120-122°C (ether). IR: 1740, 1675, 1560 cm^{-1}. ^1H NMR: 0.91 (*s*, 3H, C_{8a}-Me), 2.51 (*s*, 3H, C_5-Me), 3.56 (*s*, 3H, C_8-COOMe), 3.62 (*s*, 1H, H_8), 3.67 (*m*, 2H, H_3), 3.67 (*s*, 3H, C_6-COOMe), 4.03 (*m*, 2H, H_2), 4.34 (*s*, 1H, H_7), 5.90(*d*, J=2.4 Hz, 1H, $H_{5'}$), 6.22(*m*, 1H, $H_{4'}$), 7.30(*s*, 1H, $H_{3'}$). MS *m/z* (%): 335 (11, M^+), 320 (2), 304 (14), 276 (100).

Dimethyl 7-(2-thienyl)-5,8a-dimethyl-2,3,7,8-tetrahydro-7*H*-oxazolo[3,2-*a*]pyridin-6,8-dicarboxylate (**3g**) (25%). M.p.127-129°C (MeOH). IR: 1740, 1670, 1550 cm^{-1}. ^1H NMR: 0.96 (*s*, 3H, C_{8a}-Me), 2.54 (*s*, 3H, C_5-Me), 3.49 (*s*, 1H, H_8), 3.54 (*s*, 3H, C_8-COOMe), 3.69 (*s*, 3H, C_6-COOMe), 3.70 (*m*, 2H, H_3), 4.04 (*m*, 2H, H_2), 4.57 (*s*, 1H, H_7), 6.85 (*d*, J= 3.5 Hz, 1H, $H_{5'}$) 6.88(*dd*, J_1=5.0, J_2=3.5 Hz, 1H, $H_{4'}$), 7.12 (*d*, J=5.0 Hz, 1H, $H_{3'}$). MS *m/z* (%): 351 (10, M^+), 336(2), 320(11), 292(100).

Dimethyl 7-(2-pyrrolyl)-5,8a-dimethyl-2,3,7,8-tetrahydro-7*H*-oxazolo[3,2-*a*]pyridin-6,8-dicarboxylate (**3h**) (32%). M.p.173-175°C (MeOH). IR: 1750, 1670, 1550 cm^{-1}. ^1H NMR: 0.86 (*s*, 3H, C_{8a}-Me), 2.53 (*s*, 3H, C_5-Me), 3.40 (*s*, 1H, H_8), 3.45 (*s*, 3H, C_8-COOMe), 3.66(*s*, 3H, C_6-COOMe), 3.70(*m*, 2H, H_3), 4.03 (*m*, 2H, H_2), 4.42 (*s*, 1H, H_7), 5.95 (*m*, 1H, $H_{5'}$), 6.09 (*dd*, J_1= 5.8, J_2=2.8 Hz, 1H, $H_{4'}$), 6.56 (*m*, 1H, $H_{3'}$), 8.26 (*m*, 1H, NH). MS *m/z* (%): 334 (32, M^+), 319 (1), 303(10), 275(100).

Methyl 7-phenyl-5-methyl-2,3,7,8-tetrahydro-7*H*-oxazolo[3,2-*a*]pyridin-6-carboxylate (**3i**) (43%). M.p.116-118°C (MeOH). IR: 1685, 1570 cm^{-1}. ^1H NMR: 1.67 (*ddd*, J_1=11.8, J_2=10.5, J_3=5.3 Hz, 1H, $H_{8\beta}$), 2.26 (*ddd*, J_1=11.8, J_2=3.7 J_3=2.4 Hz, 1H, $H_{8\alpha}$), 2.58 (*s*, 3H, C_5-Me), 3.48 (*s*, 3H, C_6-COOMe), 3.54 (*m*, 2H, H_3), 3.83 (*ddd*, J_1=9.5, J_2=8.8 J_3=6.9 Hz, 1H, H_2), 4,15 (*ddd*, J_1=8.8, J_2=5.8, J_3=3.2 Hz, 1H, H_2), 4.21 (*m*, $W_{h/2}$=5.8 Hz, 1H, H_7), 4.35 (*dd*, J_1=10.5, J_2=3.7 Hz, H_{8a}), 7.10-7.30 (*m*, $5H_{arom}$). MS *m/z* (%): 273 (74, M^+), 258 (23), 242(18), 214(100), 196 (41). Anal. cal. for $C_{16}H_{19}O_3N$: C 70.32, H 6.96 , N 5.10 %, found: C 70.32, H 7.09, N 4.93 %.

Reaction between methyl 2-(3-chlorobencyliden)acetylacetate and methyl N-(2-hydroxyethylamino)crotonate.

According to the general procedure of preparation of oxazolo[3,2-*a*]pyridines, **1b** (40.0 g, 168 mmoles) and **2a** (26.4 g, 168 mmoles) in MeOH (120 ml) were refluxed for 24 h. The solvent was removed and **5** (13.5g, 20%) was obtained by crystallization. After evaporation of solvent the mother liquors were chromatographed over silica gel (850g, eluents hexane/EtOAc 7:3, 4:6, 1:1 and EtOAc/MeOH 1:0.1) yielding **3b** (23.5 g, 37%), **4** (4.1 g, 6.2%), **6** (7 7 g, 12%), **7** (16 g, 17%) and **8** (2.1 g, 3.1%).

Dimethyl 2-(3-chlorophenyl)-6-hydroxy-4-(2-hydroxyethylamino)-6-methylcyclohex-3-en-1,3-dicarboxylate (**5**) M.p.177-179°C (MeOH). IR: 3300, 1740, 1650, 1590 cm^{-1}. ^1H NMR: 1.17 (*s*, 3H, C_6-Me), 2.46 (*d*, J=10.6 Hz, 1H, H_1), 2.51 (*d*, J=17.2 Hz, 1H, H_5), 2.63 (*d*, J=17.2 Hz, 1H, H_5), 3.16 (*s*, 3H, C_1-COOMe), 3.45 (*s*, 3H, C_3-COOMe), 3.10-3.40 (*m*, 2H, -NHC**H**$_2$-), 3.50-3.60 (*m*, 2H, -**CH**$_2$**OH**), 4,09 (*d*, J=10.6 Hz, 1H, H_2), 4.50 (*s*, 1H, C_6-OH), 4.84(*t*, J=5.1Hz, 1H, -CH_2**OH**) 6.90-7.30 (*m*, $4H_{arom}$), 9.05(*t*, J=5.0Hz, NH). ^{13}C NMR: 28.1(C_6-Me), 39.9(C_5), 40.3(C_4), 44.4(-$NHCH_2$-), 49.2(C_1-COOMe), 50.8(C_3-COOMe), 58.3(C_1), 60.3(-CH_2OH), 67.4(C_6), 90.3(C_3), 126.1($C_{4'}$), 125.3($C_{6'}$), 126.6($C_{2'}$), 129.3($C_{5'}$), 132.3($C_{3'}$), 150.6($C_{1'}$), 157.9(C_4), 168.9(C_3-CO), 172.4(C_1-CO). UV λ max: 297 and 206 nm (ε=27.300, 25.200). Anal. cal. for $C_{19}H_{22}O_6NCl$: C 57.36, H 6.03 , N 3.51 %, found: C 57.0 H 6.08, N 3.45 %.

Dimethyl 2-(3-chlorophenyl)-4-(2-hydroxyethylamino)-6-methylcyclohexen-3,5-dien-1,3-dicarboxylate (**6**) M.p.142-144°C (MeOH). IR: 3540, 3260, 1715, 1670, 1640, 1580 cm^{-1}. ^1H NMR: 1.83 (*s*, 3H, C_6-Me), 3.09 (*s*, 1H, H_1), 3.53 (*s*, 3H, C_1-COOMe),3.40-3.50 (*m*, 2H,-NHC**H**$_2$-), 3.70-3.80 (-**CH**$_2$**OH**), 3.72(*s*, 3H, C_3-COOMe), 4,53 (*s*, 1H, H_2), 6.29 (*s*, 1H, H_5), 7.10-7.30 (*m*, $4H_{arom}$), 9.12(*t*, J=5.1 Hz, NH). ^{13}C NMR: 24.3(C_6-Me), 40.2(C_2), 45.0(-$NHCH_2$-), 50.4(C_1-COOMe), 52.3(C_3-COOMe), 52.9(C_1), 62.1(CH_2OH), 86.4(C_3), 117.9(C_5), 126.4($C_{4'}$), 125.4($C_{6'}$), 127.3($C_{2'}$), 129.4($C_{5'}$), 133.9($C_{3'}$), 142.6(C_6), 146.3($C_{1'}$), 155.1(C_4), 170.1(C_3-CO), 172.0(C_4-CO). MS *m/z* (%): 379 (61, M^+), 364 (2), 348 (13), 320(100). UV λ max: 348, 215 and 202 nm (ε=5.500, 11.000, 15.200)

Dimethyl 2-(3-chlorophenyl)-4-hydroxy-4-methyl-6-oxocyclohexan-1,3-dicarboxylate (**7**) M.p.164-166°C (MeOH). IR: 3480, 1725, 1600, 1480 cm^{-1}. ^1H NMR: 1.24 (*s*, 3H, C_4-Me), 2.37 (*d*, J=13.5 Hz,1H, H_5) 2.94 (*d*, J=13.5 Hz,1H, H_5), 3.34 (*s*, 3H, C_3-COOMe), 3.36 (*d*, J=12,2 Hz, 1H, H_3), 3.43 (*s*, 3H, C_1-COOMe), 3.85 (d, J=12,6 Hz,1H, H_1), 4.01 (*dd*, J_1=12.6 J_2=12.2 Hz, 1H, H_2), 7.20-7.50 (*m*, $4H_{arom}$).^{13}C NMR: 28.2(C_4-Me), 43.7(C_2), 50.9(C_3-COOMe), 51.4(C_1-COOMe), 53.4(C_5), 56.1(C_3), 61.4(C_1), 72.6(C_4), 127.1($C_{4'}$), 127.1($C_{6'}$), 127.7($C_{2'}$), 130.0($C_{5'}$), 132.8($C_{3'}$), 142.8($C_{1'}$), 168.6(C_1-CO), 170.8(C_3-CO), 202.8(CO). Anal. cal. for $C_{17}H_{19}O_6$: C 57.50, H 5.35 %, found: C 57.66, H 5.49 %.

Dimethyl 4-(3-chlorophenyl)-1-(2-acetoxyethyl)-1,4-dihydropyridin-3,5-dicarboxylate (**8** Ac) It was purified after acetylation in the usual way. M.p.147-149°C (MeOH). IR: 1740, 1690, 1580 cm^{-1}. ^1H NMR: 1.89 (s, 3H, -OAc), 2.49 (*s*, 6H, C_6-Me, C_2-Me), 3.73 (*s*, 6H, C_3-COOMe, C_5-COOMe), 3.4-3.6 (*m*, 2H, N-**CH**$_2$-), 3.8-4.0 (m, 2H, -CH_2OAc), 5.13 (*s*, 1H, H_4), 7.0-7.20 (*m*, $4H_{arom}$).^{13}C NMR: 18.6(C_2-Me, C_6-Me), 20.6(OCO**CH**$_3$) 38.2 (C_4), 43.1(-NCH_2-), 51.4(C_3-COOMe, C_5-COOMe), 63.4(-CH_2-OAc), 107.5(C_4), 125.1($C_{1'}$), 126.4($C_{5'}$), 127.2($C_{3'}$), 129.3($C_{6'}$), 134.1($C_{4'}$), 147.9($C_{2'}$), 148.5(C_2, C_5), 166.2(C_3-COOMe, C_5-COOMe), 170.4($OCOCH_3$).

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