

UNIVERSITY OF LATVIA

**ACID-MEDIATED RING TRANSFORMATIONS OF  
PARTIALLY HYDROGENATED PYRIDINE  
DERIVATIVES**

Svetlana Stupņikova

**Abstract of the dissertation**

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**Reviewers of dissertation:**

Dr. hab. chem., prof. E. Lukevic,

Dr. chem. A. Prikšane,

Dr. chem., prof. V. Kokars

**Scientific supervisors:**

Dr. hab. chem., prof. A. Zicmanis,

Dr. chem. V. Lūsis

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## Introduction

Cyclohexane, cyclohexanone and fluorenone derivatives are versatile intermediates for synthesis of many biologically important compounds (polycyclic terpenes, terpenoids, steroids and others). Usually the preparation of these skeletons is a multi step process involving preparation of highly functionalized derivatives.

Investigation of new route to poly functionalized cyclohexen-2-ones or dihydrofluorenones via recyclization of pyridine derivatives is a matter of current interest. The research was aimed at investigation of scope and limitations of acid mediated ring transformations of partially hydrogenated pyridine derivatives particularly 5-oxo-4*H*-4a,5-dihydroindeno[1,2-*b*]pyridines i.e. polycyclic analogues of 3,4-dihydropyridine. It was designed to extend the selection of 4a-substituted indeno[1,2-*b*]pyridines in order to obtain 1*H*-dihydrofluorenone derivatives with 9a-angular substituents. Acid mediated tandem recyclization of appropriately functionalized dihydroindeno[1,2-*b*]pyridines followed by an intramolecular cyclization could be a new approach to the gibbane framework. Besides, the intramolecular reaction of angularly substituted 4a-alkenyl or 4a-alkynyl dihydroindenopyridines with cycloenone  $\beta$ -carbon atom could give new bridged heterocycles.

The development of strategy for pyridine ring transformation resulted in elaboration of new versatile preparation methods of attractive synthetic targets from easily accessible di- and tetrahydropyridines, and indeno[1,2-*b*]pyridines:

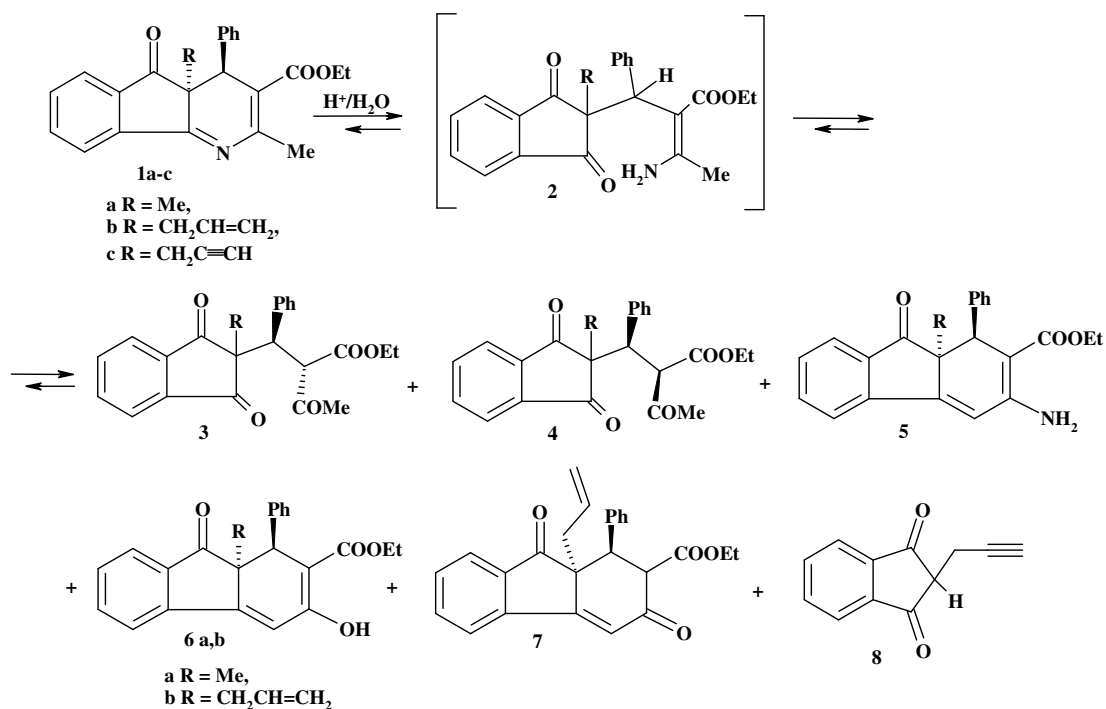
- hydrolysis of 4a-substituted 4a,5-dihydroindenopyridines in water-containing acidic medium resulted in formation of diastereomeric ethyl  $\alpha$ -acetyl- $\beta$ -(2-substituted-2,3-dihydro-1,3-dioxo-1*H*-inden-2-yl)- $\beta$ -phenyl propionates. The cyclization of these indenylpropionates with benzylammonium acetate is a new route to 3-aminofluorenone derivatives; gibbane-like compound – benzo[*a*]azulene-6,10-dione derivative is obtained in tandem recyclization/ cyclization reactions of  $\beta$ -[(2-propargyl)-2,3-dihydro-1,3-dioxo-1*H*-inden-2-yl]- $\beta$ -phenyl-propionate;
- intramolecular rearrangement of 4a-methyl-4,4a,5,9b-tetrahydro-1*H*-indenopyridine in aqueous acidic medium affords 2,3,4,6-tetrahydropyrido[2,1-*a*]isoindole;

- rearrangement of ethyl 4-phenyl-2-methyl-5-oxo-2,3,4,5-tetrahydro-1*H*-indeno[1,2-*b*]-pyridine-3-carboxylate in the presence of oxygen resulted in formation of hexahydro-pyrrolo[1,2-*b*]isoquinoline and hexahydropyrido[2,1-*a*]isoindole derivatives;
- intramolecular cyclization of 4a-allyl-4a,5-dihydroindeno[1,2-*b*]pyridine in the presence of sulfuric acid or tin chloride leads to 7,8,9,9a-tetrahydro-4*bH*-5-aza-4*b*,8:7,9a-dimethano-benzo[*a*]azulen-10-one;
- depending on acidity of reaction medium and structure of starting compounds recyclization of 1,4-dihydropyridines afforded various diastereomeric cyclohexenone derivatives. The influence of electron withdrawing substituents at C<sub>3</sub> and C<sub>5</sub> atoms on hydrolysis process of poly substituted monocyclic 1,4-dihydropyridines was studied. Tendency to eliminate 3- and 5-substituents under acidic hydrolysis conditions is as follows: CN << COOEt < COMe;
- preparation method of 4a-alkyl-5-oxo-4*H*-4a,5-dihydroindeno[1,2-*b*]pyridine regioisomers are improved.

Acid catalysed pyridine ring transformation is a new, conceptually different approach to highly functionalized derivatives of cyclohexenone and dihydrofluorene.

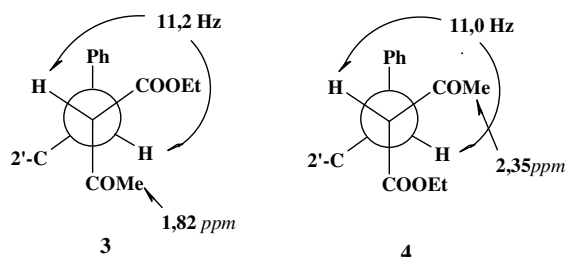
**SYNTHESIS OF 9a-SUBSTITUTED 1H-FLUORENONES FROM 4a-SUBSTITUTED  
4H-4a,5-DIHYDROINDENO[1,2-b]PYRIDINE DERIVATIVES IN AQUEOUS  
ACIDIC MEDIUM**

Hydrolysis of dihydroindenopyridines **1a-c**<sup>1</sup> in water-containing acidic medium resulted in cleavage of azometine C<sub>9a</sub>=N bond followed by hydrolysis of enamine moiety leading to formation of diastereomeric ethyl  $\alpha$ -acetyl- $\beta$ -(2,3-dihydro-1,3-dioxo-1*H*-inden-2-yl)- $\beta$ -phenylpropionates **3** and **4** (main path). Intramolecular interaction between the terminal CH<sub>3</sub> of open-chain enamine **2** and indandione CO group proceeds in a smaller extent and results in formation of 9a-substituted 3-aminofluorenones **5**. Similar intramolecular condensation of indandione derivatives **3** or **4** affords fluorenedione **7** or the corresponding enol **6**. Besides disubstituted indandiones and recyclisation products **5-7**, 2-monosubstituted indandione **8** was also found among products of 4a-propargylindenopyridine **1c** hydrolysis. Occurrence of indan-1,3-dione **8** is caused by retro-Michael reaction of compounds **3** and **4**.



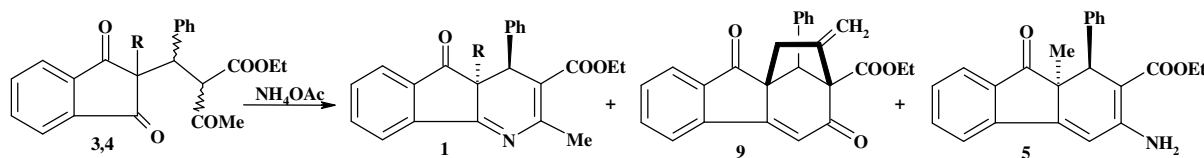
<sup>1</sup> 4a-Alkyl-5-oxo-1*H*-4,5-dihydroindeno[1,2-*b*]pyridines **1a-c**, **16** are prepared by alkylation of 5-oxo-1*H*-4,5-dihydroindeno[1,2-*b*]pyridine with appropriate alkylation agents in the presence of sodium hydride in acetonitrile [1].

Side chain configuration of indandiones **3** and **4** was determined by NMR spectroscopy. The singlet attributable to the acetyl group of diastereomer **3** is shifted up-field in comparison with the same signal of isomer **4** under influence of indandione carbonyl function.

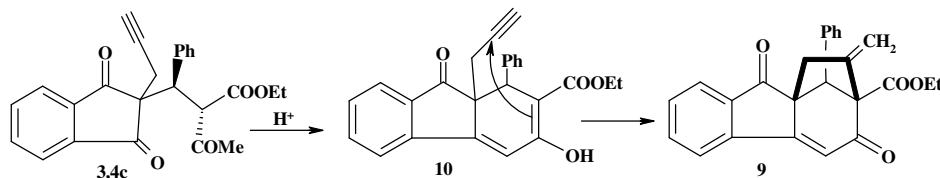


Characteristic feature of fluorenone **5-7** derivatives is 4-H proton signal at 6,56-6,69 ppm in PMR spectra.

The cyclisation of  $\alpha$ -acetyl- $\beta$ -(2,3-dihydro-1,3-dioxo-1*H*-inden-2-yl)- $\beta$ -phenylpropionates **3** and **4** with ammonium acetate affords 4a-substituted indenopyridines **1a-c** as main products and 3-amino-9a-methylfluorenone **5** in yields up to 15%.

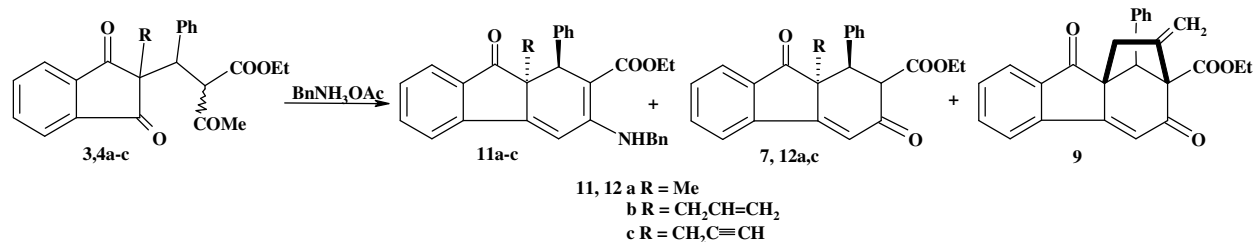


If propargyl derivatives **3c**, **4c** were used as starting compounds, besides indenopyridine **1c** and 3-aminofluorenone **5**, a gibbane type bridged tetracycle, namely, 7,8,9,9a-tetrahydro-7,9a-methanobenzo[*a*]azulene **9** was isolated (yield 9%). Occurrence of the azulene involves the intramolecular condensation of indandione derivatives **3c** or **4c** leading to 3-hydroxy-1,9a-dihydrofluorenone **10**, followed by interaction between enol  $\beta$ -C atom and  $\text{C}\equiv\text{C}$  bond of side chain substituent.

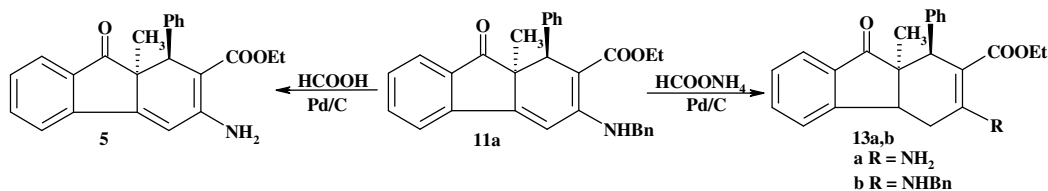


To suppress the pyridine ring formation on course of indandione derivatives **3,4** cyclization, ammonium acetate was replaced by benzylammonium acetate. Under these conditions the formation of aminofluorenone becomes predominant and the corresponding 9a-substituted 3-benzylaminofluorenones **11a,b** are isolated in 60% yield. Formation of *N*-benzylaminofluorene proceeds simultaneously with the cyclisation leading to 3-oxofluorenone derivatives **7,12a,c**.

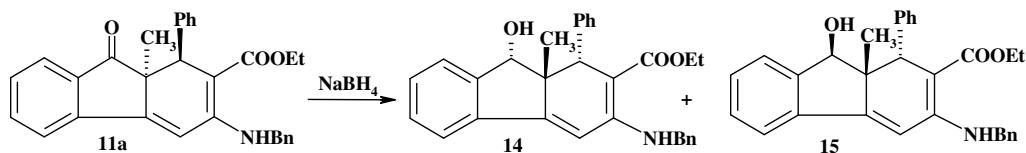
Transformation of 3-oxocompounds **7,12a,c** into aminoderivatives **11** does not proceed under reaction conditions. The cyclisation of propargylindandione **3c** and **4c** affords tetracyclic diketone **9** as minor product.



Debenzylation of fluorenes **11a** could be achieved by formic acid in the presence of Pd/C catalyst in methanol under reflux. Ammonium formate applied instead of formic acid caused hydrogenation of C<sub>4</sub>=C<sub>4a</sub> bond under the similar conditions at room temperature and afforded benzylamino derivative **13b**, whereas the debenzylation was achieved and compound **13a** was formed under reflux.

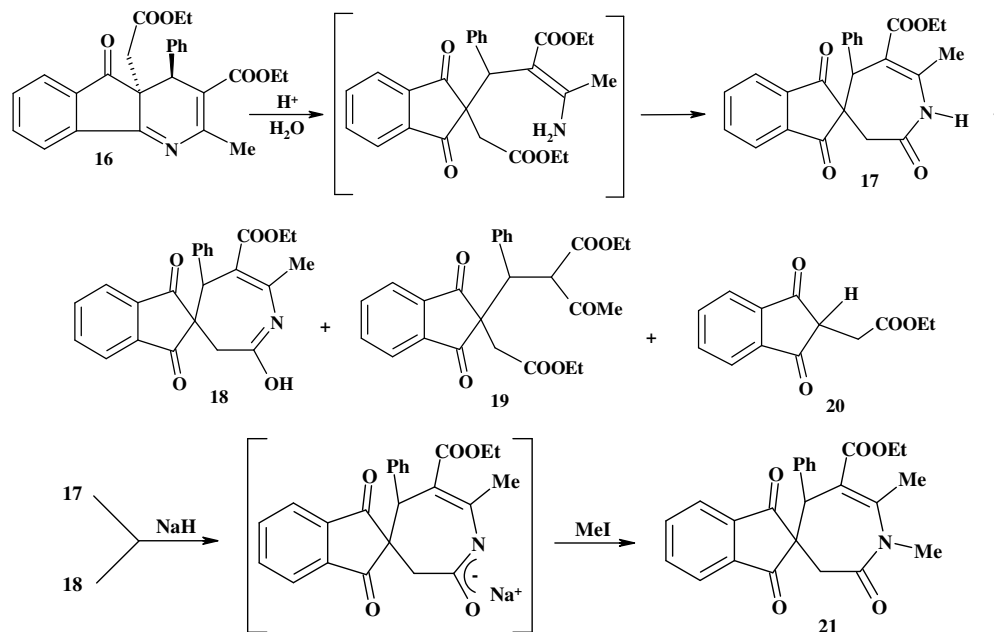


9-Hydroxy diastereomers **14** and **15** were obtained by reduction of 3-(*N*-benzylamino)fluorenone **11a** with NaBH<sub>4</sub>. Arrangement of substituents for compounds **14** and **15** was determined by NMR studies. The signal corresponding to 9a-methyl group of isomer **15** is shifted up-field (20.6 ppm) under influence of hydroxyl group in comparison with the same signal of isomer **14** (28.5 ppm) in <sup>13</sup>C-NMR spectrum. This fact together with observed Overhauser effect between 9-H and 9a-CH<sub>3</sub> group of isomer **14** indicate *trans*-location of 9-OH and 9a-CH<sub>3</sub> groups and *cis*-location of these substituents in **15** respectively.



Due to distinctive 4a-substituent the behaviour of 4a-ethoxycarbonylmethyl indenopyridine **16** is different under acid hydrolysis conditions. The first act – hydrolytic breakage of pyridine ring is the same, but further transformation of open chain enamine is different. The principal course is the intramolecular interaction between amino function and ester carbonyl group leading

to amide formation and azepine ring closure. Spiro(azepine-4,2'-indandione) could be isolated as a lactam **17**, as well as its enol form **18**. 2,2-Disubstituted indandione **19** and retro-Michael product **20** are isolated as minors.

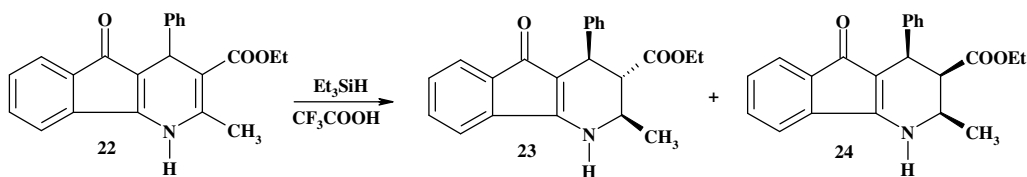


Coexistence of two forms – lactam and lactol – was confirmed by transformation of compounds **17** and **18** into the *N*-methyl derivative: treatment of azepinone derivatives with  $NaH$  followed by interaction with methyl iodide converted the both in the same product — azepinone **21**.

## RING TRANSFORMATIONS OF 5-OXOTETRAHYDROINDENO [1,2-*b*]PYRIDINES

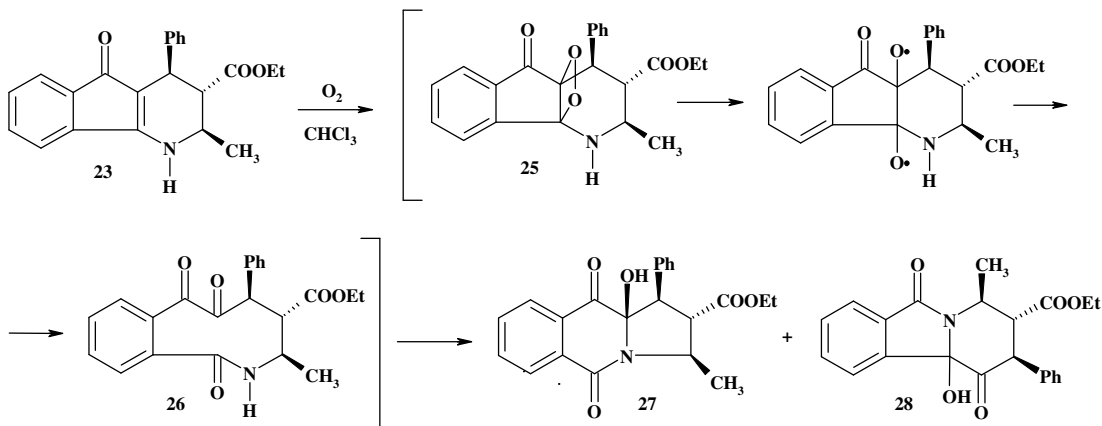
The starting compounds – tetrahydro[1,2-*b*]indenopyridines are prepared from corresponding 1*H*-dihydroindenopyridine **22** via hydrogenation of  $C_2=C_3$  bond followed by subsequent alkylation if 4a-substituted derivative is required. Regioselectivity of 1,4-dihydropyridine **22** reduction with triethylsilane in trifluoroacetic acid medium is high –  $C_{9a}=C_{4a}$  double bond remained untouched, but stereoselectivity is only moderate – two tetrahydroindenopyridine diastereomers **23** and **24** are formed in ratio 6:1 (de 71%).



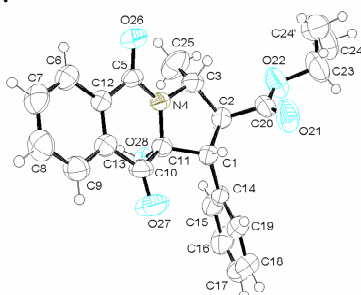


The reduction of C=C bond includes protonation with  $\text{CF}_3\text{COOH}$  of  $\text{C}_3$  possible from both sides of pyridine ring and hydride transfer from  $\text{Et}_3\text{SiH}$  to immonium ion, respectively to  $\text{C}_2$ . The last is more accessible from the side opposite to 4-phenyl group. Diastereomers **23** and **24** have different configuration of  $\text{C}_3$ .

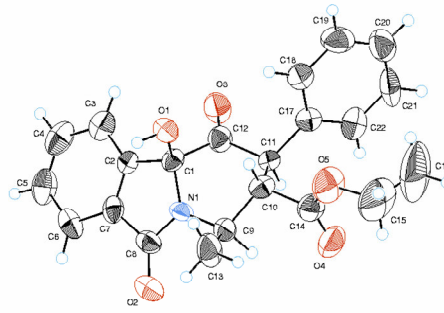
The predominant *trans*-isomer **23** is unstable in the presence of oxygen and easy undergoes oxidative ring transformation resulting in occurrence of 10*a*-hydroxy-5,10-dioxo-1,2,3,5,10,10*a*-hexahydropyrrolo[1,2-*b*]isoquinoline **28** and 10*b*-hydroxy-1,6-dioxo-1,2,3,4,6,10*b*-hexahydropyrido[2,1-*a*]isoindole **27**.



The rearrangement includes addition of oxygen molecule to  $\text{C}_{4a}\text{-C}_{9a}$  bond followed by cleavage of this bond and formation of intermediate – nine membered cyclic triketone. The intramolecular attack of nitrogen atom lone pair on carbonyl groups leads to pyrrolo[1,2-*b*]isoquinoline **28** and pyrido[2,1-*a*]isoindole **27**. Structures of compounds **27** and **28** were confirmed by X-ray analysis (Fig. 1 and Fig. 2).

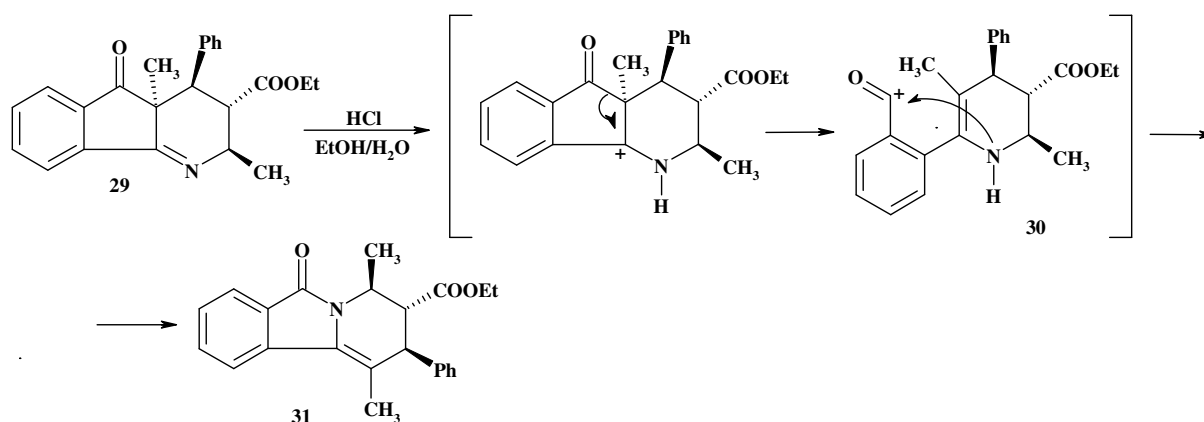


**Figure 1.** X-ray of compound **27**

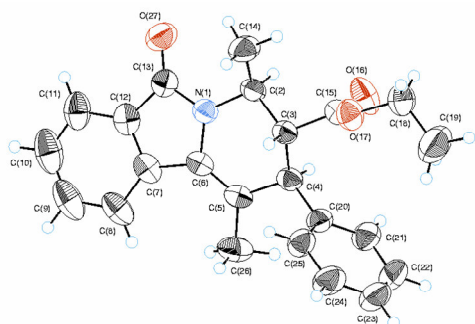


**Figure 2.** X-ray of compound **28**

Hydrolysis of 4a-methyltetrahydroindenopyridine **29** in aqueous acidic medium affords 6-oxo-2-phenyl-2,3,4,6-tetrahydropyrido[2,1-*a*]isoindole **31** (Fig. 3).



The rearrangement of 4a-methylindenopyridine **29** into 2-phenyl-6-oxo-2,3,4,6-tetrahydropyrido[2,1-*a*]isoindole **31** includes protonation of C=N bond and C<sub>4a</sub>-C<sub>5</sub> bond cleavage resulting in formation of acylium ion **30**. The last interacts with pyridine ring nitrogen producing annealed isoindole skeleton.



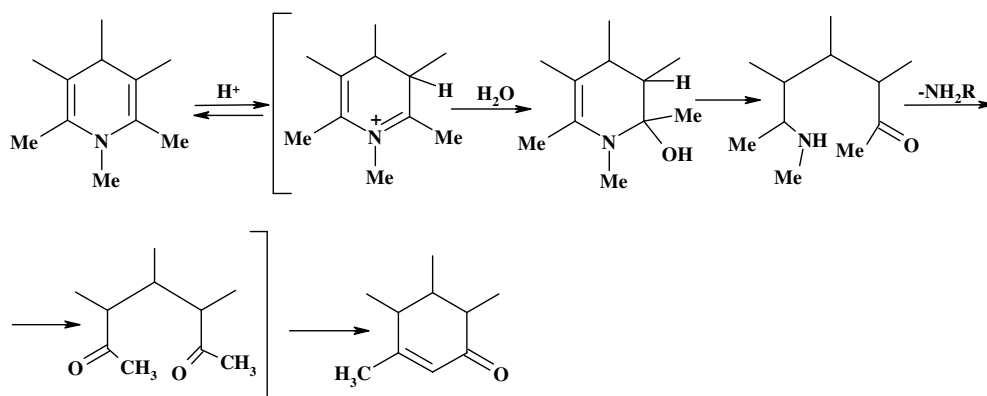
**Figure 3.** X-ray of compound **30**

The rearrangements of indeno[1,2-*b*]pyridine skeleton to pyrrolo[1,2-*b*]isoquinoline or pyrido[2,1-*a*]isoindole derivatives are first observed.

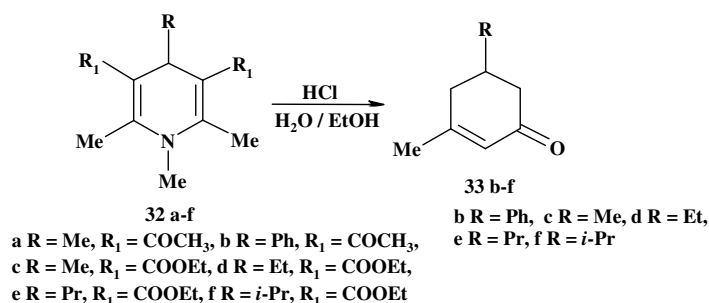
### 3. RECYCLIZATION OF 4-SUBSTITUTED 1,2,6-TRIMETHYL-1,4-DIHYDRO-PYRIDINES IN ACIDIC MEDIUM

Recyclization of *N*-substituted 1,4-dihydropyridines (1,4-DHP) proceeds as acidic hydrolysis of enaminocarbonyl moiety resulting in formation of acyclic heptane-1,5-dione as an

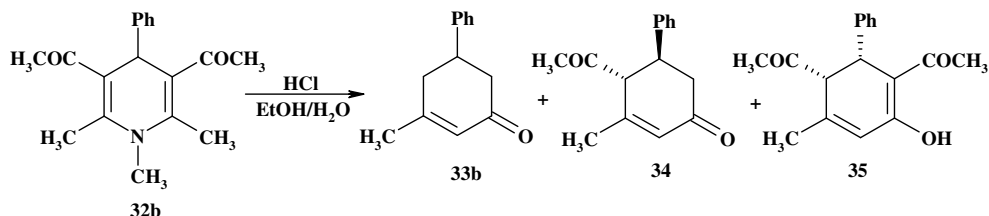
intermediate. The last undergoes intramolecular condensation of terminal CH<sub>3</sub> and keto CO groups affording cyclohexenone derivatives.



Recyclization of 3,5-diacetyl- and 3,5-diethoxycarbonyl-1,4-DHP **32a-f** in strongly acidic medium (2,4M HCl) affords 5-substituted 3-methylcyclohexenones **33b-f** as main products in yields 54-84%. Recyclization of dihydropyridine ring proceeds simultaneously with elimination of 3- and 5-substituents under reaction conditions.

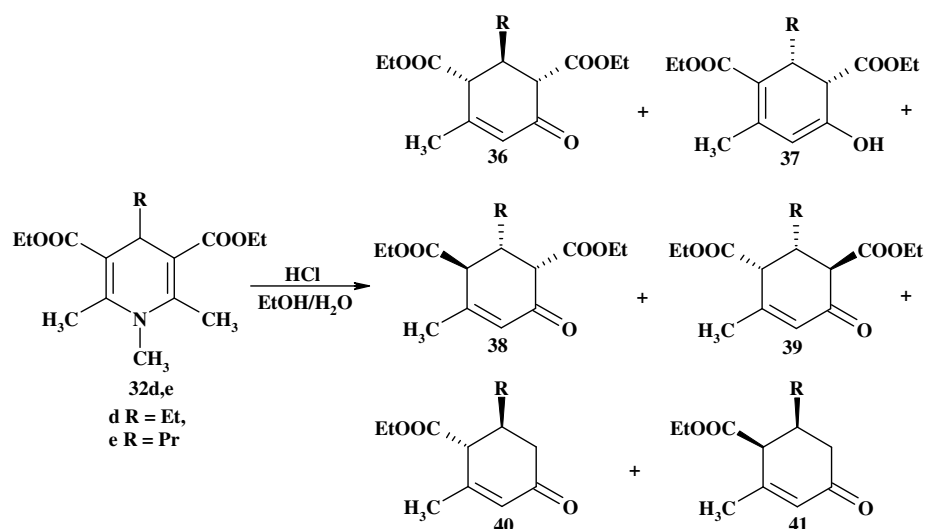


Elimination of carbonyl functions is retarded in less acidic medium. Thus 3-methyl-5-phenylcyclohexen-2-one, 4-acetyl-5-phenylcyclohexenone **34** and 1,5-diacetyl-6-phenylcyclohexadiene **35** are isolated when 5-acetyl-DHP **32b** is hydrolysed in 1,5M HCl.

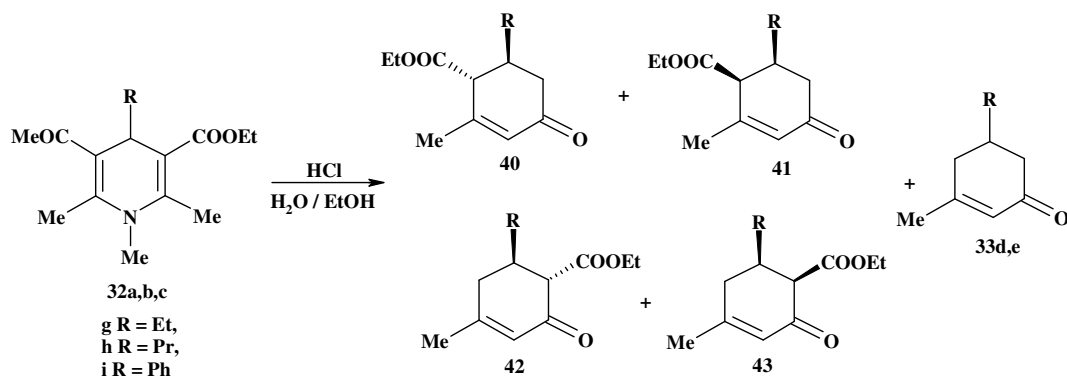


Recyclization of 3,5-diacetyl-1,4-DHP is more facile in comparison with this of 1,4-DHP-3,5-dicarboxylates. Treatment of 4-ethyl- and 4-propyl-1,4-DHP-3,5-dicarboxylates **32d,e** with

0,6M HCl in H<sub>2</sub>O/EtOH medium affords mono- and diethoxycarbonyl cyclohexenones as a mixture of regio/stereoisomers **36-41**.



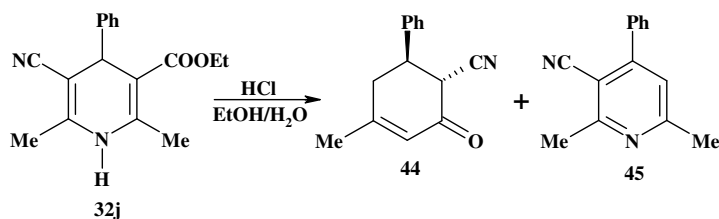
Acidic hydrolysis (1,0M HCl) of unsymmetrical 5-acetyl-3-ethoxycarbonyl-1,4-DHP **32g,h** predominantly proceeds with formation of cyclohexenone monocarboxylates **40-43** (mixture of regio/diastereomers).



Hydrolysis of enamine moieties of 1,4-DHP **32g,h** results in formation of asymmetric diketone. Both terminal methyl groups of the intermediate are capable of intermolecular condensation. Unequal methyl groups participating in cyclohexenone ring closure afford different regioisomers **40,41** and **42,43**. Configuration of new generated sp<sup>3</sup>-carbons is determined by protonation of enamine moieties in the initial steps of recyclization process.

Recyclization of 5-acetyl-3-ethoxycarbonyl-4-phenyl-1,4-DHP **32i** affords single regioisomer, i.e. diastereomers **40** and **42** are formed.

Hydrolysis (6M HCl) of 5-cyano-4-phenyl-1,4-DHP **32j** affords nitrile **44** as a sole recyclization product. Pyridine carbonitrile **45** isolated as by-product is produced due to easy oxidation of DHP ring.



The aptitude for elimination of 1,4-dihydropyridine 3-substituents under acidic hydrolysis/recyclization condition decreases in range COMe>COOEt>CN.

Structures of cyclohexenone derivatives are elucidated by one- and two-dimensional NMR spectroscopy. Signals corresponding to cyclohexenone 4-H and 6-H protons can be attributed using gHMBC spectra, where interaction of the protons with C=C bond or C=O group appears and can be easily observed. The arrangement of substituents at cyclohexenone positions C<sub>4</sub>, C<sub>5</sub>, C<sub>6</sub> is determined by Overhauser effect observed between 4- and 6-H protons in (H,H)-NOESY spectra and by coupling constants measurements in <sup>1</sup>H-NMR spectra.

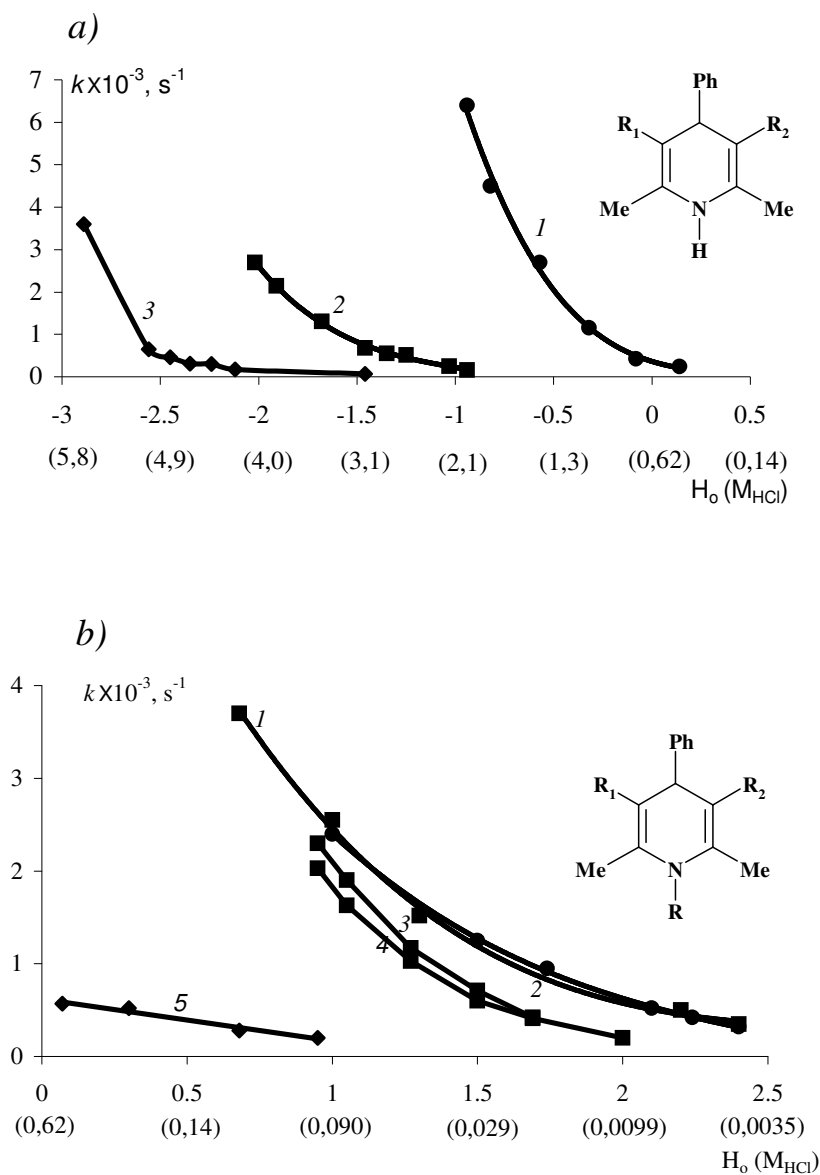
## INFLUENCE OF REACTION MEDIUM AND DIHYDROPYRIDINE 3,5-SUBSTITUENTS ON RING CLEAVAGE

Cleavage of dihydropyridine ring in aqueous acidic medium involves three steps: a) enamine protonation resulting in reactive imonium ion formation; b) water addition to the imonium ion leading to  $\alpha$ -hydroxyamine; c) elimination of amine. Elimination of amine is the rate limiting step in acidic medium. The process begins with reversible protonation stage. Consequently, it depends on basicity of enamine (pK<sub>a</sub> of protonated enamine form) as well as acidity of reaction medium (concentration of hydroxonium ion).

Effective rate constants of DHP hydrolysis were measured in 50% hydrochloride H<sub>2</sub>O/EtOH solution. To characterize acidity of reaction medium Hammett function H<sub>0</sub> was used.

Hydrolysis rate measurements were performed under pseudo-first order reaction conditions – large excess of water and acid in reaction medium.

Hydrolysis of *N*-unsubstituted DHP demands more acidic conditions than corresponding *N*-substituted DHP (Picture 1). The tendency towards elimination of 1,4-dihydropyridine 3- and 5-substituents under acidic hydrolysis conditions grows in range: CN << COOEt < COMe.



Picture 1. Influence of acidity on 1,4-dihydropyridine cleavage:

a) 1 –  $R_1 = R_2 = \text{Ac}$ ; 2 –  $R_1 = R_2 = \text{COOEt}$ ; 3 –  $R_1 = \text{CN}$ ,  $R_2 = \text{COOEt}$

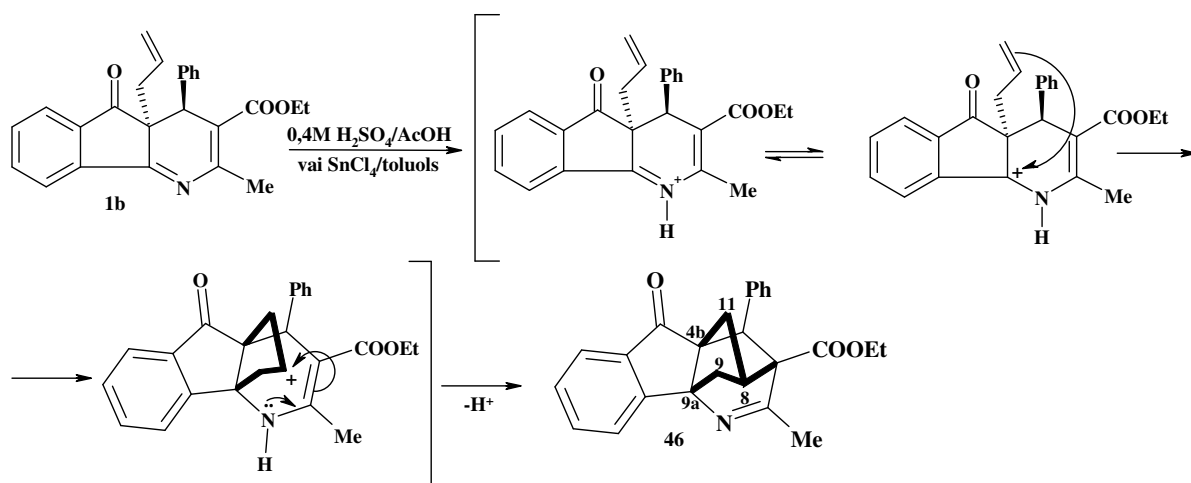
b) 1 –  $R = \text{Me}$ ,  $R_1 = R_2 = \text{COOEt}$ ; 2 – **32b**; 3 –  $R = \text{Ph}$ ,  $R_1 = R_2 = \text{COOEt}$ , 4 –  $R = 4\text{-MeOPh}$ ,  $R_1 = R_2 = \text{COOEt}$ ; 5 – **32j**

Concerning the effect of *N*-substituent on 1,4-DHP ring cleavage, it was revealed that *N*-methyl, *N*-phenyl- and more electron donating *N*-(4-methoxyphenyl)substituents have no influence on hydrolysis rate. This would be explained by the steric hindrance of 2,6-CH<sub>3</sub> groups and a lack of conjugation between *N*-substituent and enamine part of DHP ring.

### INTRAMOLECULAR CYCLIZATION OF 4a-ALLYL-5-OXO-4H-4a,5-DIHYDROINDENO-[1,2-*b*]PYRIDINE IN ANHYDROUS ACIDIC MEDIUM

Intramolecular cyclization of 4a-allylindenopyridine **1b** in the presence of tin chloride in toluene or sulphuric acid in acetic acid affords 7-ethoxycarbonyl-6-methyl-12-phenyl-7,8,9,9a-tetrahydro-4b*H*-5-aza-4b,8:7,9a-dimethanobenzo[*a*]azulen-10-one (**46**).

Formation of azaazulene **46** from indenopyridine **1b** under acid catalysis in anhydrous conditions involves protonation of 3,4-dihydropyridine nitrogen followed by intramolecular interaction of formed imonium ion with terminal =CH<sub>2</sub> group of 4a-allyl substituent, which resulted in carbonium ion formation, and further interaction between secondary carbonium ion and β-carbon of enamine moiety.



Structure of azaazulene **46** was elucidated by NMR spectroscopy. Chemical shifts at 63,5 ppm and 64,2 ppm correspond to C<sub>4b</sub> and C<sub>9a</sub>. Proton signals of C<sub>(9)</sub>H<sub>2</sub>-C<sub>(10)</sub>H-C<sub>(11)</sub>H<sub>2</sub> bridge were identified by 2D{<sup>1</sup>H-<sup>1</sup>H} spectroscopy. Signals at 1,82 ppm and 1,98 ppm correspond to 9-

CH<sub>2</sub> group of azaazulene, whereas signals at 1,44-1,60 ppm and 2,44 ppm – 11-CH<sub>2</sub> group; signal at 2,85 ppm corresponds to 8-CH group.

It must be pointed, that the formation of bridged polycycle by addition of allyl substituent to dihydropyridine ring without spacer is first observed.

## CONCLUSION

1. Hydrolysis of ethyl 4a-substituted 2-methyl-4-phenyl-5-oxo-4*H*-4a,5-dihydroindeno[1,2-*b*]pyridine-3-carboxylates in water-containing acidic medium results in cleavage of azometine C<sub>9a</sub>=N bond. Depending on structure of starting compounds 4a-substituent  $\alpha$ -acetyl- $\beta$ -(2,3-dihydro-1,3-dioxo-1*H*-inden-2-yl)- $\beta$ -phenylpropionates or spiro(6-ethoxy-carbonyl-2-hydroxy-7-methyl-5-phenyl-1*H*-2,3,4,5-tetrahydroazepine)-4,2'-indan-1',3'-dione derivative are formed as main products. Occurrence of 9a-substituted 1,9a-dihydrofluorene-9-ones as well as 7-ethoxycarbonyl-11-phenyl-8-methylene-7,8,9,9a-tetrahydro-7,9a-methanobenzo[*a*]azulene-6,10-dione are also observed.
2. 9a-Substituted 3-amino-1,9a-dihydrofluoren-9-ones have been prepared by cyclization of ethyl  $\alpha$ -acetyl- $\beta$ -(2-substituted-2,3-dihydro-1,3-dioxo-1*H*-inden-2-yl)- $\beta$ -phenylpropionates with benzylammonium acetate and following *N*-debenzylation.
3. Intramolecular cyclization of ethyl 4a-allyl-2-methyl-4-phenyl-5-oxo-4*H*-4a,5-dihydroindeno[1,2-*b*]pyridine-3-carboxylate affords 7-ethoxycarbonyl-6-methyl-12-phenyl-7,8,9,9a-tetrahydro-4*bH*-5-aza-4*b*,8:7,9a-dimethanobenzo[*a*]azulen-10-one.
4. Reduction of ethyl 4-phenyl-5-oxo-4,5-dihydro-1*H*-indeno[1,2-*b*]pyridine-3-carboxylate with triethylsilane in trifluoroacetic acid medium proceeds regioselectively and ethyl 2,3,4,5-tetrahydro-1*H*-indeno[1,2-*b*]pyridine-3-carboxylate diastereomers are formed. Oxidative ring transformation of ethyl (2*R*\*,3*S*\*,4*R*\*)-2-methyl-4-phenyl-5-oxo-2,3,4,5-tetrahydro-1*H*-indeno[1,2-*b*]pyridine-3-carboxylate affords (1*R*\*,2*S*\*,3*R*\*,10*aR*\*)-5,10-dioxo-10a-hydroxy-3-methyl-1-phenyl-1,2,3,5,10,10a-hexahydropyrrolo[1,2-*b*]isoquinoline-2-carboxylate and (2*S*\*,3*R*\*,4*S*\*)-1,6-dioxo-10*b*-hydroxy-4-methyl-2-phenyl-1,2,3,4,6,10*b*-hexahydropyrido[2,1-*a*]isoindole-3-carboxylate.



5. Rearrangement of ethyl 4a-methyl-3,4,4a,5-tetrahydro-2*H*-indeno[1,2-*b*]pyridine-3-carboxylate in aqueous acidic medium leads to ethyl 1,4-dimethyl-2-phenyl-6-oxo-2,3,4,6-tetrahydropyrido[2,1-*a*]isoindole-3-carboxylate.
6. Preparative synthesis of 5-substituted 3-methylcyclohex-2-enones is elaborated by recyclization of 4-substituted 3,5-diacetyl- or 3,5-diethoxycarbonyl-1,2,6-trimethyl-1,4-dihydropyridines.
7. Recyclization of 4-substituted 1,2,6-trimethyl-1,4-dihydropyridine 3,5-dicarboxylates produces diastereomeric ethyl 2-alkylcyclohex-4-en-6-one-1,3-dicarboxylate, ethyl 6-alkyl-2-methyl-4-oxocyclohex-2-ene- or 6-alkyl-4-methyl-2-oxocyclohex-3-ene monocarboxylates depending on reaction conditions. The elimination aptitude of dihydropyridine 3- and/or 3,5-substituents under acidic hydrolysis/recyclization conditions grows in range: CN << COOEt < COMe.

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