REACTIONS OF 1,4-DIHYDROPYRIDINES (REVIEW)

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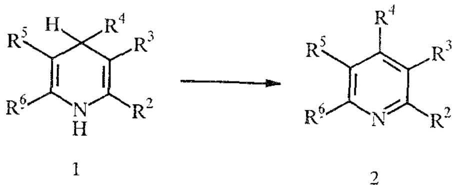
The literature published over the period 1986-1990 on the chemical properties (oxidation, addition, substitution, reactions of the functional groups, etc.) of 1,4-dihydropyridines is correlated.

This review encompasses the literature on the chemical properties of 1,4-dihydropyridines (DHP) over the period 1986-1990 and is constructed in accordance with the same principle as a previous publication dealing with the same topic [1]. The literature on the synthesis of 1,4-dihydropyridines in the last 5 yr was correlated in a recent review [2].

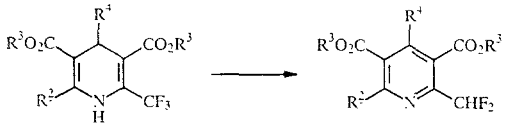
1. OXIDATION

1.1. Oxidation of N-Unsubstituted 1,4-Dihydropyridines


1 2

The use of a few new reagents for the oxidation of 1,4-dihydropyridines should be noted. Cerium ammonium nitrate oxidizes *1* (R^3, R^5 = COR, R = H, OH, OAlk) to the corresponding pyridines *2* at room temperature, which are obtained in almost quantitative yields [24, 25]. Oxidation with tin tetrachloride also takes place at 20°C [32].

The dehydrofluorination [1] of 2-trifluoromethyl-1,4-dihydropyridines *3* by the action of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) or tertiary amines has been studied in greater detail [40, 41].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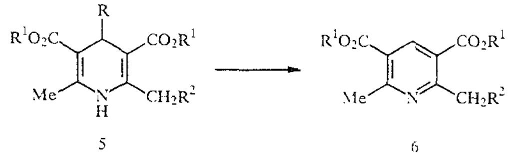
3, 4 R^2 = CF_3, Me, Et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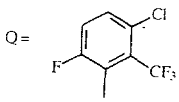
5, 6 a R^2 = H, b R^2 = F



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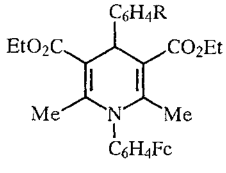
Dihydropyridines *5a* (R = alkyl, cycloalkyl, benzyl) are oxidized by nitric acid with splitting out of the substituent from the 4 position, while *5a* (R = aryl) retain this substituent [15]. A new (for dihydropyridines *5a, b*) reaction involving the splitting out of a 4-phenyl substituent that contains at least two electron-acceptor groups in the ortho and ortho′ positions (for example, if R = Q) was observed. In this case aromatization to pyridines *6a, b* occurs via the action of alkaline agents under mild nonoxidizing conditions [42].

1.2. Oxidation of N-Substituted 1,4-Dihydropyridines

Hydrogen peroxide [20, 43], acridinium cations [44, 45], halogens, lead tetraacetate, Malachite green, chloranil, and N-bromosuccinimide [45] have been used for the oxidation of N-substituted 1,4-dihydropyridines to pyridinium salts.



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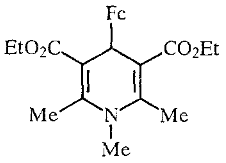

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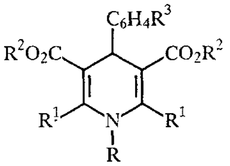
7, 8 Fc = ferrocenyl

The oxidation of *7, 8* with 2,2,6,6-tetramethyl-1-oxopiperidinium perchlorate leads to pyridinium salts with an unsubstituted ferrocenyl group; on the other hand, however, the 1,4-dihydropyridine structure is retained when these substances are treated with triphenylmethyl perchlorate, and Fc is oxidized to the ferricinium cation [28].

Splitting out of the substituent attached to the N atom to give a pyridine occurred in some cases in the oxidation of N-substituted 1,4-dihydropyridines. Splitting out of the CO_2R group occurred in the case of oxidation with o-chloranil [46] or sulfur [46-48], while detachment of the NRR^1 group was observed when N-amino-1,4-dihydropyridine was treated with hydrogen chloride in dioxane [49-51].

1.3. Electrochemical Oxidation



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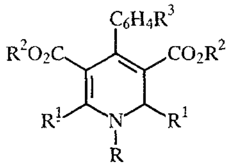

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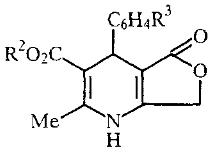

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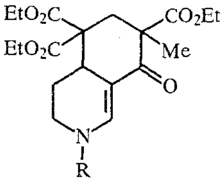
N-Substituted *9* (R = Me, $C_6H_4R^4$; R^1 = Me) are oxidized electrochemically with greater difficulty than the corresponding 1,2 isomers *10* (the difference is 0.2-0.3 V) [52]. N-Aryl-2,6-unsubstituted 1,4-dihydropyridines *9* (R = $C_6H_4R^4$; R^1 = H) are oxidized with greater difficulty (by ~ 0.15 V) than the 2,6-dimethyl analogs [53]. Tetrahydrofuropyridines *11* are oxidized with greater difficulty (by ~ 0.2 V) than monocyclic 1,4-dihydropyridines *9* (R = H, R^1 = Me) [54]. Ferrocenyl-1,4-dihydropyridines *7* and *8* are oxidized to ferrociniapyridinium dications, and relatively stable cation radicals of dihydropyridines with a ferricinium cation as a substituent have been recorded [55].

2. REDUCTION

Tetrahydropyridines *12* were obtained from the corresponding 1,4-dihydro compounds by catalytic hydrogenation (with Pd/C as the catalyst) [56]. Triethylsilane in trifluoroacetic acid reduces 1,4-dihydropyridines to, depending on the reaction time, tetrahydropyridines *13* [57] or piperidines *14* [58].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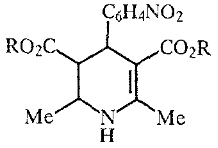
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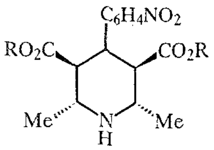
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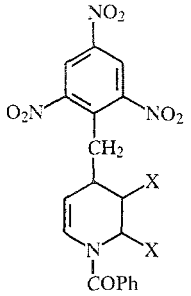
12 R = Me, CH2Ph

3. ADDITION REACTIONS

Tetrahydropyridines *15* are formed by the addition of a halogen to the dihydropyridine double bond on treatment with bromine or phosphorus pentachloride. The addition of chlorine to both C=C bonds, as well as partial chlorination of the 2,6-methyl groups, occurs in the action of chlorine or N-chlorosuccinimide on dihydropyridines *5a* [61, 62].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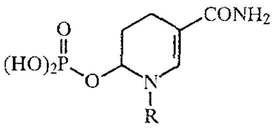
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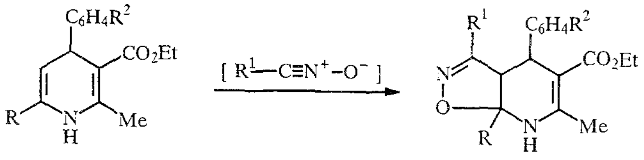
15 X = Br [59], Cl [60]

1-Substituted 1,4-dihydronicotinamides add phosphoric acid to give tetrahydropyridine *16* [63]. 3,5-Disubstituted 1,4-dihydropyridines do not react with nitrile oxides, but *17* does react with them via a 1,3-dipolar cycloaddition mechanism to give isoxazolopyridines *18* [64]. Cyclization to *18* (R^1 = Me) occurs in the action of hydroxylamine on 3-acetyl-1,4-dihydropyridine [65].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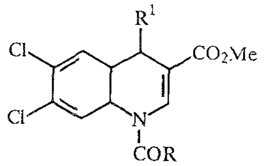
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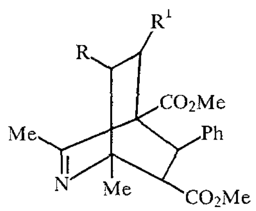
17, 18 R = H, Me; *18* R^1 = Me, CO_2Et, COPh, CN, OEt, SO_2Ph

1,4-Dihydropyridines are capable of acting as dienophiles in reactions with dienes. The addition of 3,4-dichlorothiophene 1,1-dioxide to dihydropyridines proceeds regioselectively with the elimination of SO_2 to give tetrahydroquinoline *19* [66].

Under the influence of Lewis acids, *5a* are capable of adding highly active olefins and heterocycles (bicyclic *20* are formed), but they do not react with, for example, methylstyrene, cyclohexene, and methylenecyclopentane.



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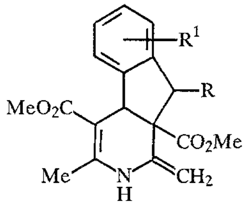
20 R = H, $R^1 = CH_2SiMe_3$ [67, 68], R^1 = Ph [68]; $R+R^1$ = XCH=CH (X = CH_2, O, S) [69]

Intramolecular-addition reactions that proceed chiefly by the action of Lewis acids on dihydropyridines have been studied extensively; alkaline agents [70, 71] or increasing the temperature [72] have been used only in individual cases.



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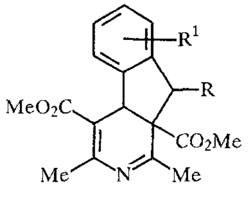

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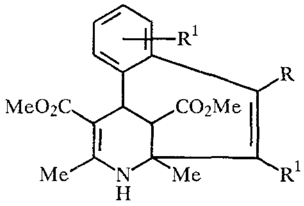

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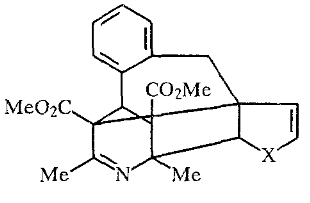
21 R = Me [73], H [71, 74], OMe [75, 76]; *22* R = Me [73], OMe [75, 76] *23* $R = R^1$ = H [73], $R + R^1$ = —CH=CH—S— [77, 78]



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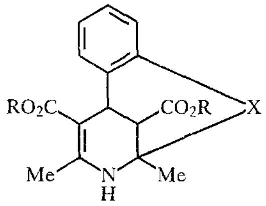

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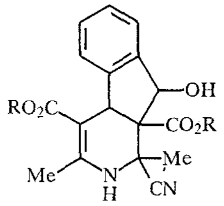
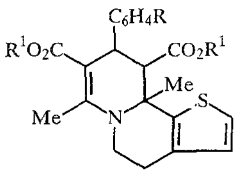
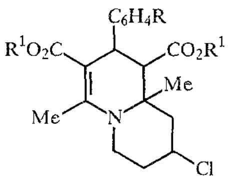


26 [71]

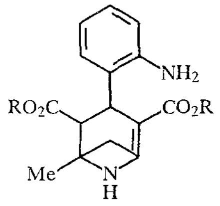
24 X = O, S [78]; *25* X = S [70], O [79—81], NH [72], CH—CH=CH_2 [82]



27 [83, 84]



28 [84, 85]



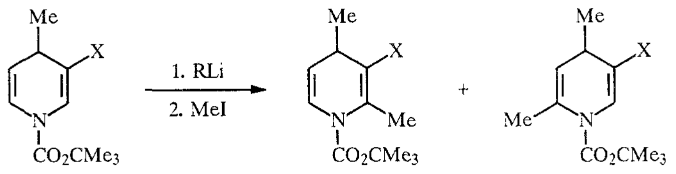
29 [72]

Cyclization products *21-26* were obtained starting from 4-(o-substituted)-phenyl-1,4-dihydropyridines, while systems *27* and *28* were obtained from 1-substituted 1,4-dihydropyridines. Bicyclic system *29* was formed as a result of the addition of the 2-methyl group to the 6 position.

4. REACTIONS INVOLVING SUBSTITUTION OF THE DIHYDROPYRIDINE RING

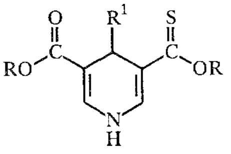
New examples of known reactions [1] involving the formylation of 1-acyl-1,4-dihydropyridines in the 3 position [47] and the formation of 3-alkylpyridines in the reaction of 1,4-bis(trimethylsilyl)-1,4-dihydropyridines with aldehydes or ketones [86] have been described.

Alkyl groups are introduced into the α position of dihydropyridine *30* through lithium derivatives. 2-Methyl isomer *31* predominates if X = Cl, Br, or $OCONEt_2$, while 6-methyl isomer *32* prevails if X = OMe or Me; their ratio also depends on the organolithium compound (R = n-Bu, sec-Bu, Ph, mesityl) [46].



30 31 32

The N-alkylation of 1,4-dihydropyridines has already become a standard procedure. In most cases the use of sodium hydride is necessary for the formation of the anion. Both monocyclic 1,4-dihydropyridines [87-94] and hexahydroquinolines [95] and tetrahydrofuropyridines [96, 97] have been N-alkylated. Formation of anions is attained and solid calcium hydroxide in DMSO [96, 98]. The N—H bond is cleaved more readily in the case of 1,4-dihydropyridine-3,5-dicarbothionic acid esters *33* [10], as well as in the case of 1,4-dihydrobenzothienopyridine dioxides *34*, the N-alkyl derivatives of which were obtained in the presence of alkali metal hydroxides in dimethoxyethane or acetonitrile.



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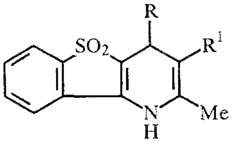

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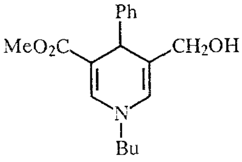

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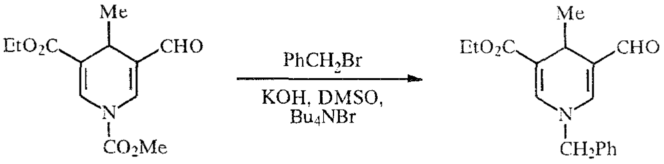
N-Butyl-1,4-dihydropyridine *35* was formed in an N-alkylation reaction in the presence of potassium hydroxide and a phase-transfer catalyst [99]. The N-ethoxymethyl group in 1,4-dihydropyridines is readily replaced by hydrogen by the action of an acid [90, 91, 100-107], the $CO_2CH_2CCl_3$ group is readily replaced by the action of zinc powder [48], and the CO_2Me group is readily replaced by potassium hydroxide [99]. The replacement of the N-substituent to give dihydropyridine *36* has been accomplished [108].



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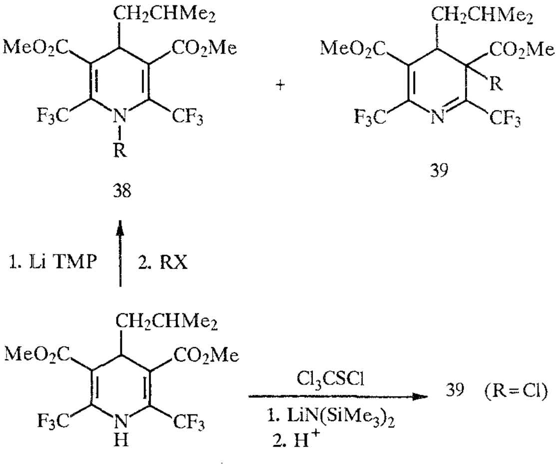
The alkylation of *37* gives, in addition to N-alkyl derivative *38*, isomerization product *39* with substitution in the 3 position, while exclusively a 3,4-dihydropyridine is obtained in the chlorination of *37* [109].



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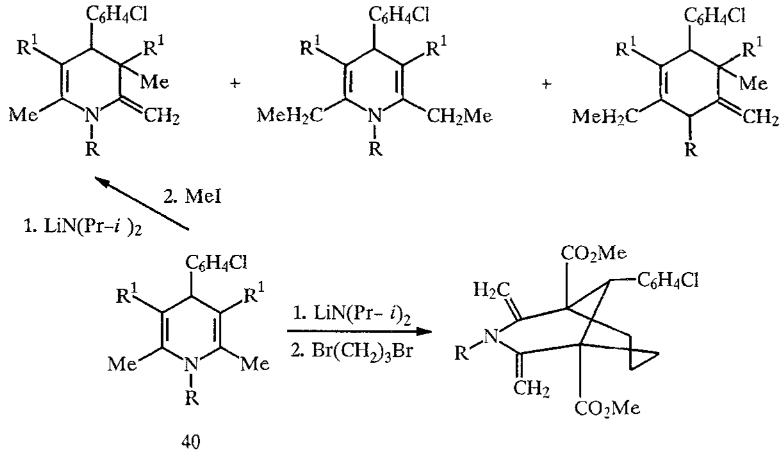
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R = Me, CH_2Ph; $R^1 = CN, CO_2Me$

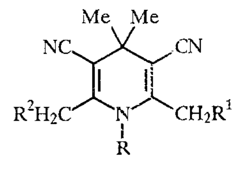
Reactions involving substitution in the 3 position with isomerization, as well as substitution of the 2,6-methyl groups, were observed in the alkylation of 1-substituted 1,4-dihydropyridines *40* [110].

5. REACTIONS INVOLVING SUBSTITUENTS OF THE DIHYDROPYRIDINE RING

5.1. Reactions Involving Substituents in the 2,6 Positions

The bromination of dihydropyridine *5a* under mild conditions leads to 2-bromomethyl derivatives *5* (R^2 = Br). Pyridinium [21, 111-121] and phenyltrimethylammonium [122, 123] bromide perbromides have been used as brominating agents. The action of N-bromosuccinimide was studied systematically, and the possibility of obtaining 2,6-bis(bromomethyl), 2-dibromomethyl-6-bromomethyl, and 2,6-bis(dibromomethyl) derivatives in addition to 2-bromomethyl-1,4-dihydropyridines was demonstrated [121, 124, 125]. Addition of chlorine to the ring double bonds occurs in addition to substitution of the 2,6-methyl groups in the chlorination of *5a* [61, 62]. The halogen atoms in the 2-CH_2Br or 2-CH_2Cl groups are exchanged by means of nucleophilic reagents for I [125, 126], OH [98, 115], OR [111, 115], SR [111-113, 115, 116, 120, 124, 125, 127-129, 147], NR_2 [115, 117-119, 130], N^+R_3 [21, 121, 126], N_3 [115, 125, 131], $CHRR^1$, CN [115], SeR [132], and P^+R_3 [126] groups, as well as N-heterocycles [111-115, 119, 120, 122-125, 133]. The 2-dibromomethyl group is converted to a formyl group under the influence of silver nitrate [115].

Depending on the conditions, the nitration of dihydropyridine *41a* leads to nitro compounds *41b* or *41c*, the nitromethyl groups of which were converted to nitrilo groups by means of phosphorus trichloride [134]. The 2-methyl group of the dihydropyridine is capable of undergoing the Mannich reaction [114, 133].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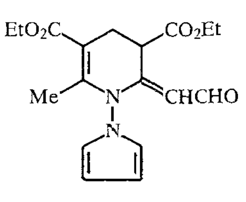
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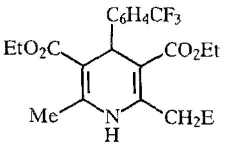
41 a $R^1 = R^2 = H$, b $R^1 = NO_2$, $R^2 = H$, c $R^1 = R^2 = NO_2$

The Vilsmeier—Haack reaction also takes place at the 2-methyl group with simultaneous isomerization to tetrahydropyridine *42* [135, 136]. See Section 4 (the reactions of *40* [110]) for information regarding alkylation of the 2,6-methyl groups. The 2-methyl groups are metallated by butyllithium, and dihydropyridines *43* were obtained by the subsequent action of electrophilic reagents; isomerization to tetrahydropyridines *44* also occurs with some reagents. The action of acetone on the lithium derivative gives a mixture of tetrahydropyridine *44* [E = $C(OH)Me_2$] and lactone 45 [137].



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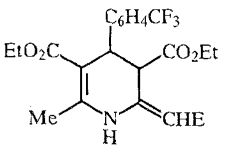

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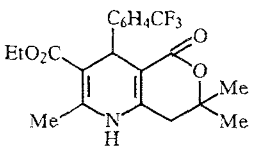

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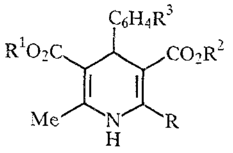
43 E = SR, $PO(OEt)_2$, $SiMe_3$, CONHR, CO_2Na; *44* E = CHO, COMe, CO_2Et

Treatment of the hypothetical 2-hydroxy-1,4-dihydropyridines *46a* with phosphorus oxychloride gave 2-chloro derivatives *46b*, the structure of which raises no doubts [138, 139]. The chlorine atoms in 2,6-dichlorodihydropyridines *47* are exchanged by means of nucleophilic reagents for OR^3, SR^3, and NR^3R^4 groups [24, 140]. The 2-amino groups in *48a* [141] and *48b* [142] undergo acylation.



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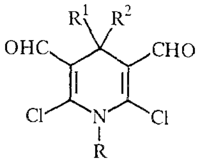

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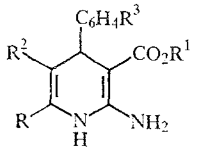

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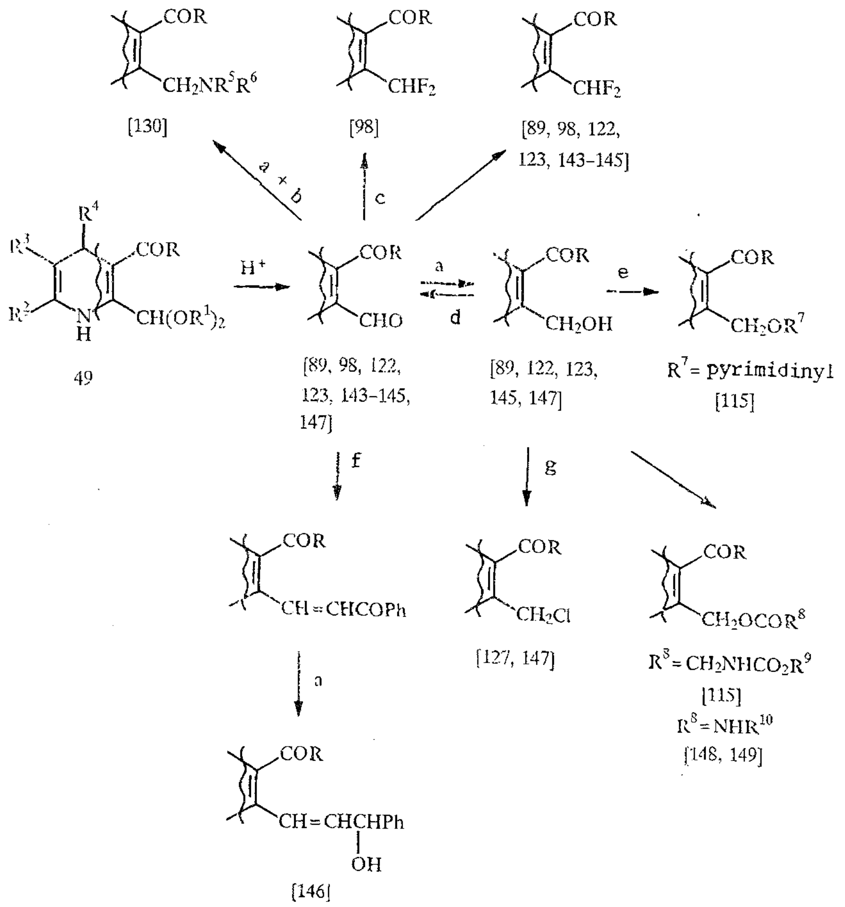
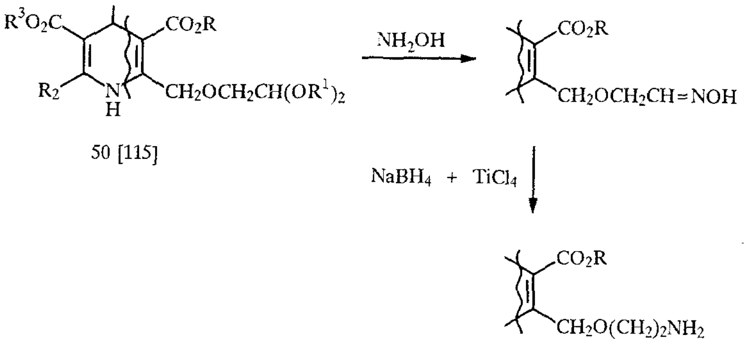
46 a R = OH, b R = Cl; *48* a R = Me, b R = NH_2

Acetals *49* and *50* were used as the reactive starting compounds:



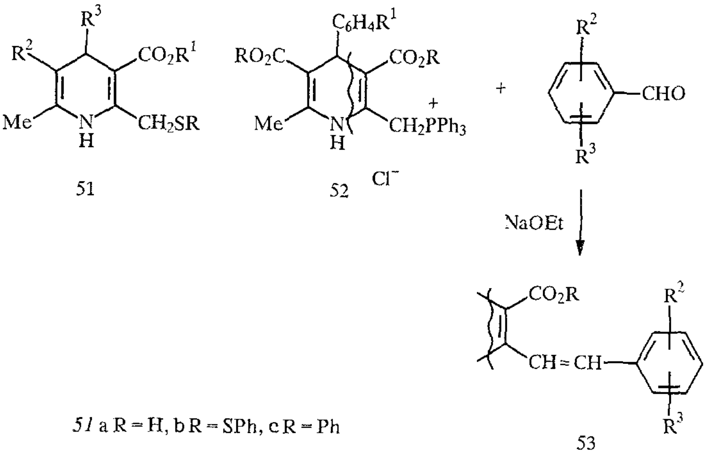


50 [115]

[115]

a NaBH$_4$, b NHR^{5}R^6, c Et$_2$NSF$_3$, d C$_5$H$_5$NH+ClCrO$_3^-$, e NaH + R^{7}Cl, f PhCOCH=PPh$_3$,
g SO$_2$Cl$_2$/imidazole

Acyl derivatives [150, 151], as well as disulfides *51b* [128], were obtained from 2-thiomethyldihydropyridines *51a*. Phenylthio derivatives *51c* were oxidized to sulfoxides and sulfones [95]. 2-Styryl derivatives *53* were obtained from phosphonium salts *52*.



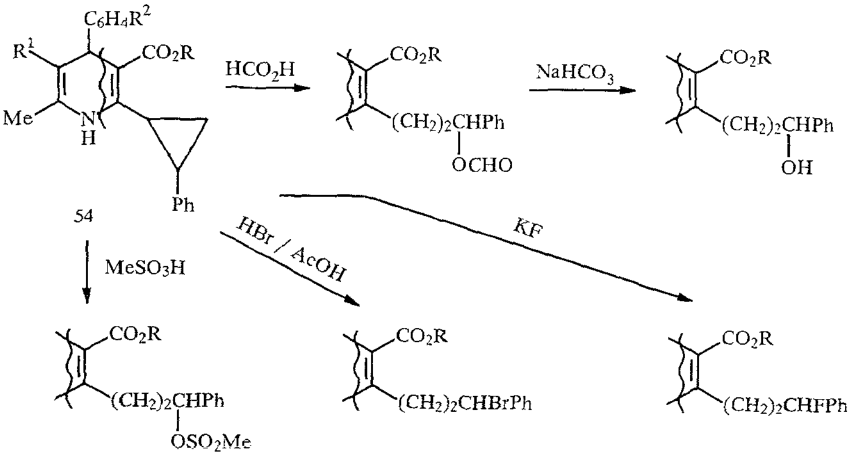
51

52

51 a R = H, b R = SPh, c R = Ph

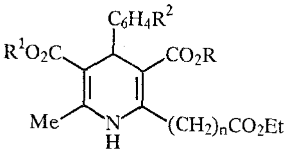
53

Reactions involving cleavage of the cyclopropane ring in dihydropyridines *54* have been accomplished [131].

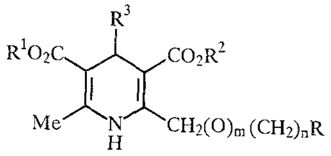


54

The hydrolysis of the ester groups in the 2 position of dihydropyridines *55* proceed without difficulty [7, 114, 147].



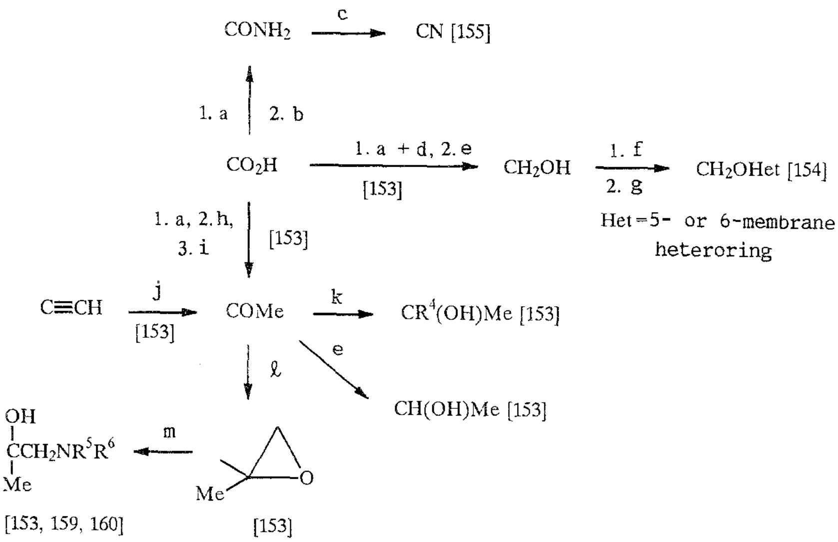
55



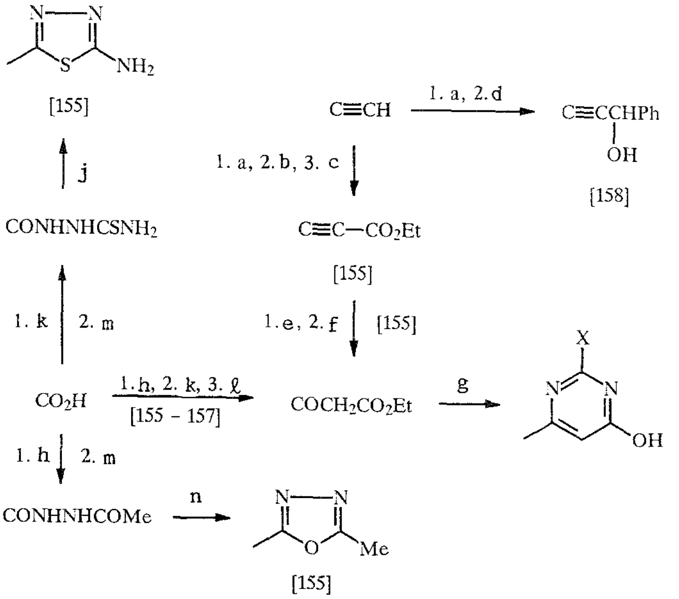
56

55 $n = 0, 1, 2$; *56* $m = 0, n \geq 0$; $m = 1, n \geq 1$

Methods for obtaining a wide variety of derivatives of dihydropyridines *56* with variation of functional groups R in the side chain of the α substituent that involve, for example, modification of carboxylic acids *56* ($R = CO_2H$) or ethynyl derivatives *56* ($R = C{\equiv}CH$) have been developed:

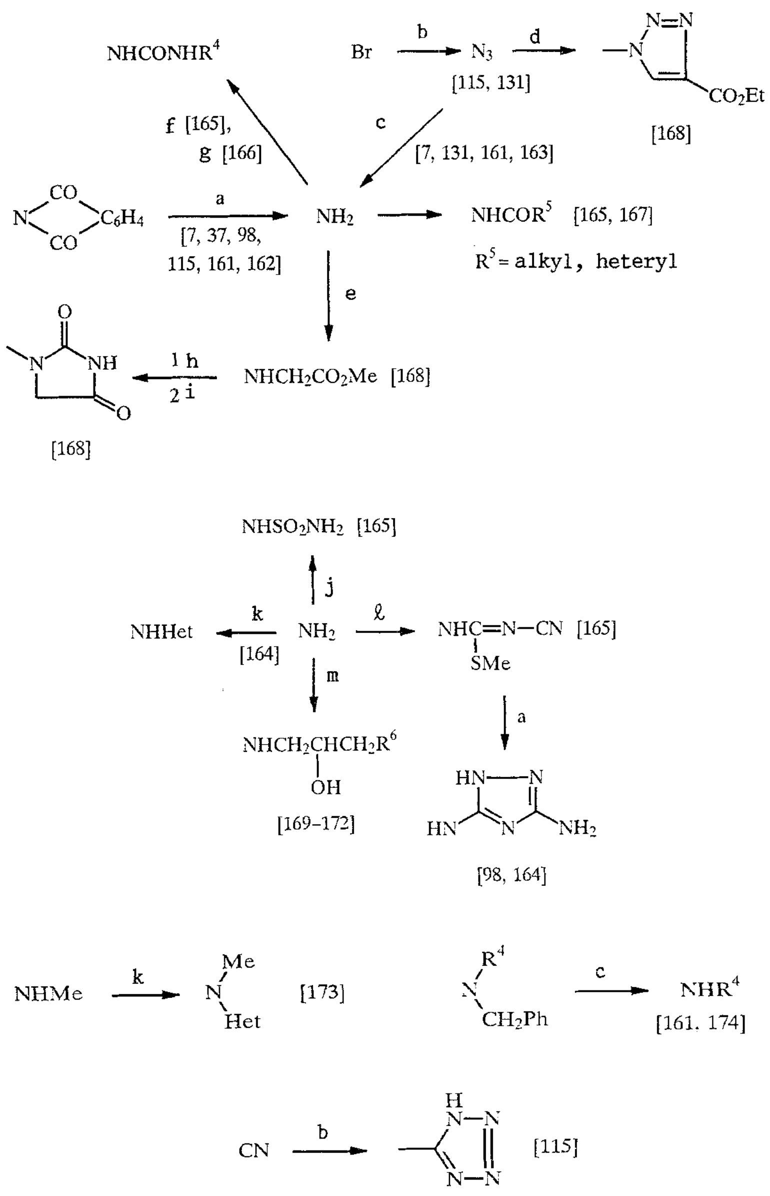


a CDI, b NH_3, c $(CF_3CO)_2O$, d 4-Me-morpholyl, e $NaBH_4$, f NaH, g HetCl
h 2,2-dimethyl-1,3-dioxane-4,6-dione, i $AcOH/H_2O$,
j $HgSO_4/H_2SO_4$, k R^4Li, ℓ $Me_3S{=}OI^{\pm}$, m NHR^5R^6 + base



a BuLi, b CO_2, c $EtBr/PhCH_2NMe_3OH$, d PhCHO, e Et_2NH,
f $H_2O/AcOH$, g $HN{=}CX{-}NH_2$, h CDI, i $NH_2NHCSNH_2$, j $POCl_3$, k 2,2-dimethyl-1,3-dioxane-4,6-dione, ℓ EtOH, m $MeCONHNH_2$, n P_2O_5

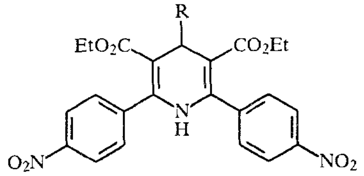
The formation and transformations of amino groups R in dihydropyridines *56* constitute a second group of reactions:



a NH_2NH_2, b NaN_3, c H_2/Pd, d $MeCH_2CO_2Et$, e $BrCH_2CO_2Me$, f R^4NCO, g NH_2CONHR^4,
h KNCO/AcOH, i NaH, j $NH_2SO_2NH_2$, k HetX (X=Cl, SMe), ℓ $(MeS)_2C{=}NCN$, m 2-R^6CH_2-oxirane,
Het= imidazolyl, pyrimidinyl, pyrazinyl, thiadiazolyl

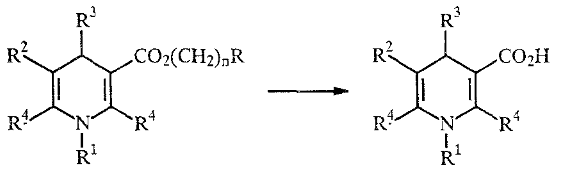
The goal of these reactions was frequently the construction or introduction of heterocycles in the side chain of the α substituent of dihydropyridines *56* [98, 115, 133, 153, 155-157, 164, 168, 173] (only characteristic examples from each study are presented).

In the electrochemical reduction of dihydropyridines *57* one of the nitro groups is initially reduced [14].

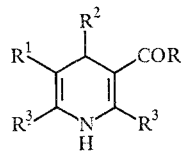


57

5.2. Reactions Involving Substituents in the 3,5 Positions



58 59



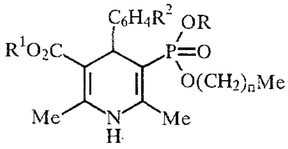
60

60 a R = H, b R = Me, CH2OMe

Hydrolysis of the ester groups in the 3 position of N-unsubstituted *58* (R^1 = H) occurs if the ester radical contains an electron-acceptor substituent R: CN [7, 89, 98, 115, 144, 161, 175-178], CO_2R^5 [115], SO_2R^5, SOR^5 [179], OSO_2R^5 [180], S^+Me_2 [181], and N^+Me_3 [182]. tert-Butyl esters *58* (n = 0, R = CMe_3) are also hydrolyzed [183-185]. The reports of the hydrolysis of n-alkyl esters in an alcohol medium [186, 187] seem doubtful, but it is possible that dimethyl sulfoxide facilitates this reaction substantially [188]. Esters of N-substituted dihydropyridines *58* (R^1 = CH_2OR^5) are hydrolyzed more readily [91, 105, 106]. The synthesis of carboxylic acids *59* by treatment of the allyl ester with palladium diacetate has been described [189]. The transesterification of 1,4-dihydropyridine-3,5-dicarboxylic acid esters is achieved in the presence of alkoxides [90, 161, 190-192] or acid [193]. Reactions involving the esterification of acids *59* are widely used [19, 98, 100-107, 115, 144, 161, 163, 175-178, 180, 182, 184, 189, 194-228]. One of the ways to obtain aminoalkyl esters is the reaction of acids *59* with aziridinium or azetidinium salts in the presence of sodium hydride [229, 230]. The ester carbonyl in the 3-CO_2R and 3-COSR groups is thionated by the Lawesson reagent to give, respectively, 3-CSOR and 3-CS_2R groups [10]. The amidation of acids *59* [231, 232], their decarboxylation [7] and reduction to aldehydes [233], and alkylation of the amides [234, 235] have been accomplished.

Aldehydes *60a* were also obtained from the corresponding acetals [46] or from 3-oxazolyl-1,4-dihydropyridines [99, 108]. Aldehydes *60a* react with amines and hydrazines [233], while ketones *60b* form derivatives with O-alkylhydroxylamines [236]. Dialdehyde *47* forms dioximes and bis(hydrazones), but the formyl groups do not undergo the Perkin reaction and are not oxidized by potassium permanganate [140]. The formyl group in *60a* is reduced to a hydroxymethyl group by sodium borohydride [237] or lithium aluminum hydride [99, 108]. The 3-hydroxymethyl groups undergo alkylation [99, 108] and acylation [238].

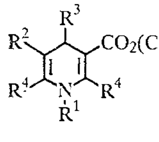
3-Arylsulfinyl groups are oxidized to sulfonyl groups [239]. 3-Nitro groups are hydrogenated catalytically to amines [240]. Phosphonic acid monoesters *61* (R = H) were obtained by hydrolysis of diesters *61* [R = $(CH_2)_2CN$] [241].



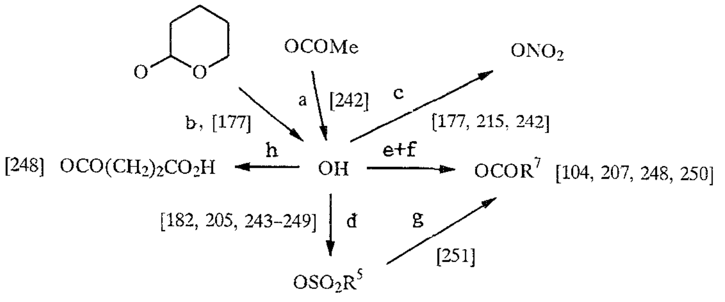
61

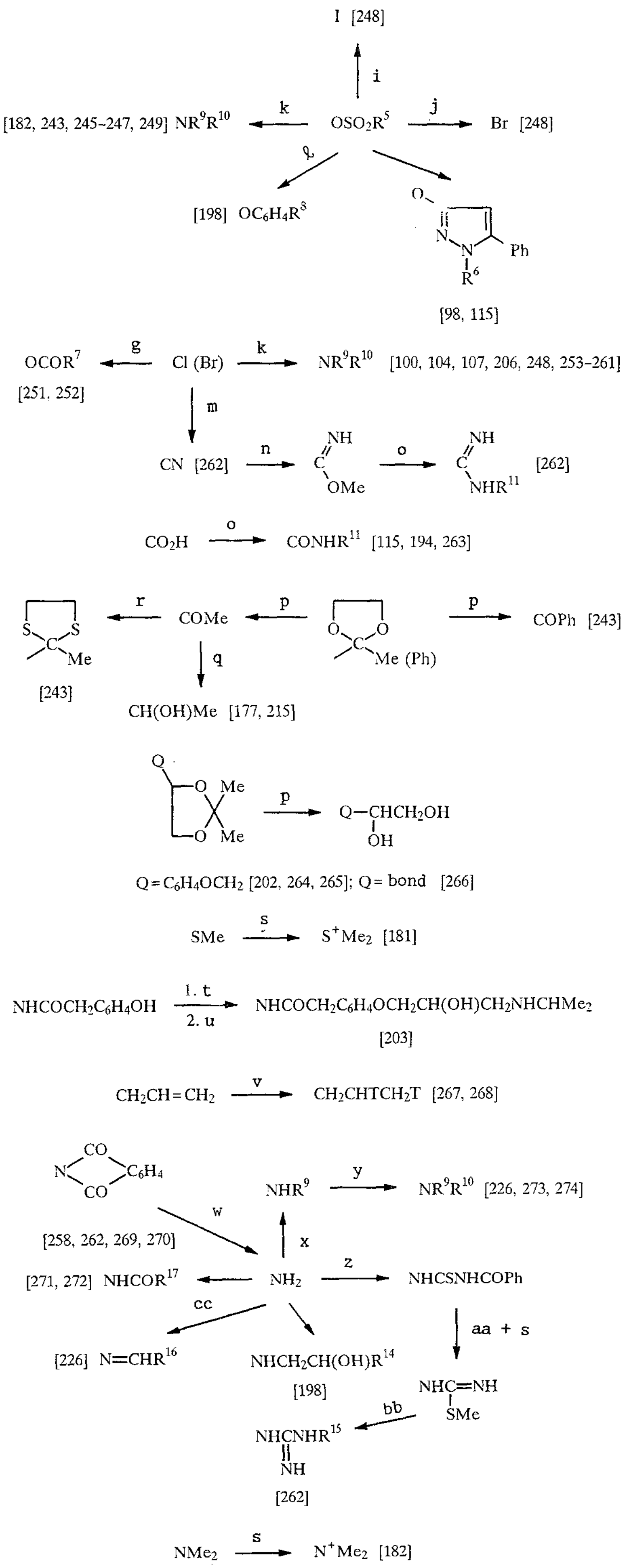
Various transformations of radical R in the ester group of dihydropyridines A—R *58* have been accomplished:

A =

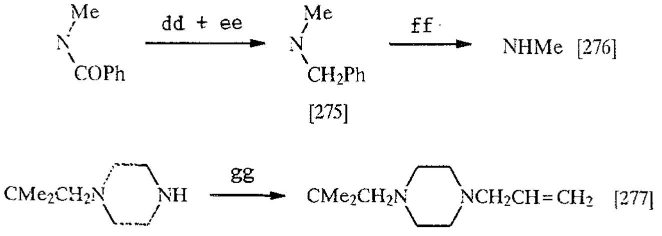


; n >1; R=OH, Cl, Br, CO_2H, COMe, SMe, NH_2 etc.





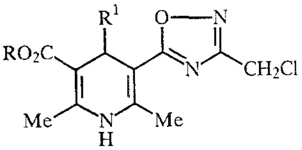
I [248]
i
[182, 243, 245-247, 249] NR⁹R¹⁰
k
OSO₂R⁵
j
Br [248]
ℓ
[198] OC₆H₄R⁸
O
N
N
Ph
R⁶
[98, 115]
OCOR⁷
g
Cl (Br)
k
NR⁹R¹⁰ [100, 104, 107, 206, 248, 253-261]
[251, 252]
m
CN [262]
n
NH
C
OMe
o
NH
C
NHR¹¹
[262]
CO₂H
o
CONHR¹¹ [115, 194, 263]
S
S
C
Me
[243]
r
COMe
p
O
O
C
Me (Ph)
p
COPh [243]
q
CH(OH)Me [177, 215]
Q
O
Me
O
Me
p
Q—CHCH₂OH
OH
Q = C₆H₄OCH₂ [202, 264, 265]; Q = bond [266]
SMe
s
S⁺Me₂ [181]
NHCOCH₂C₆H₄OH
1. t
2. u
NHCOCH₂C₆H₄OCH₂CH(OH)CH₂NHCHMe₂
[203]
CH₂CH=CH₂
v
CH₂CHTCH₂T [267, 268]
CO
N
C₆H₄
CO
[258, 262, 269, 270]
w
NHR⁹
y
NR⁹R¹⁰ [226, 273, 274]
x
[271, 272] NHCOR¹⁷
NH₂
z
NHCSNHCOPh
cc
aa + s
[226] N=CHR¹⁶
NHCH₂CH(OH)R¹⁴
[198]
NHC=NH
SMe
bb
NHCNHR¹⁵
NH
[262]
NMe₂
s
N⁺Me₂ [182]



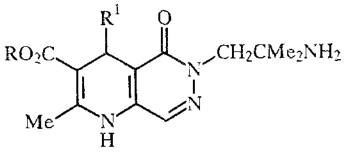
$OC_6H_4(CH_2)_2NH_2 \xrightarrow{hh} OC_6H_4(CH_2)_2NHCH_2CH(OH)CH_2OPh$ [218]

a NaOH, b HCl, c $AcONO_2$, d R^5SO_2Cl, e CDI, f R^7CO_2H, g R^7CO_2Na, h 2,5-dioxotetra-hydrofuran/4-dimethylaminopyridine i NaI, j LiBr, k NHR^9R^{10}, *l* $HOC_6H_4R^8$; m NaCN, n MeOH/HCl, o NH_2R^{11}, p H^+, q $NaBH_4$, r $HS(CH_2)_2SH$, s MeI, t chloromethyl-oxirane/NaOH, u Me_2CHNH_2, v T_2 [catalyst−$(Ph_3P)_3RhCl$ or $Pd/BaSO_4$], w NH_2NH_2, x R^9Cl, y $R^{10}Cl$, z PhCONCS, aa K_2CO_3, bb $R^{15}NH_2$, cc $R^{16}CHO$, dd $POCl_3$, ee $LiBH_4$, ff $H_2(Pd/C)$, gg $ClCH_2CH{=}CH_2/Et_3N$, hh phenoxymethyloxirane.

The chlorine atom in 3-oxadiazolyl-1,4-dihydropyridines *62* is replaced by various nucleophilic reagents [278]. N-Alkylation in the side chain of pyridopyridazines *63* has been accomplished [279].



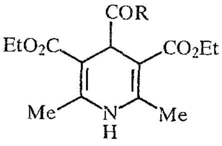
62



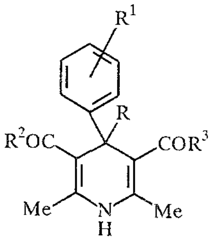
63

5.3. Reactions Involving Substituents in the 4 Position

Amide *64* [R = $NH(CH_2)_2SO_3H$] was obtained from 1,4-dihydropyridine-4-carboxylic acid *64* (R = OH) by reaction of its pentafluorophenyl ester with taurine [280].



64

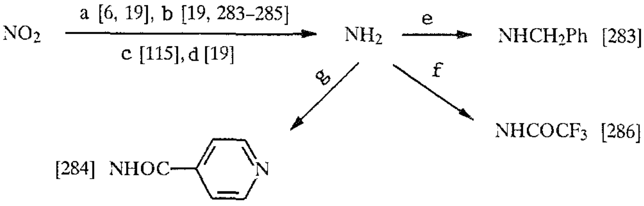


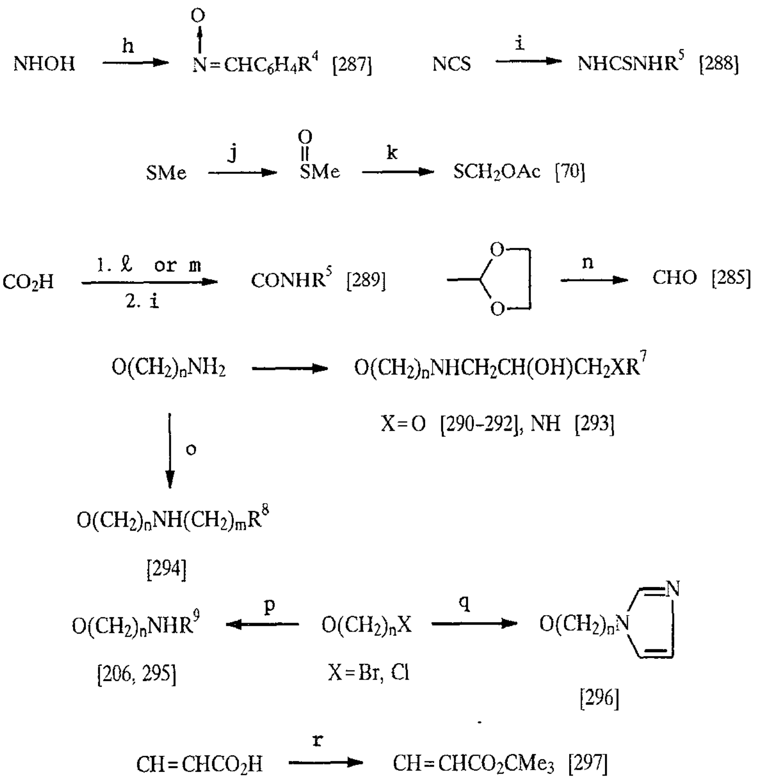
65

65 a R = H, b R = Me

A method for the nitration of 4-phenyl-1,4-dihydropyridines *65* in the phenyl ring with a mixture of $H_2SO_4 + NaNO_3$ has been developed [281]. Only the 4-nitro derivative ($R^1 = 4\text{-}NO_2$) was obtained from *65a* [281], while the 3- and 4-nitro isomers were formed in a ratio of 1:2 from 4,4-disubstituted *65b* [282].

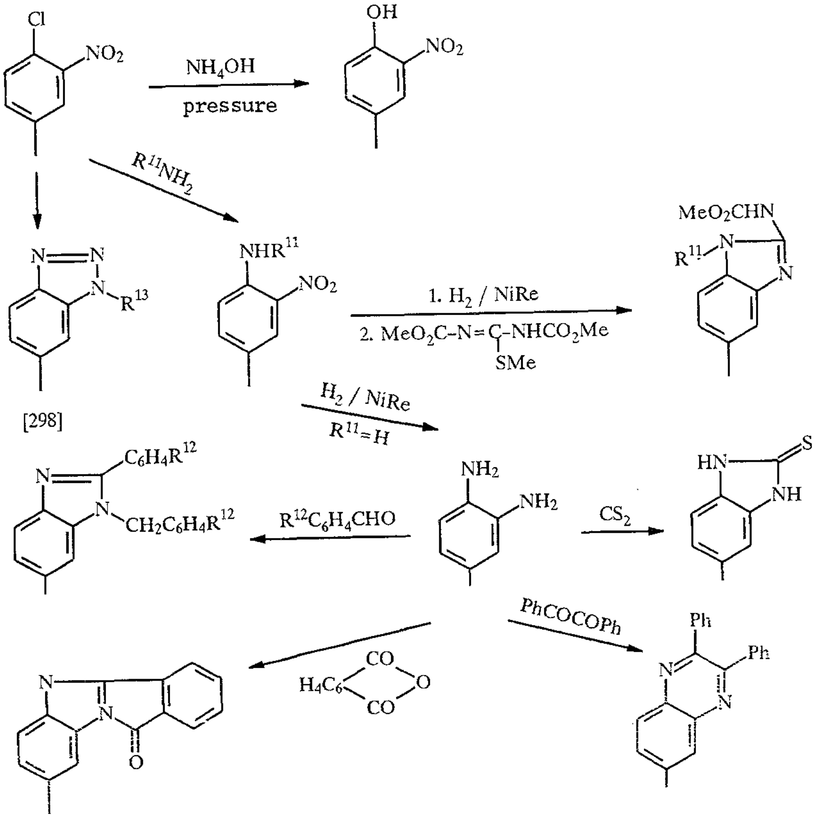
Reactions of substituent R^1 in the 4-phenyl ring in dihydropyridine *65a* have been accomplished:

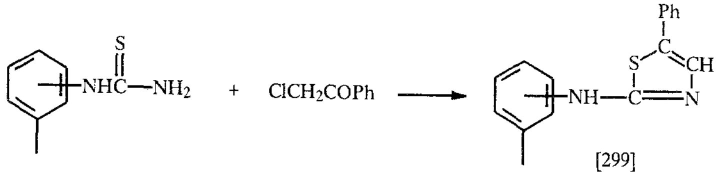




a H_2/Pd-C, b H_2/Raney Ni, c $SnCl_2$, d $NaBH_4$, e $PhCH_2Br$, f $(CF_3CO)_2O/C_5H_5N$, g isonicotinyl chloride, h $R^4C_6H_4CHO$, i R^5NH_2, j $3\text{-}ClC_6H_4CO_3H$, k $Ac_2O/NaOAc$, ℓ CDI, m R^6SO_2Cl, n HCl, o $R^8(CH_2)_mBr$, p R^9NH_2, q imidazole sodium salt, r $Me_2NCH(OCMe_3)_2$

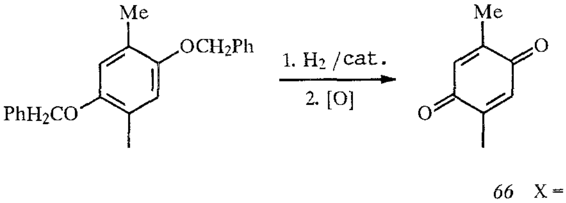
The increase in the reactivity of the substituents in the 4-phenyl radical adjacent to a nitro group was used, and construction of heterorings attached to the phenyl ring of dihydropyridines *65a* was also carried out [285]:

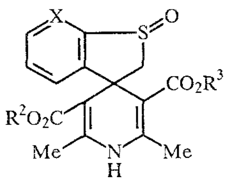




[299]

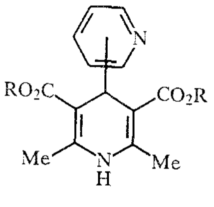
A 4-phenyl radical with the appropriate substituents was converted to a quinone [80]:





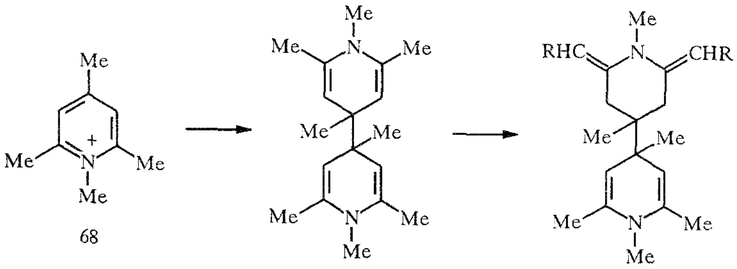
66 X = CH, N

Raney nickel under mild conditions reduces the sulfoxide group in spirocyclic dihydropyridine *66*, while desulfuration to give 4,4-disubstituted 1,4-dihydropyridine *65b* occurs under more severe conditions [282].



The methylation of 4-pyridyl-1,4-dihydropyridines *67* with methyl iodide in acetone takes place at the nitrogen atom of the 4-pyridyl substituent to give pyridinium salts [300, 301].

Sodium borohydride reduces these salts to 4-(N-methyltetrahydropyridyl)-1,4-dihydropyridines [300], while 4-pyridyl derivatives *67* are reduced to 4-[N-(alkoxycarbonyl)dihydropyridyl]-1,4-dihydropyridines in the presence of chloroformic acid esters [302].



68

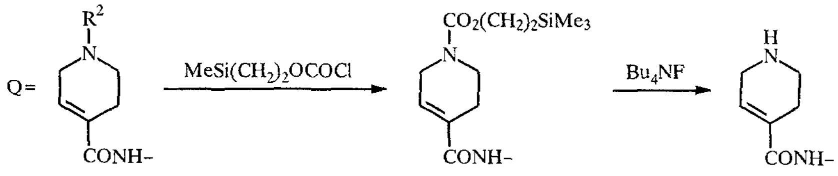
69

70

70 a R = H, b R = COR^1 [303, 304], c R = CSNHCOR^2 [304—306], d R = CN [305, 307]

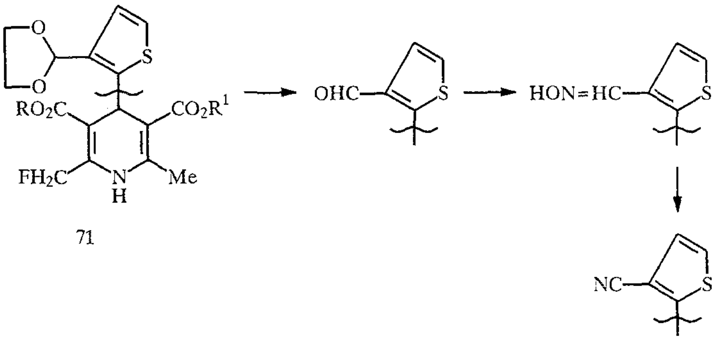
Bis(dihydropyridine) *69*, which was obtained by the electrochemical reduction of tetramethylpyridinium cation *68*, is isomerized in protic solvents to 4-(2,6-dimethylenepiperidyl)-1,4-dihydropyridine *70a* [303, 304], the methylene groups of which are capable of forming derivatives *70b, c*. Thioamides *70c* were used to obtain nitriles *70d* and also to form heterorings in the side chain in reactions with hydrazines or diamines [306].

In the case of dihydropyridine *65a*, which contains the substituent R^1 = Q in the para position of the 4-phenyl radical, it has been shown that it is possible to selectively debenzylate the tertiary amines under mild conditions (demethylation proceeds less readily) [308]:



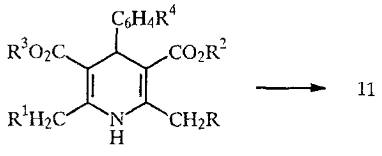
$R^2 = CH_2Ph$, Me

Reactions of the functional groups in the 4-thienyl substituent of dihydropyridines *71* have been carried out [115].



5.4. Cyclization and Reactions of the Cyclization Products

Tetrahydrofuro[3,4-b]pyridines *11* were obtained by cyclization of dihydropyridines *72*, which contain suitable substituents R = F [42], Cl (309], and OAc [310]. Lactone *11* was formed as a side product in the oxidation of 2-methyl derivative *72* (R = H) with cerium ammonium nitrate in the presence of sodium bromate [25]. The bromination of 2,6-dimethyldihydropyridine *72* (R = R^1 = H) with pyridinium bromide perbromide [21, 206, 311, 312] or N-bromosuccinimide [21, 23, 121, 125, 311] with subsequent heating of the intermediate bromo derivatives *72* (R = Br, R^1 = H) is often used to obtain lactones *11*. This method was also used to synthesize dilactones *73* [21, 22, 121, 125] through dibromo derivatives *72* (R = R^1 = Br). In contrast to the N-unsubstituted analogs, the N-substituted (alkyl or aryl) 2,6-bis(bromomethyl)-1,4-dihydropyridines are not lactonized [124, 125]; 2-dibromomethyl-1,4-dihydropyridines also do not cyclize [125].



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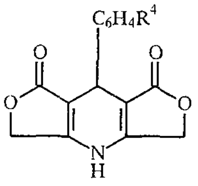
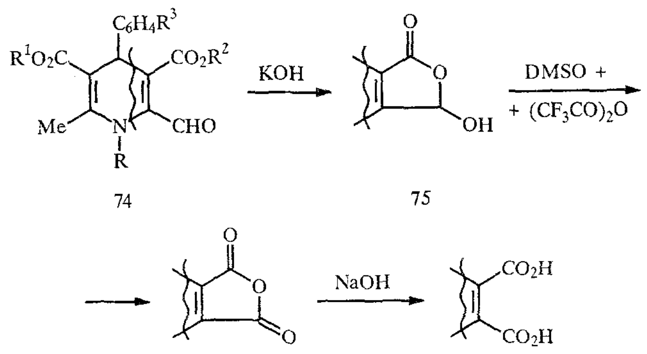


73

Hydroxylactones *75* were obtained by cyclization of 2-formyldihydropyridines *74* (R = alkyl) [313] or from lactones *11* through the 7-bromo derivatives [313, 314]. The oxidation of hydroxylactones *75* with subsequent hydrolysis leads to 1,4-dihydropyridine-2,3-dicarboxylic acids [313].



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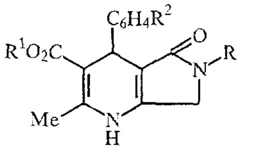
75

The bromination of 2,6-dimethyldihydropyridine-3,5-dicarboxylic acid monoamides gives pyrrolopyridines *76* [315], which were also obtained by heating 2-phthalimidomethyl-1,4-dihydropyridine-3,5-dicarboxylic acid diesters [118]. Dilactam *77* was obtained from dibromo derivatives *72* ($R = R^1 = Br$) and methylamine [125].



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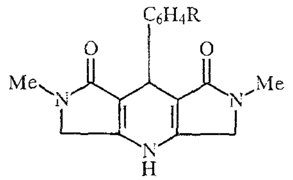
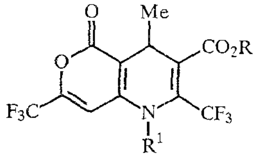


77

The formation of six-membered lactones *45* [137] and *78* [109] has been observed.



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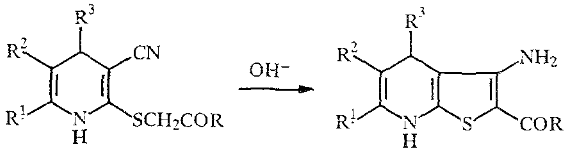
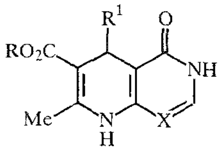


79

80

2-Substituted methylthio-1,4-dihydropyridines *79* undergo cyclization to thienopyridines *80* when they are treated with alkalis [12, 316-320].

Naphthyridines *81a* [321-323] and pyridonaphthyridines *82* [324] were obtained by the action of sodium hydride and 1,3,5-triazine on *65a*, while 2-amino-1,4-dihydropyridines *48a* undergo cyclization to pyridopyrimidines *81b* [325]. The alkylation of heterocycles *81* takes place at the oxygen atom [321, 322, 325, 326].



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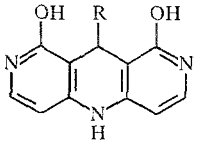
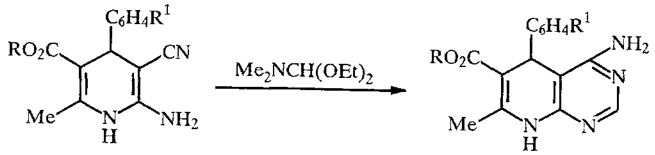


82

81 a X = CH, b X = N

2-Amino-3-cyano derivatives *83* undergo cyclization with dimethylformamide diethylacetal to give pyridopyrimidines *84* [327]. The action of phenyl isocyanate on diamine *48b* gives pyridodipyrimidine *85* [142].



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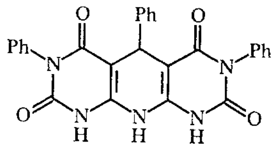
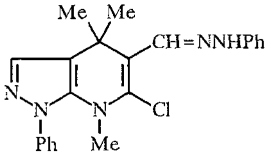


85

Heterocyclic systems *86-88* were obtained from dialdehyde *47* [140, 328].



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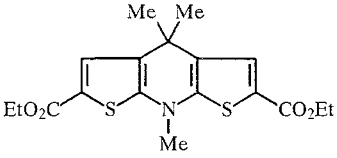

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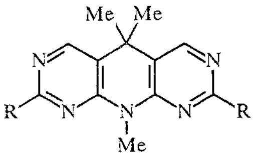
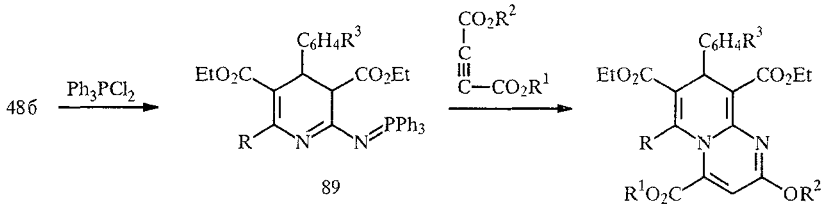


88

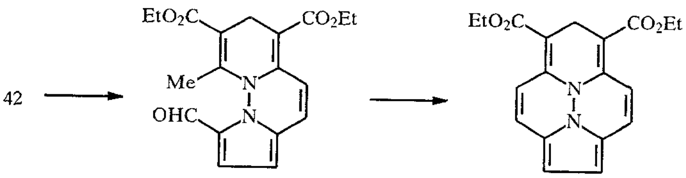
The formation of iminophosphoranes *89* is accompanied by isomerization of the 1,4-dihydropyridines to the 4,5-dihydro isomers; the latter undergo cyclization with acetylenedicarboxylic acid diesters to give pyrido[1,2-*a*]pyrimidines *90* with reversion to the 1,4-dihydro structure [329].



89

90

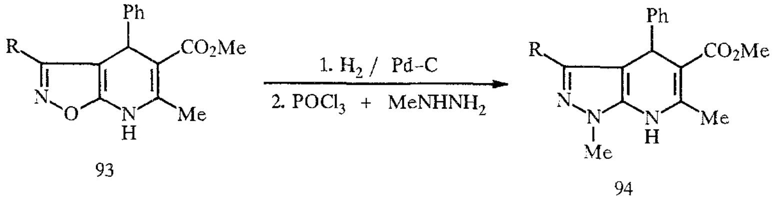
Heterocycles *91* and *92* were obtained from the Vilsmeier—Haack reaction product *42* [135].



91

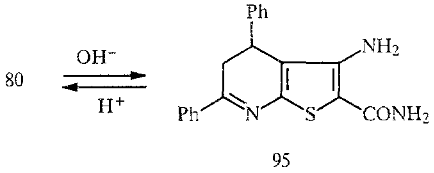
92

Opening of the isoxazole ring of isoxazolopyridine *93* with subsequent ring closing to give pyrazolopyridine *94* has been accomplished [6].

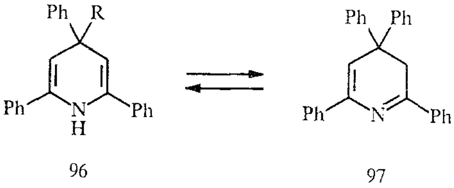


6. ISOMERIZATION AND REARRANGEMENTS

A facile tautomeric transition between dihydrothienopyridines *80* and *95* has been observed [318].

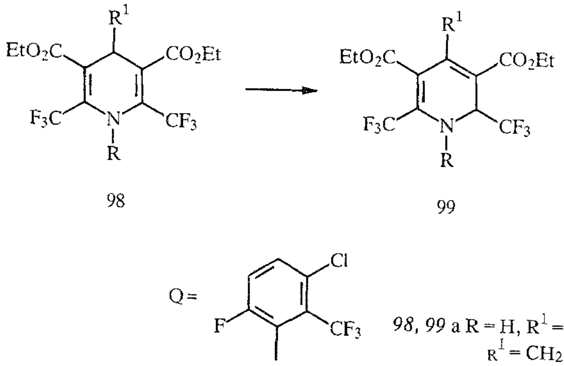


In nonpolar solvents 1,4- and 3,4-dihydropyridines *96a* and *97* exist in a tautomeric equilibrium [330].



96 a R = Ph, b R = CH_2Ph

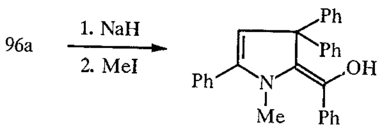
On treatment with alkalis, 2,6-bis(trifluoromethyl)-1,4-dihydropyridine *98a* gives, in addition to a 4-unsubstituted pyridine of the *6* type (see Section 1.1), isomerization product *99a* [42]. The same isomerization to 1,2-dihydropyridine *99b* took place in the action of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) on 1,4-dihydro isomer *98b* [109].



98, *99* a R = H, R^1 = Q; b R = CH_2OMe, R^1 = CH_2CHMe_2

See Section 4 for the isomerization of 1,4-dihydropyridines during alkylation (*39* [109], *40* [110]), Sections 5.1 and 5.4 for the isomerization of 1,4-dihydropyridines during the reaction of the substituents in the 2 position (*42*, *91*, *92* [135, 136], *44* [137], *89*, *90* [142, 329]), and Section 5.3 for the isomerization of 4-(dihydropyridyl)-1,4-dihydropyridines (*69*, *70* [303, 304]).

The alkylation of dihydropyridine *96a* in an inert atmosphere gives normal N-alkyl derivatives, but rearrangement product *100* is obtained in the presence of air oxygen.

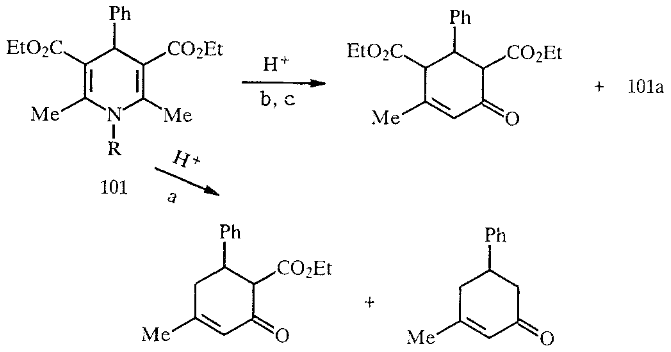


100

7. CLEAVAGE OF THE DIHYDROPYRIDINE RING

The previously noted acidic hydrolysis of N-methyl derivatives of 4,5-dihydroindeno[1,2-b]pyridine [331] was examined in greater detail in [332].

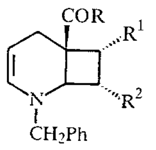
In an acidic medium the ring of dihydropyridine *101* is cleaved with subsequent recyclization to cyclohexenone derivatives. In the case of N-alkyl and N-aryl derivatives *101b, c* a small amount of dealkylation (dearylation) product *101a* was also observed [333].



101 a R = H, b R = Me, c R = Ph

8. PHOTOCHEMICAL TRANSFORMATIONS

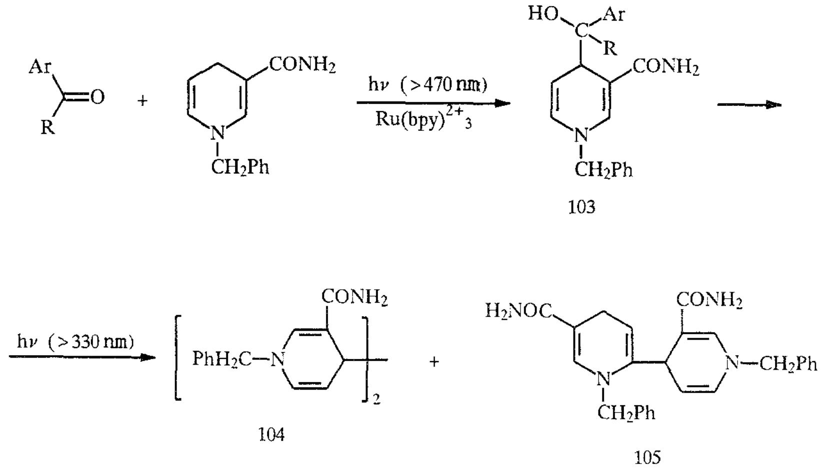
1-Benzyl-1,4-dihydronicotinic acid derivatives photochemically add acrylonitrile to give cyclobutapyridines *102a, b* [334].



102

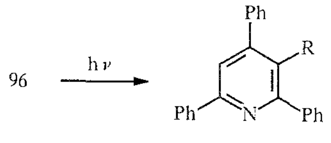
102 R = OEt, NH_2 ; a R^1 = CN, R^2 = H, b R^1 = H, R^2 = CN

One of the chief pathways of the photosensitized reaction of 1-benzyldihydronicotinamide with carbonyl compounds is addition to the 4 position (*103*) [335]; further irradiation of *103* leads to dimers *104* and *105* [336].



Ar = Ph, R = H, CF$_3$; Ar = C$_6$H$_4$CN-p, R = H

Migration of one aryl radical in the 3 position occurs in the photochemical oxidation of tetraphenyldihydropyridine *96a* (to give pyridine *106a*), while a benzyl group is split out in the case of analog *96b* [337].



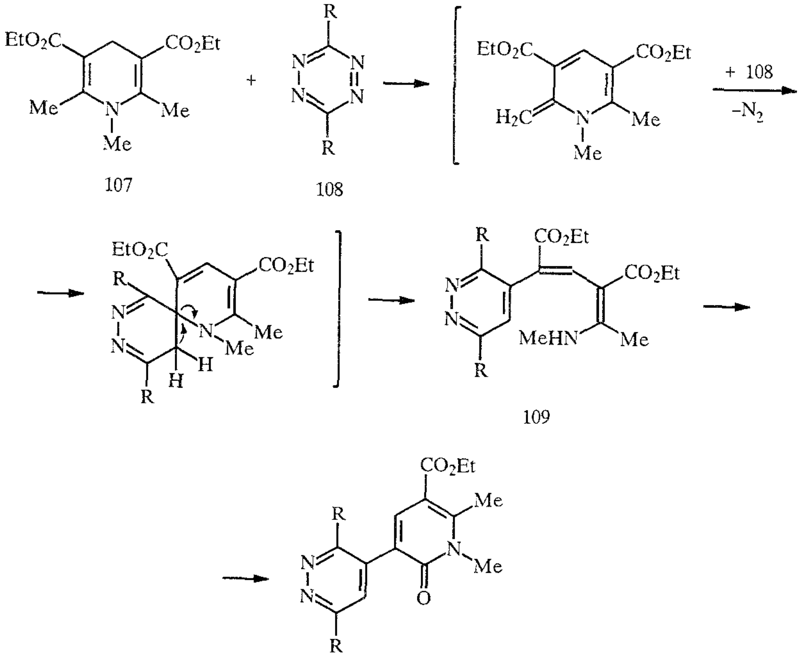
106

106 a R = Ph, b R = H

The photochemical stability of nifedipine and its analogs has been studied [338].

9. OTHER REACTIONS

The reaction of N-methyldihydropyridine *107* with tetrazine *108* proceeds peculiarly; it leads, as a result of successive oxidation, addition, ring opening, and recyclization, to pyridazines *109* and *110* [339].



110

108—110 R = pyridyl

TABLE 1. Reagents for the Aromatization of N-Unsubstituted 1,4-Dihydropyridines

Reagent	Literature	Reagent	Literature
O_2	[3—5]	NaOCl	[33]
$NaNO_2$ /AcOH	[6—14]	H_2O_2	[4]
HNO_3	[15—23]	NH_2OH	[5]
$(NH_4)_2Ce(NO_3)_6$	[24, 25]	Nitrobenzene	[34]
CrO_3	[26, 27]	Chloranil	[35]
S	[28]	DDQ*	[36—39]
$KMnO_4$	[7]	DBU,** or tertiary amines	[40,41]
MnO_2	[4, 29—31]		
$SnCl_4$	[32]	NaCN, Et_4NCN	[42]

---

*DDQ is 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

**DBU is 1,8-diazabicyclo[5.4.0]undec-7-ene.

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