SYNTHESIS OF 1,4-DIHYDROPYRIDINES IN CYCLOCONDENSATION REACTIONS (REVIEW)

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The 1986-1990 literature on the formation of 1,4-dihydropyridines in the Hantzsch synthesis and other cyclocondensation reactions is summarized and correlated.

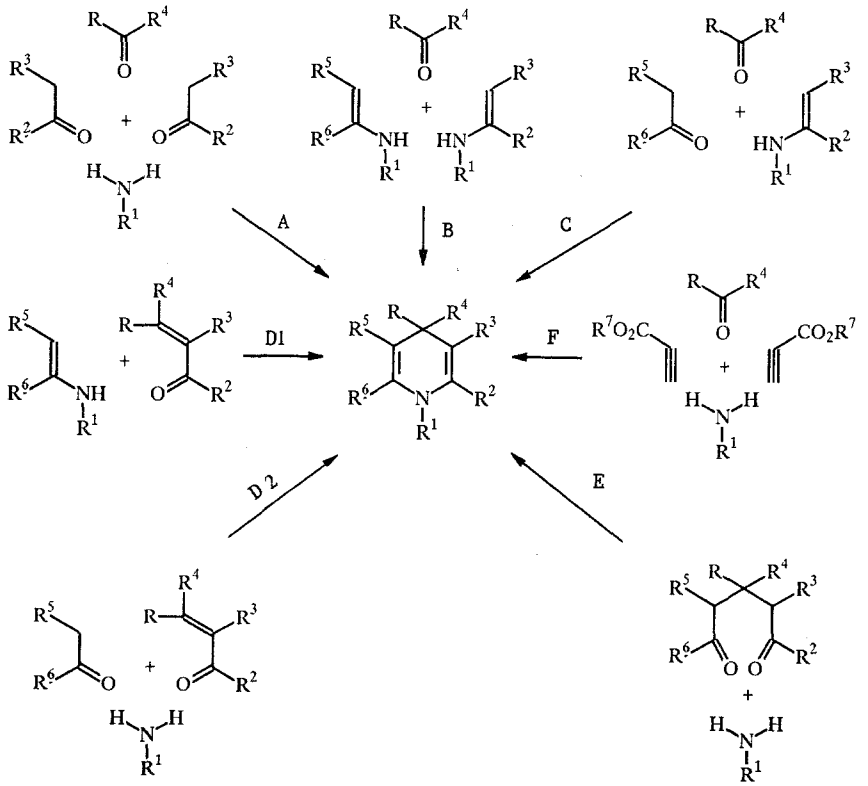
This review covers the literature for 1986-1990, and it is organized on the same principle as our previous review [1].

Derivatives of 1,4-dihydropyridine are most often obtained by cyclocondensation reactions, particularly by various modifications of the Hantzsch synthesis. The 1,4-dihydropyridines have taken on practical importance as modulators of calcium ion transport through cell membranes. The most widely studied are calcium antagonists, for which there are a number of reviews [2-7], monographs, and reviews dealing with particular preparations [8-12]. Studies have also been made of calcium agonists [13, 14] and the interrelations between structure and inhibition or activation of calcium transport [15-18]. Research is continuing on the antioxidant activity of 1,4-dihydropyridines [19]. These substances have been found to exhibit radioprotector [20, 21], cryoprotector [22], bronchodilating [23], antiasthmatic [24], antithrombolytic [25-29], heptoprotector [30], and antiepileptic [31, 32] properties. 1,4-Dihydropyridines have been reported as potentiators of antitumor agents [33-40], enzyme blockers [41], and fluorescent probes [42].

1. HANTZSCH SYNTHESIS AND RELATED CYCLOCONDENSATIONS

In the following scheme we show the main variants and modifications of the Hantzsch synthesis that are used in obtaining 1,4-dihydropyridines:

Scheme



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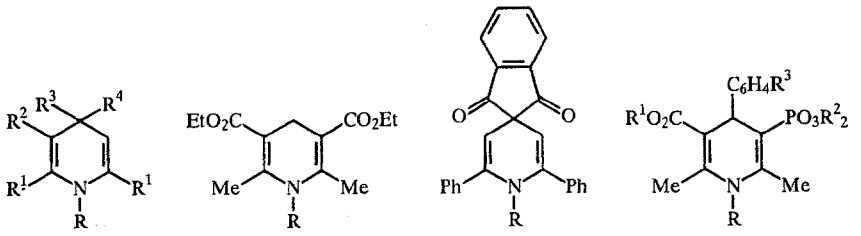
1.1. Monocyclic 1,4-Dihydropyridines

1.1.1. Substituents in Position 1. The synthesis of 1-substituted 1,4-dihydropyridines is largely episodic in character. By cyclization of 1,5-dicarbonyl compounds by ammonium acetate, amines, amides, or hydrazines (method E), the 1,4-dihydropyridines *1-3* are obtained.

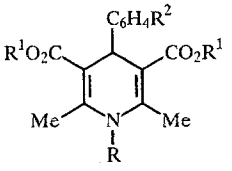


1 2 3 4

1a) R^1 = H; R^2 = H; R^3 = R^4 = Me, Ph; R = $(CH_2)_nCO_2Me$,$(CH_2)_nNMe_2$, $COCH_2NMe_2$, $CONHR^5$, CO-(hetaryl, 2-thiazolyl [43, 44]. *1b*) R^1, R^3, R^4 = C_6H_4 R^5, R^2 = H, R = H [45, 46], CH_2Ph, Ph [47], Me [46, 47]. *1c*) R^1 = R^4 = H; R^2, R^3 = alkyl; R = alkyl, aralkyl, cycloalkyl, Ar, hetaryl [48]. *2a*) R = 1-pyrrolyl [49]. *2b*) R = $C_6H_4R^1$ [50]. *3*) R = H, NHPh [51]. *4*) R = Me, Et, Pr, CH_2Ph, $CH_2CH{=}CH_2$, $(CH_2)_2OMe$, NMe_2.

5-Phosphonato-1,4-dihydropyridines *4* were synthesized by the D1 method from esters of N-substituted aminocrotonic acids [52, 53]. For 1-methyl-2-trifluoromethyl-1,4-dihydropyridines, see compound *22* in Sec. 1.1.2 [54].

The 1,4-dihydropyridines *5a-c* are not obtained under the usual conditions of method B; the reaction is carried out in the presence of an adduct of the amine with $TiCl_4$ [55-58]. 1-Ferrocenylphenyl-1,4-dihydropyridines *5d* are synthesized from substituted benzylideneanilines and acetoacetic ester [59].

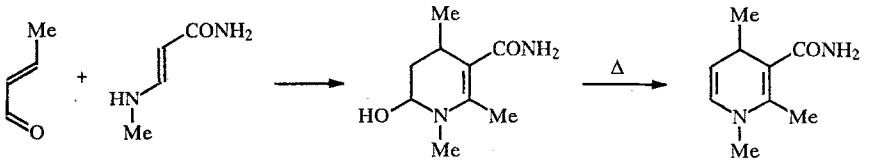


5

5a) R = CH_2Ph; *5b*) R = $(CH_2)_2CH{=}CH_2$; *5c*) R = 2-(3-thienyl)ethyl; *5d*) R = C_6H_4Fc-4 (Fc = ferrocenyl).

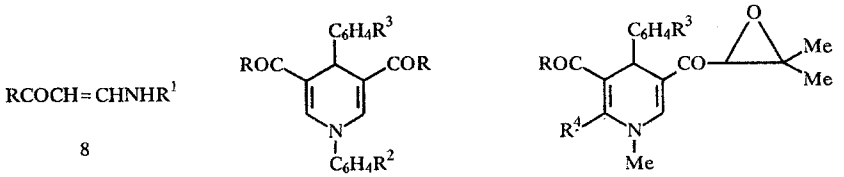
For 1-phenyl-1,4-dihydropyridine *44* [60, 61], see Sec. 1.1.4.

The amide of 1-methyl-1,4-dihydropyridine-3-carboxylic acid *7* was prepared by dehydration of the initially formed tetrahydropyridine *6* [62].



6 7

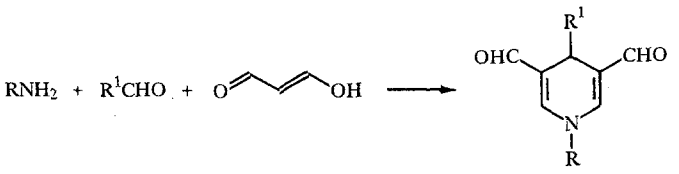
The 1,4-dihydropyridines *9a* and *10a* were obtained from the aminovinyl ketones *8a* and aldehydes; *10b* was obtained from the ketones *8b* and benzylideneacetoacetic esters.



8 9 10 [64]

8a) R^1 = $C_6H_4R^2$. *8b*) R^1 = Me. *9a*) R = Pr, Ph [63]. *9b*) R = OEt [65]. *10a*) R = 2,2-dimethyloxiranyl; R^4 = H. *10b*) R = OEt; R^4 = Me.

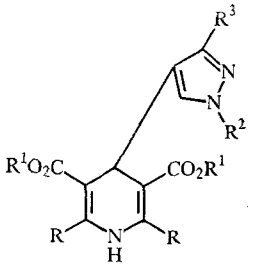
The 1-aryldihydropyridines *9b* were synthesized by method E. In contrast to the 2,6-dimethyl derivatives, in this series it is also possible to obtain dihydro derivatives *9b* in which R^2 is a strong electron-acceptor [65]. Derivatives of amino acids with aldehydes and malonic dialdehyde (as the β-dicarbonyl component) form the 1,4-dihydropyridines *11* [66, 67].



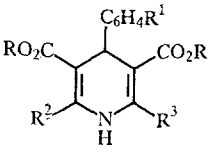
11

R = $CH_2CO_2R^2$, $CHCO_2Me$ (CH_2OH), $CHCO_2Me$ (CH_2CH_2SMe); R^1 = alkyl, $C_6H_4R^3$

1.1.2. Substituents in Positions 2 and 6. The 1,4-dihydropyridines obtained in variants of the Hantzsch synthesis are most often 2,6-dimethyl-substituted. In obtaining the 2,6-unsubstituted dihydropyridines *9b* and *12a*, esters of propiolic acid are used (variant F)



12 [30]

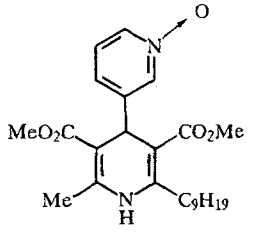


13

12a) R = H. *12b*) R = Me. *13*) R^2 R^3 = Et, Pr, Bu, CH_2Ph, cyclopropyl, cyclohexyl.

For 6-unsubstituted 4,4-disubstituted dihydropyridines *50* [68], see Sec. 1.1.4.

Of the general class of compounds containing alkyl, benzyl, or cycloalkyl groups in positions 2 and 6 in place of the methyl group, only individual compounds have been synthesized (*13* [69], *14* [70], *15* [71], *41* [72]).



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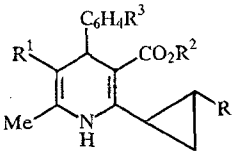

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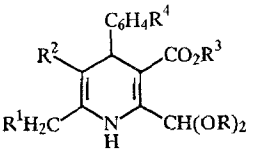
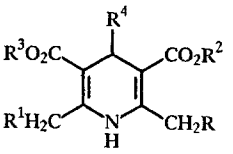


16

15) R = Ph, 2-thienyl; R^1 = CO_2R^2, CN. *16a*) R^2 = CO_2R^5; R^1 = H [73-75], 1-imidazolyl, 3-pyridyloxy [76, 77]. *16b*) R = $PO_3R_2^5$; R^1 = H [53, 78].

The 2-dialkoxymethyl-1,4-dihydropyridines *16*, prepared by method D or C, are starting materials for the introduction of a number of other substituents into position 2.

On the basis of derivatives of substituted acetoacetic acids, by method D or C, series of dihydropyridines *17-19* have been obtained with substituted 2-methyl groups.



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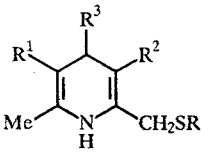
17) R^1 = H; R = Cl [29, 79-82], F [73, 83-85], CO_2Me [86], OAc [87, 88], $OCH_2CO_2R^5$ [89, 90], dioxolanylmethoxy [91], $OCH_2C{\equiv}CH$ [89, 90, 92], $O(CH_2)_nNR^5R^6$ [73, 75, 93-96], $O(CH_2)_nN_3$ [90, 94], $O(CH_2)_nN(CO)_2C_6H_4$ [73, 90, 94, 97], $O_m(CH_2)_n$Het (Het = imidazolyl [98, 99], pyridyl [29, 99]), $OCONHR^5$ [100, 101], 4-benzoylpiperidino [102]; R^1 = F; R = 1-imidazolyl [76, 77].



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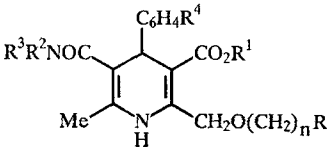

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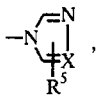
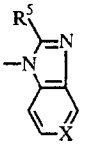
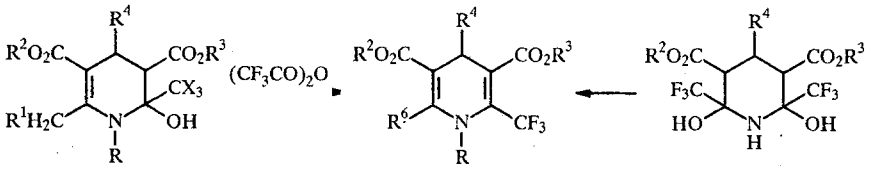
19 R=  , X=CH [105], N [106]; R=  , X=CH [107], N [108]

18 R = Ph, $R^1 = CO_2R^4$, $R^2 = PO_3R_2^5$ [103]; R = $C_6H_4R^4$, $R^1 = CO_2R^5$, CN, $R^2 = CO_2R^6$ [104]

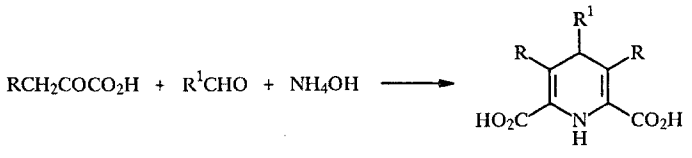
Of the derivatives of trifluoroacetoacetic acid, the 2-hydroxytetrahydropyridines *20* or 2,6-dihydroxypyridines *21* have been obtained, the dehydration of which affords the 1,4-dihydropyridines *22*.



20 22 21 [85]

20a) X = F; R = H, Me; R^2 = H; R^4 = H, Me, Et, CH_2CHMe_2 [54, 109]. *20b*) X = F; R = H; R^1 = 1-imidazolyl; $R^4 = C_6H_4R^5$ [76, 77]. *20c*) X = Cl; R^1 = H; $R^4 = CH_2CHMe_2$ [109]. *22*) $R^6 = CF_3$, CH_2R^1.

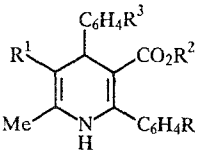
It has been shown that the methylene (or methyl) group of α-ketopropionic acids is sufficiently active to enter into the Hantzsch reaction, forming the dicarboxylic acids *23* [110].



R=H, Ph; R^1=Ph, CO_2H

For the 2,5-diphenyl-1,4-dihydropyridines *1b* and *3*, see Sec. 1.1.1 [45, 46, 51].

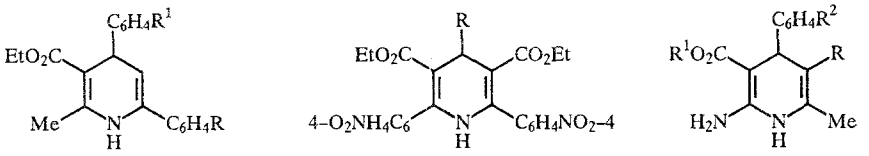
On the basis of esters of substituted benzoylacetic acids, the dihydropyridines *24a-c* have been synthesized by method C.



24

24a) $R^1 = CONR^4R^5$; R = F [111] or R = Q, where Q is azolyl or azinyl [112]. *24b*) $R^1 = CO_2R^6$; R = Q [113]. *24c*) R^1 = CN; R = H [114].

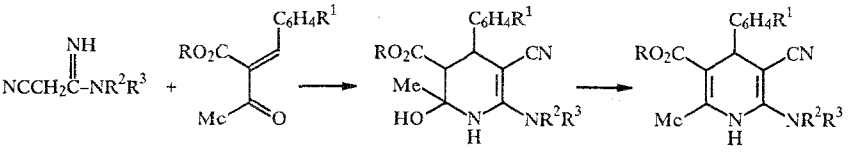
In some cases, the 2-phenyldihydropyridines *25* have been obtained (synthesis method D1), whereas other compounds of this series have been obtained only in the oxidized form [115]. The 2,6-bis(4-nitrophenyl)-1,4-dihydropyridines *26* were obtained by method A in acetic acid with ammonium acetate [116]. From an ester of amidinoacetic acid, the 2-amino-1,4-dihydropyridines *27* have been synthesized by method D.



25 26 27

27a) R = CO_2R^3 [117-122]; *27b*) R = $PO_3R_2^3$ [53, 123]; *27c*) R = OPh [124].

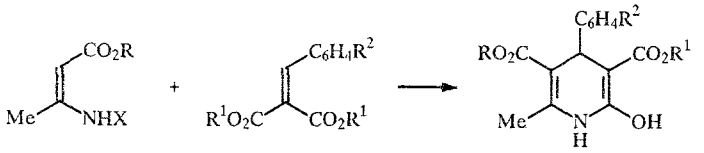
The amidines *28* with esters of benzylideneacetoacetic acids *29* form the 2-hydroxytetrahydropyridines *30*, which are readily dehydrated to 1,4-dihydropyridines *31* [125] (these are obtained at once if $R^2 = R^3 = H$ [126]).



29 30 31

$R^2 = R^3$ =H, Me, Et; $R^2 + R^3 = (CH_2)_5$, $(CH_2)_2O(CH_2)_2$

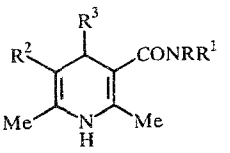
An unusual structure was ascribed to the products of the reaction of aminocrotonic acid esters *32* with benzylidenemalonates, namely that of the 2-hydroxy-1,4-dihydropyridines *33* [127, 128].



32 33

1.1.3. Substituents in Positions 3 and 5. Even though a great many esters of 1,4-dihydropyridine-3,5-dicarboxylic and -3-carboxylic acids have already been studied, new variations of the esters have been investigated in recent years, in some cases esters containing extremely complex groupings (Table 1). By far the greatest majority of these compounds contain different substituents in positions 3 and 5.

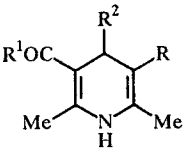
A number of amides of 1,4-dihydropyridine-3-carboxylic acid have been synthesized: *7, 19, 24a, 34.*



34

R = H and R^1 = substituted or unsubstituted alkyl, cycloalkyl, or alkenyl [134, 145, 223, 225, 273, 276]; R = H and R^1 = $C_6H_4R^4$ [141, 229, 277, 278]; NRR^1 = 1-piperazinyl [279]; R^2 = CO_2R^5 [134, 141, 145, 223, 225, 229, 272, 276-279] or R^2 = NO_2 [278, 279].

The following 1,4-dihydropyridines have been obtained: 3-acyl-5-alkoxycarbonyl- (*35a*), 3-acyl-5-cyano- (*35b*), and 3-acyl-5-phosphonato- (*35d*), as well as the 3,5-diacyl-1,4-dihydropyridines *9a, 10,* and *35c*.

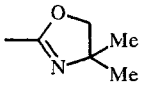


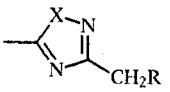
35

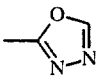
35a) R = CO_2R^3; R^1 = Me [280, 281], $(CH_2)_2CHMe_2$ [282], CH_2OMe [280], $CH_2SO_2NR^4R^5$ [166, 185]. *35b*) R = CN, R^1 = Me [114]. *35c*) R = COR^1; R^1 = Me [283, 284], Et...C_9H_{19}, CH_2OEt [285]. *35d*) R = $PO_3R_2^3$; R^1 = Me [103].

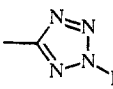
For 3,5-diformyl-1,4-dihydropyridine, see compound *11*.

Other compounds that enter into different versions of the Hantzsch synthesis are the acetonyl derivatives of oxazoline, oxadiazole, thiadiazole, and tetrazole, forming dihydropyridines with the following substituents in position 3:

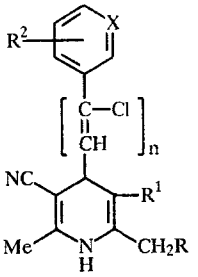
 [286],

 X=O, S [287],

 [183, 206, 254, 288],

 [254]

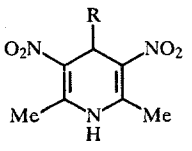
1,4-Dihydropyridines with cyano groups in β-positions have been obtained: *18, 24, 31, 36.*



36

36a) n = 0; R = H [103, 114, 129, 289], R = Cl [82]; R^1 = CN [129, 289], R^1 = COMe [114], R^1 = CO_2R^3 [114, 129], R^1 = $PO_3R_2^4$ [103]; X = CH [82, 103, 114, 289], X = N [129]. *36b*) n = 1; R = H, R^1 = CN; X = CH [290].

From nitroacetone or enamines obtained from nitroacetone, or from benzylidene derivatives, 3-nitro-1,4-dihydropyridines have been synthesized [72, 82, 87, 103, 124, 130-133, 158, 160, 177, 178, 186, 238, 268, 270, 273, 278, 279, 288]. The 3,5-dinitro derivatives *37* were obtained by method A (for *37a*, hexamethylenetetramine was used as a source of formaldehyde [291].



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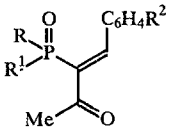

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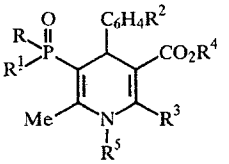


39

37a) R = H. *37b*) R = Ph. *38a, 39a*) R, R^1 = OR^6 [52, 53, 103, 123, 215, 228, 292-295]. *38b, 39b*) RR^1 = $O(CH_2)_nO$ [53, 159, 215, 227, 261, 262, 296-300]. *38c, 39c*) R = OR^6; R^1 = NR^7R^8 [214, 215]. *38d, 39d*) R, R^1 = NR^7R^8 [213, 215].

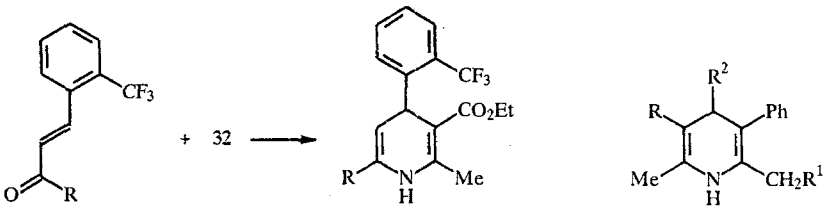
TABLE 1. Esters of 1,4-Dihydropyridine-3-carboxylic and -3,5-dicarboxylic Acids

Ester	Literature	Ester	Literature
Alkyl (other than methyl or ethyl)	70, 82, 87, 90, 128-143	(Aminomethyl)furylalkyl	231
Alkenyl	73, 132, 133, 142, 144-150	Azetidinyl	73, 120, 121
Cycloalkyl	73, 97, 118, 128, 143, 151-155	Pyrrolidinyl	232
(Cycloalkyl)alkyl	156	Pyrazolylhydroxyalkyl	233
Aralkyl	70, 133, 157-161	Isoxazolylalkyl	234
Arylalkenyl	162-164	Imidazolylaralkenyl	235
Alkoxyalkyl	35, 128, 138, 158, 160, 165-173	Benzothiazolylalkyl	27, 236
Aryloxyalkyl	167, 168, 174, 175	Phthalimidoalkyl	223, 237, 238
Hydroxyalkyl	176	Pyridylalkyl	26, 35, 128, 198, 210, 225, 229, 239-241
Acyloxyalkyl	176-179	Pyridylaralkyl	198
Alkoxycarbonylalkyl	178	Pyridylalkoxyalkyl	242
Alkylthioalkyl, arylthioalkyl	28, 173, 180, 181	Pyridylcarbonylhydroxyalkyl	179
Acylthioalkyl	182	Pyridylcarbonylaminoalkyl	196
Cyanoalkyl	73, 74, 90, 130, 183	(Pyridylmethyl)aralkenyl-hydroxyalkyl	243-248
Haloalkyl	73, 184-194	Imidazopyridylalkyl	111
Haloaralkyl	87	Piperidinoalkyl	102, 151, 217, 249-254
Nitroxyalkyl	119, 195, 196	Piperidinoalkoxyalkyl	117
Phosphonatoalkyl	197	N-(Aralkyl)piperidyl	127, 128, 255, 256
Furylalkyl, furylaralkyl	198	N-(Thienylalkyl)piperidyl	122
Thienylalkyl	128	Morpholinoalkyl	128
Oxetanyl, thietanyl	73	Piperazinylalkyl	128, 227, 254, 257-265
Tetrahydropyranyl	73	Piperazinylaralkyl	266, 267
Tetrahydropyranylhydroxyalkyl	199	(Tetrahydropyridazinyl)-aralkyl	87, 268, 269
Tetrahydropyranylhydroxyaralkyl	200	(Tetrahydropyridazinyl)-phenylaminoalkyl	270
Dioxolanylalkyl	154, 201, 202	(Phenothiazinyl)alkylamino-alkyl	271
Dioxolanylalkoxyaralkyl	203, 204	Tetrahydroisoquinolinylalkyl	272
1-Tosyl-3-triphenylmethoxypropyl	205	Acylamidoalkyl	273
Esters containing sugar groups	130, 206-208	Sulfonamidoalkyl	273
Aminoalkyl (acyclic amino groups)	82, 128-130, 144, 153 156, 161, 184, 209-229	Hydrazinoalkyl	274
Aminoaralkyl	230	Bis-1,4-dihydropyridines connected at positions 3 and 3′ through an ester bridge	275

Dihydropyridines *39* containing phosphonate or phosphonamide groups were obtained by method D from α,β-unsaturated ketones *38*.

Method D was also used to obtain 1,4-dihydropyridines with an SO_2R group (R = Alk [24, 301], Ar [24, 301, 302], NR^1R^2 [303]) or an $SOC_6H_4R^3$ group [304] in position 3.

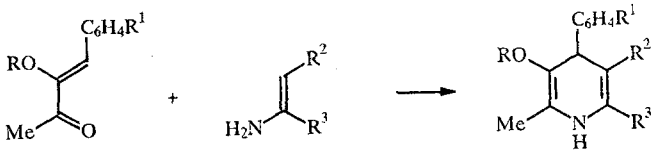
Feasibility studies have been made of the synthesis of 1,4-dihydropyridines that do not contain electron-acceptor groups in positions 3 and 5. The compounds that are not substituted in these positions are stable only when stabilizing substituents are present in the other positions (compounds *1, 3, 23, 25*). For the synthesis of the 3-unsubstituted 1,4-dihydropyridines *7* and *40*, an α-unsubstituted α,β-unsaturated ketone or aldehyde was used [305]; compound *40b* is extremely unstable.



40 41

40a) R = Me. *40b*) R = H. *41*) R = NO_2, CO_2Me; R^1 = H, Me, Ph.

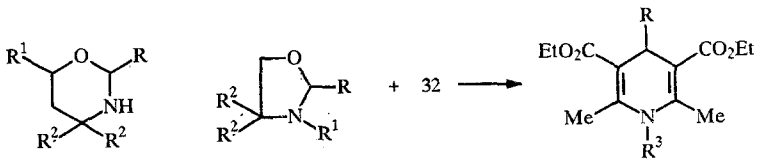
Benzyl ketones and their benzylidene derivates are capable of forming 3-phenyl-1,4-dihydropyridines *41* [72]. For 3,5-diphenyl-1,4-dihydropyridine, see *23*. Success has been reported in obtaining (although in small yields) even compounds of the type of *42* with alkoxy and aryloxy groups in position 3 [124].



42

R = Me, Ph, R^2 = NO_2, CO_2R^4, R^3 = Me, NH_2

1.1.4. Substituents in Position 4. The substituent in position 4 in a 1,4-dihydropyridine is determined by the aldehyde that is used in the Hantzsch synthesis. In method B, in place of the aldehyde it is possible to use derivatives of oxazolidine *43a* or tetrahydrooxazine *43b*, which, with acid catalysis, are capable of transferring their C_2 fragment to nucleophilic carbon atoms of enamines [60, 61].



43b 43a 44

44) R = H, Me, $C_6H_4R^4$, CH_2Ph, CH_2OH, CH_2OAc, CH_2CO_2Et; R^3 = H, Ph.

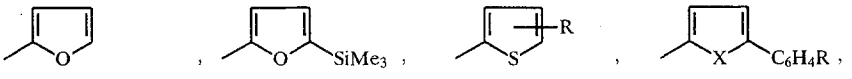
The aldehyde has also been replaced by a diacetate [306] and by an azomethine salt [290]. In place of the α,β-unsaturated ketone, in variant D1, β-haloketones have been employed [307, 308].

4-Unsubstituted 1,4-dihydropyridines have been obtained through variant E from 1,5-diketones (compound *2*) [49, 50], and through variant A by the use of formaldehyde [26, 207, 208, 283] or hexamethylenetetramine [285, 291], and also through variant B [60, 61].

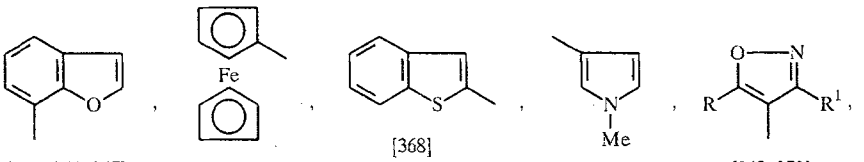
Dihydropyridines containing the following groups in position 4 have been synthesized: Alkyl [27, 28, 48, 54, 60, 62, 66, 67, 109, 116, 173, 181, 236, 277, 283, 309, 310]; cycloalkyl and cycloalkenyl [84, 125, 205, 268, 309]; aralkyl [60, 198, 309]; $RC_6H_4CH{=}CH$ [311]; $RC_6H_4CCl{=}CH$ [290]; CH_2CHO [66]; CO_2H [110]; CO_2Me [26]; CH_2OH, CH_2OAc, CH_2CO_2Et [60]; and also sugar groups [125, 205, 312].

The most common substituent in position 4 is a substituted or unsubstituted phenyl group [24, 26, 29, 48, 52, 53, 55-61, 63-67, 69, 71-77, 79-83, 85-87, 89-100, 102-108, 110-125, 127, 128, 131, 132, 134-170, 173-180, 182, 183, 185-197, 199-206, 209, 212-223, 225-235, 237, 239, 242-276, 278-282, 284, 286-289, 291, 292, 294-307, 311-356]; more rarely, the substituent may be a phenyl group substituted by heterocycles (imidazolyl [315], furyl or thienyl [329, 331]), or sugar groups [334]. 4,4'-Phenylenebis-1,4-dihydropyridines have also been synthesized [311, 312].

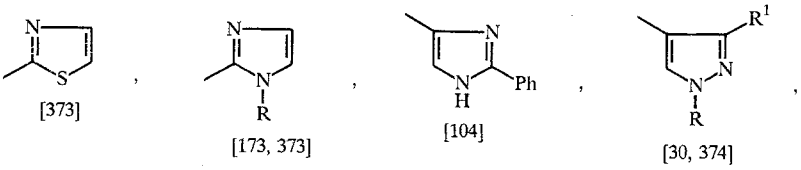
More and more attention is being given to 4-hetaryl substituents:



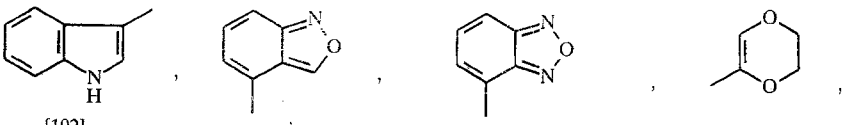
[59, 79, 102, 104, 357, 358] [359] [73, 79, 82, 93, 360] (X=O, S) [361-363]



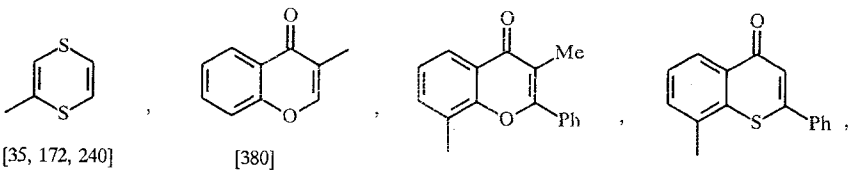
[211, 364-367] [59] [368] [73] [369-372]



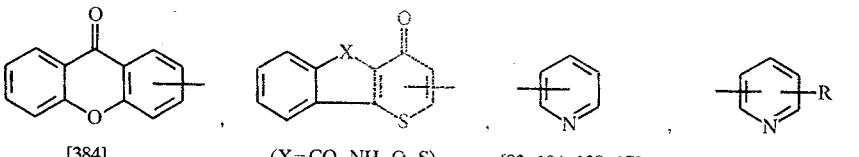
[373] [173, 373] [104] [30, 374]



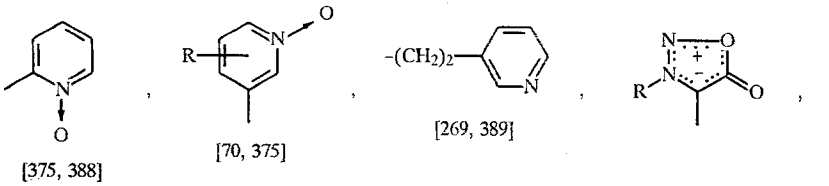
[102] [375, 376] [77, 88, 99, 120, 154, 224, 268, 269, 279, 308, 377-379] [35, 171, 240, 241]



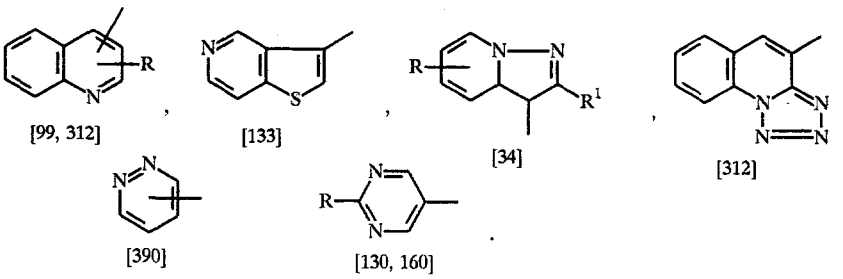
[35, 172, 240] [380] [381] [268, 269, 279, 382, 383]



[384] (X=CO, NH, O, S) [385] [82, 104, 129, 173, 198, 268, 269, 284] [184, 210, 230, 266, 293, 386, 387]



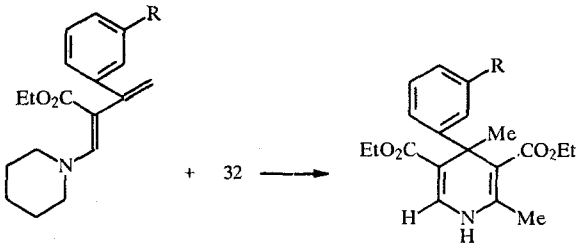
[375, 388] [70, 375] [269, 389] [375]



[99, 312] [133] [34] [312] [390] [130, 160]

For the series of 4,4-disubstituted dihydropyridines *1* and *3*, see above.

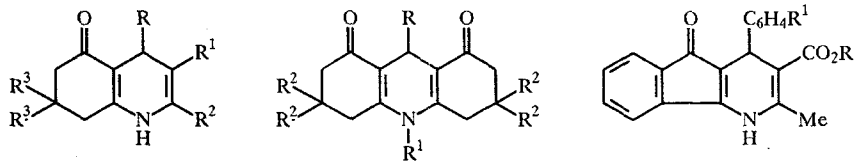
A new modification of the reaction has made it possible to obtain for the first time the 4,4-disubstituted 3,5-dialkoxycarbonyl-1,4-dihydropyridines *45* by means of cyclocondensation [68].



45

1.2. Polycyclic 1,4-Dihydropyridines

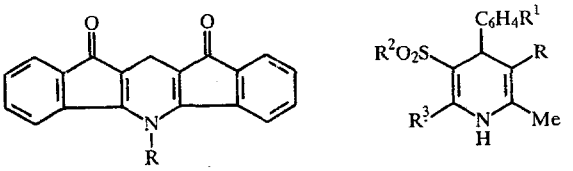
From cyclohexanedione, the hexahydroquinolines *46* and decahydroacridines *47* have been obtained. For compounds of the type of *47d*, urea and phenyl isocyanate, respectively, have been used as the nitrogen-containing component.



46 47 48

46a) $R^1 = CO_2R^4$, R = $C_6H_4R^5$ [104, 314, 391-393], $CR^6 = CHC_6H_4R^5$ [394], (5-nitrophenyl)thienyl-2 [363], furyl, naphthyl, pyridyl [391-393], imidazolyl, thiazolyl [373]; R_2 = Me [363, 373, 391-394], CH_2SPh [104], 1-imidazolylalkoxymethyl [314]. *46b*) R^1 = H; R, $R^2 = C_6H_4R^5$ [395]. *47a*) R = imidazolyl, thiazolyl; R^1 = H [373]. *47b*) R = (5-nitrophenyl)furyl-2; R^1 = H [363]. *47c*) R = H, Me; R^1 = Ph, 2-amino-1,2-dicyanoethenyl [396]. *47d*) R = H; R^1 = H, Ph [397, 398].

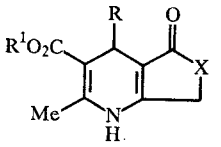
On the basis of indandione-1,3, the dihydropyridines *48* have been synthesized [399, 400], and also *49* [401, 402]. It is remarkable that the compounds *49* are formed from indandione, primary amines, and formaldehyde, even under the conditions of the Mannich reaction [401].



49 50

50a) $R^2 + R^3$ = o-phenylene; R = CN, COMe, CO_2R^4, COSEt, CSOEt, CS_2Et [400, 403, 404]. *50b*) $R^2 + R^3 = (CH_2)_n$, n = 2...6; R = CO_2R^4 [405, 406].

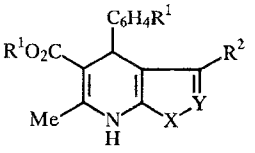
The dihydropyridines *50*, condensed with a cyclic sulfone, represent a new group of compounds. The tetrahydrofuropyridines *51a* are sometimes obtained from derivatives of tetronic acid [90], more often by method C using esters of 4-chloro- or 4-acetoxyacetoacetic acid, which are capable of closing the lactone ring; their thio analogs *51b* have also been obtained



51

51a) X = O; R = $C_6H_4R^2$ [90, 132, 325, 407], thienyl [408], thiochromenyl [383]. *51b*) X = S; R = $C_6H_4R^2$ [14].

The dihydropyridines *52-54* have been obtained by method D or C using heterocyclic amines in plane of the enamine; the dihydropyrazolopyridine *55* has been obtained from a 1,5-diketone by method E.



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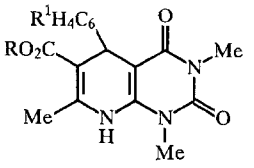
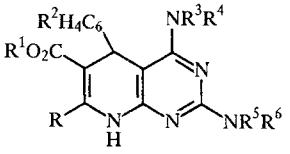
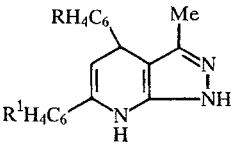


53 [414]



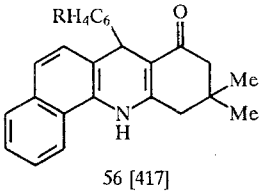
54 [126, 415]



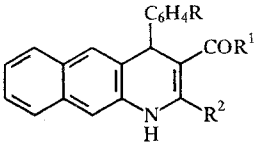
55 [416]

52a) X = NR^3; Y = N [338, 409]. *52b*) X = O; Y = N [410]. *52c*) X = S; Y = N [411, 412]. *52d*) X = S; Y = CR^4 [413].

It has been shown that 1- and 2-naphthylamines react with dicarbonyl compounds and aldehydes in a manner similar to that of enamines (although the reaction mechanism may be more complex), to form the heterocycles *56* and *57* with the 1,4-dihydropyridine structure rather than the 1, 2 structure, as had been assumed previously.



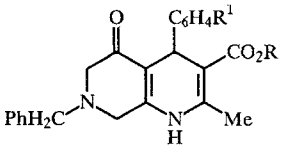
56 [417]



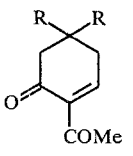
57

57) $R^1 + R^2 = CH_2CMe_2CH_2$ [418]; $R^1 + R^2$ = o-phenylenoxy [419].

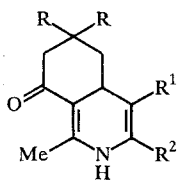
By using a derivative of dioxopiperine as the β-dicarbonyl component, the hydrogenated 1,7-naphthyridines *58* are obtained [420-422].



58



59

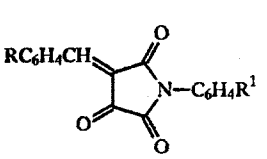


60

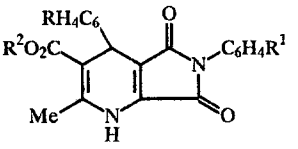
60a) R^1 = CN, COMe, CO_2Et; R^2 = Me. *60b*) $R^1 + R^2 = COCH_2CR_2^3CH_2$, R^3 = H, Me.

A new modification of the Hantzsch synthesis is the reaction of 2-acetylcyclohexenones *59* with enaminocarbonyl compounds (or enaminonitriles), leading to derivatives of isoquinoline *60a* or phenanthridine *60b* [423].

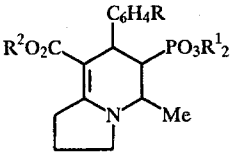
The α,β-unsaturated ketone *61* reacts with enamines to form the dihydropyridine *62* [424]. From an ester of pyrrolidinylidene-acetic acid, compound *63* is obtained [425].



61



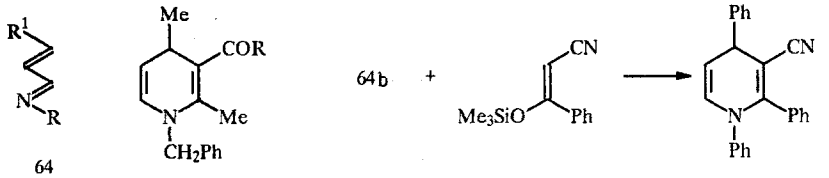
62



63

1.3. Distant Modifications of Hantzsch Synthesis

Certain cyclocondensations are similar to individual variations of the Hantzsch synthesis, and there may be grounds for considering them as further modifications of this reaction.



64

65

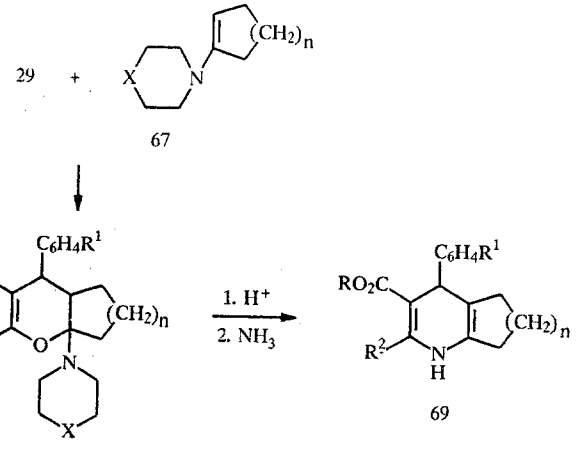
64b

66

64a) R = CH_2Ph; R^1 = Me. *64b*) R = R^1 = Ph.

The enimine *64a* is less active than α,β-unsaturated ketones; after protonation, however, it is capable of reacting with β-dicarbonyl compounds to form the dihydropyridine *65* [426]. The enimine *64b* reacts with β-siloxacinnamonitrile; as a result of desilylation of the primary adduct, the nitrile *66* is obtained [427].

α,β-Unsaturated ketones with the N,N-disubstituted enamines *67* form the pyrans *68*, which can be converted to the 1,4-dihydropyridines *69* [428]

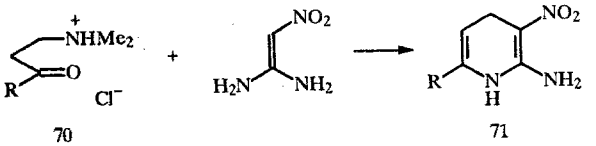


67

68

69

Enaminonitro compounds react with the β-aminoketones *70* to form the 3-nitro derivatives *71* [429].



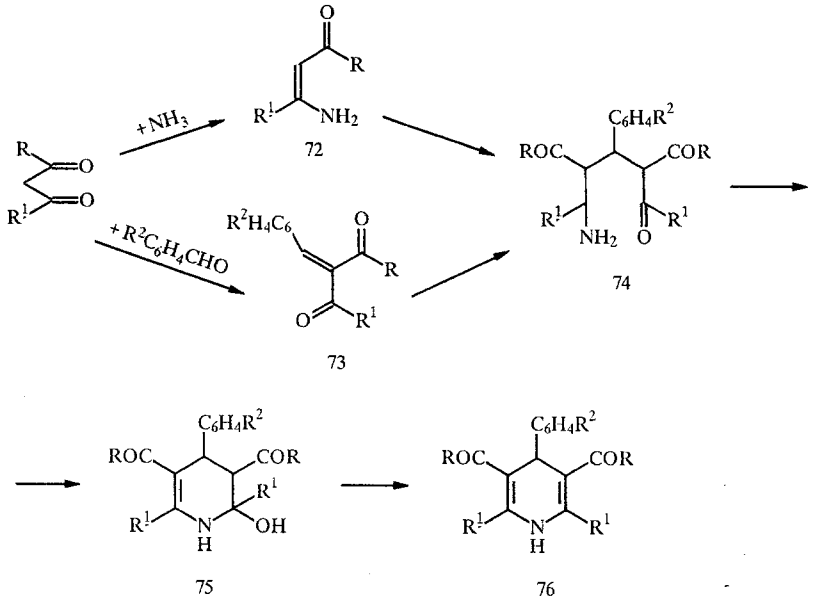
70

71

R = $C_6H_4R^1$, 2-thienyl.

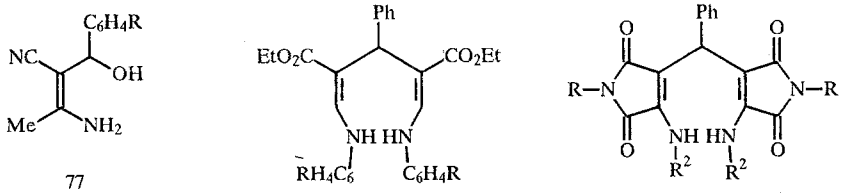
1.4. Mechanism and Intermediate Products of Reaction

The mechanism of the Hantzsch synthesis that has been assumed on the basis of isolation of certain intermediate products [430] has now been confirmed by experiment [431, 432]. NMR (^{13}C and ^{15}N) has been used to monitor the reaction of benzaldehyde with β-dicarbonyl compounds and aqueous ammonia. Of the intermediate products that have been suggested, only the enamine *72* and the chalcone *73* were detected. This eliminates the possibility of other paths of the reaction (through a 1,5-diketone, dienamine, etc.). The absence of any determinable quantities of compounds *74* and *75* shows that the slowest stage is the Michael addition reaction.



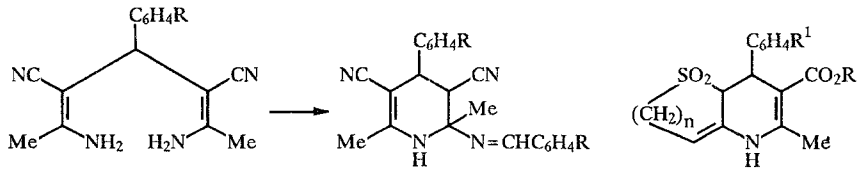
R = OMe, R^1 = Me; R = R^1 = Me; R = Me, R^1 = Ph

Nonetheless, in certain studies, products of Michael addition *74* have been segregated [82, 354, 424]. Also isolated are the 2-hydroxytetrahydropyridines *75* [54, 62, 76, 77, 109, 114, 125, 405, 406, 423, 424, 433], which are usually dehydrated very readily to form 1,4-dihydropyridines; however, when the 2-CF_3 group is present, side reactions also take place (see Sec. 1.5 [54]).



77 78 [65] 79 [424]

At the same time, from other initial components, intermediate compounds with a different structure have been obtained — products of the addition of benzaldehydes to aminocrotonitrile (*77* [434]), bis-enamines *78, 79, 80a*, and the 2-benzylideneamino-tetrahydropyridine *80b*, thus indicating the possibility of a different mechanism for the formation of 1,4-dihydropyridines.

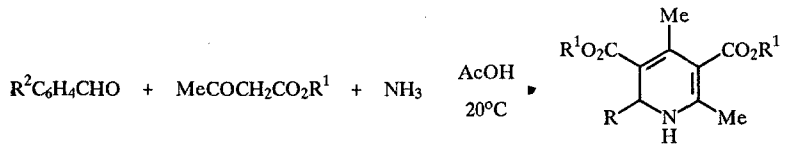


80a [289] 80 [289] 81 n=3,4,5

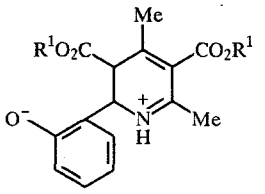
β-Ketosulfones with a seven- to nine-membered ring form compounds *81*, which can isomerize to 1,4-dihydropyridines [405].

1.5. Other Directions and Side Products of Reaction

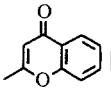
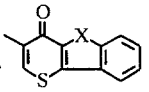
When the reaction is carried out by method A in acetic acid at room temperature, the 1,2-dihydropyridine *82a* is formed, not the 1,4-isomer [435-437]; in the case of 2-hydroxybenzaldehyde, the zwitterion *83* has also been recovered [435].



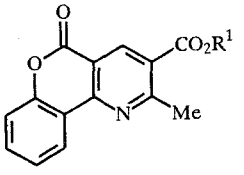
82



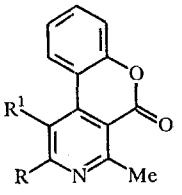
83

82a) R = $C_6H_4R^2$. *82b*) R=  [380],  X = CO, NH, O, S [385].

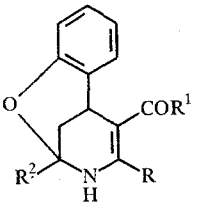
2-Hydroxybenzaldehyde as a bifunctional compound behaves very unusually under the conditions of the Hantzsch synthesis; on its basis, compounds *84-86* are also obtained.



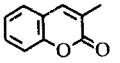
84 [435]



85



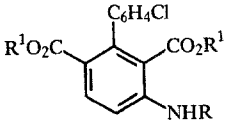
86

85, 86 Q= 

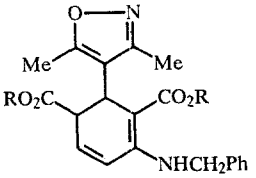
85a) R = Q; R^1 = H [438]. *85b*) R = Me; R^1 = CN [439]. *86a*) R^2 = Me; R = Me; R^1 = Me, OMe; R + R^1 = $CH_2CMe_2CH_2$ [439]. *86b*) R = Me; R^1 = OH; R^2 = Q [438].

The 1,2-dihydropyridines *82b* were formed in reactions of 3-formylchromone or derivatives of 3-formylthiopyrone with an aminocrotonate in acetic acid.

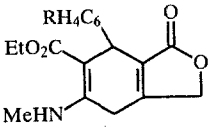
From alkyl- and aralkylaminocrotonates, instead of 1,4-dihydropyridines, the carbocyclic compounds *87-89* are obtained.



87 [343]



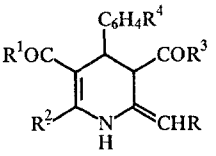
88 [371]



89 [440]

87) R = Me, CHPh.

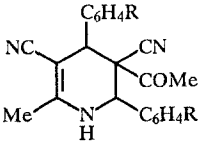
Formation of the tetrahydropyridines *90* with an exocyclic C=C bond has been noted; these are isomeric with 1,4-dihydropyridines.



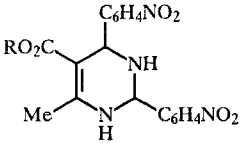
90

R = CH_2CHMe_2 [282], CO_2Et [441], $COC_6H_4R^5$ [442], isonicotinoyl [443], Cl [81], SPh [104].

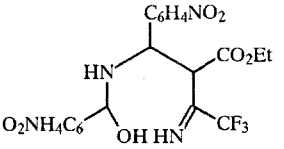
The tetrahydropyridines *91* have been isolated [114]. Formation of the tetrahydropyrimidines *92* has been observed not only under the usual conditions of the Hantzsch synthesis [444], but also under conditions such that 1,2-dihydropyridines are the main products [436]. The acyclic compounds *93* is apparently an intermediate in the formation of the tetrahydropyrimidines [445].



91

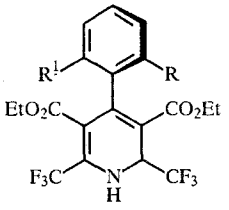


92



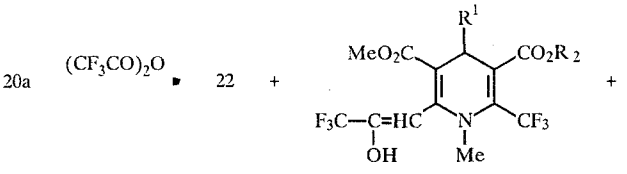
93

In the dehydration of 2,6-dihydroxypiperidines *21* by phosphoryl chloride, in addition to the 1,4-dihydropyridine products, the 1,2-dihydro isomers *94* were obtained in the form of a pair of atropoisomers [445]; and from the tetrahydropyridine *20a*, in addition to the expected 1,4-dihydropyridine *22*, compounds *95-97* were formed [54].

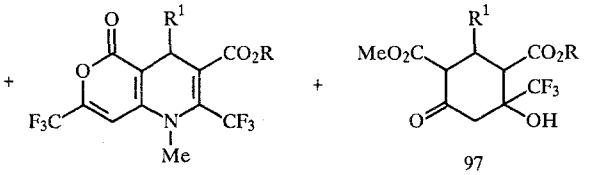


94

94a) R = H; R^1 = NO_2. *94b*) R = NO_2; R^1 = H.

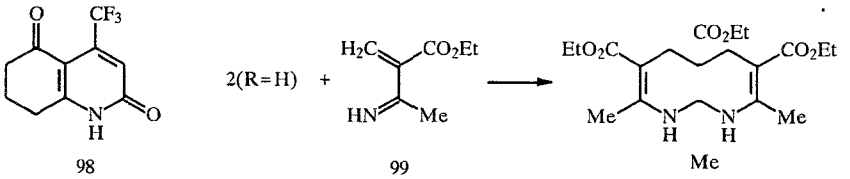


95



96 97

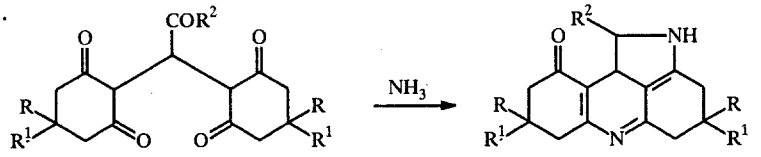
An ester of trifluoroacetoacetic acid was found to react with a cyclohexanedione and ammonia to form the quinolinone *98*; an aldehyde did not react under these conditions [373].



98 99 100

From acetoacetic ester and hexamethylenetetramine at 100°C in acetic acid, instead of the 1,4-dihydropyridine 2 (R = H), its oxidized form was obtained, i.e., pyridine, and the dimer *100* [446]; the formation of the dimer is explained by addition of the heterodiene *99* to the dienophile *2*.

Together with the dihydrothienopyridine *52d*, products were obtained from addition of the ylidene derivative at position 5 of the thiophene ring [413].



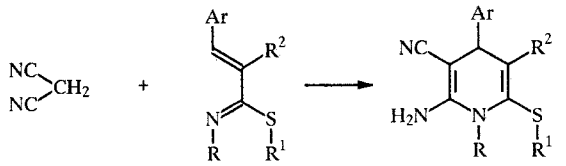
101 102

From the 1,5-diketone *101*, derivatives of the pyrrolo [4,3,2-m,n] acridinone *102* were formed [447, 448].

2. OTHER CYCLOCONDENSATIONS

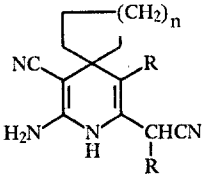
2.1. Cyclization of Nitriles and Amines

From malonodinitrile or its ylidene derivatives in cyclocondensation reactions, the dihydropyridines *103-105* have been obtained.



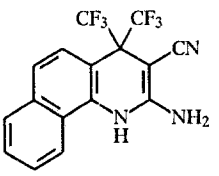
103

103) Ar = $C_6H_4R^3$ [449, 450], furyl, thienyl [451, 452]; R^2 = CN [449, 451, 452], $CONH_2$ [450]; R + R^1 = —N—C-NHCOPh [452], R + R^1 = o-phenylene [449-451].

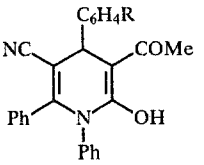


104 [453]

R = CO_2Et, CN



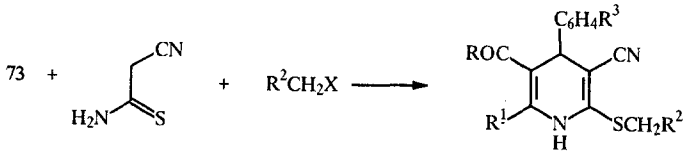
105 [454, 455]



106

The 2-hydroxy-1,4-dihydropyridine *106* is formed from the nitrile of α-benzylcinnamic acid and the aniline of acetoacetic acid [456].

Cyanothioacetamide with α,β-unsaturated ketones (or its arylidene derivatives with β-dicarbonyl compounds), with subsequent alkylation, give the nitriles *107*.

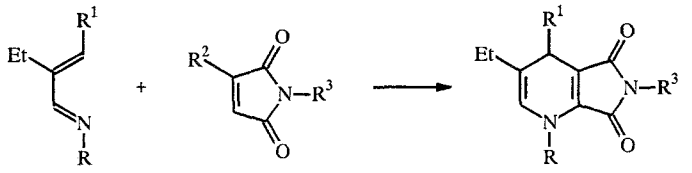


107

R^1 = Me [457, 458], Ph [459, 460]; R + R^1 = $CH_2CMe_2CH_2$ [461], C_6H_4 [433]

2.2. [4 + 2]-Cycloaddition

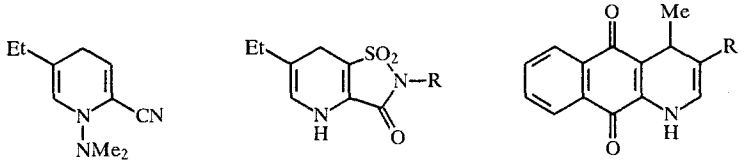
α,β-Unsubstituted hydrazones and oximes *108* add imides of chloromaleic acid *109a*.



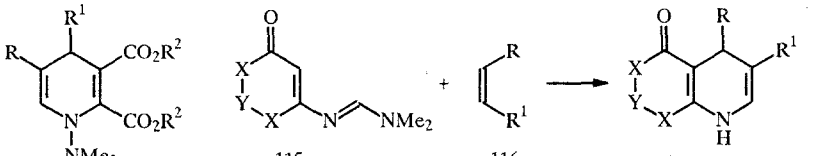
108 109 110

108a) R = NMe_2. *108b*) R = OH. *109a*) R^2 = Cl. *109b*) R^2 = H. *110a*) R = NMe_2 [462, 463]. *110b*) R = OH [464]. *110c*) R = H [465].

From the hydrazone *108a* and the imide *109b*, a tetrahydro derivative is obtained which, upon deamination, is converted to compound *110c*. The hydrazone *109a* also adds the following: nitriles of β-haloacrylic acid (with the formation of the dihydropyridine *111*) [466]; isothiazolone-1,1-dioxide (depending on the radical R, either the dihydropyridines *112* or pyridines may be obtained) [467]; derivatives of naphthoquinone (with the formation of the azaanthraquinone *113*) [468]; and esters of acetylenedicarboxylic acid (compound *114*) [469].



111 112 113



114 115 116 117

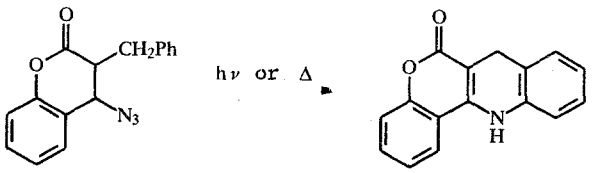
115, 117) X = CH_2, Y = CH_2, CMe_2, CHPh [470]; X = NMe, Y = CO [471]. *116, 117*) R = H, CO_2R^3; R^1 = CO_2R^3, CN.

The heterodienes *115* add the dienophiles *116* to form the dihydropyridines *117*.

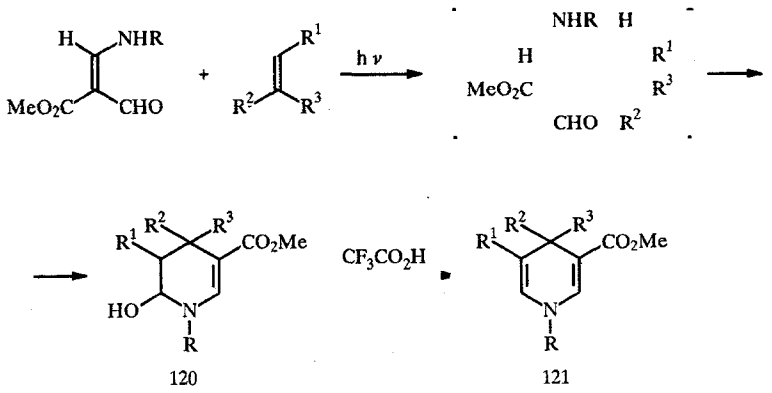
2.3. Photochemical Reactions

The azide *118* is cyclized photochemically or thermally to form the 1,4-dihydropyridines *119* [472].

Photochemical cycloaddition of alkenes to enaminocarbaldehydes leads to the tetrahydropyridines *120*, which are readily dehydrated to the 1,4-dihydropyridines *121* [473].



118 119



120 121

R = alkyl, aralkyl; R^1 = H, alkyl; R^2 = Me, CO_2Me, CN; R^3 = Me, CO_2Me.

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