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CARBON TRANSFER REACTIONS WITH HETEROCYCLES - V[1]. A FACILE SYNTHESIS OF NIFEDIPINE AND ANALOGUES

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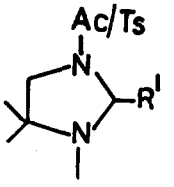
Abstract - Oxazolidines and tetrahydro-(2H)-1,3-oxazines transfer their C(2) units at the carbonyl group oxidation level to alkyl-β-amino/anilinocrotonates to form 1,4-dihydropyridines elaborated at C-4.

Synthetic activity in 1,4-dihydropyridines[2] and their analogs[3] has been stimulated by medicinal potential of nifedipine 8h and its analogs[4] as well as their hydride/enolate ion transfer and other reactions[5]. Their syntheses involve condensations of aldehydes, with amines/ammonia and alkylacetoacetates[6] or with alkyl-β-aminocrotonates[7]. In a unique approach chiral nifedipine analogs are formed from chiral pyridyl dihydrooxazoles and aryl lithium reagents[8]. Imidazolidines 1[9], tetrahydro-(2H)-1,3-oxazines 2[1] and oxazolidines 3[10] transfer their C(2) units at carbonyl level to nucleophiles in a synthetically useful manner. These reagents, like aldehydes,[11] react with indole to form bisindolylmethane derivatives 4[1]. 6-Amino/alkylamino-1,3-dimethyluracil with 1 also gives analogous products 5[12]. We envisaged that in the acid catalysed reactions of enamines 7 and perhydro-1,3-heterocycles 2,3, initially formed bisenaminylmethane derivatives 14 (see scheme) could undergo cycloelimination to give 1,4-dihydropyridine derivatives 8[13]. This approach could provide a versatile means of elaboration of 8 at C-4, depending upon substitution at C-2 of these model reagents 2,3[14].

Ethyl-β-aminocrotonate 7a, a relatively stable enamine[15] reacts with (i) 2-phenyl-3,4,4-trimethyloxazolidine 3a, (ii) 2-phenyl-4,4-dimethyloxazolidine 3b, (iii) 2-phenyl-4,4,6-trimethyltetrahydro-(2H)-1,3-oxazine 2b and (iv) 2-phenyltetrahydro-(2H)-1,3-oxazine 2a in anhydrous acetonitrile : acetic acid (10:1) to give diethyl-2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate 8a in yields (Table)[16] comparable with the reported method[6]. As projected, these reactions represent an overall transfer of $-\underset{|}{C}(H)-C_6H_5$ fragment between the nucleophilic carbons of two molecules of enamine and elimination of ammonia. Similarly, 7a reacts with (i) 2-methyl-3-phenyloxazolidine 3d and 2,4,4,6-tetramethyltetrahydro-(2H)-1,3-oxazine 2d, (ii) 3-phenyloxazolidine 3c and tetrahydro-(2H)-1,3-oxazine 2c and (iii) 2-benzyl-4,4,6-trimethyltetrahydro-



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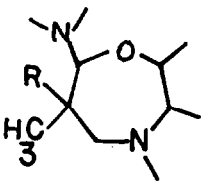

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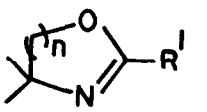

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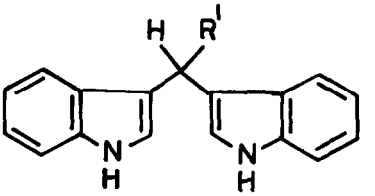

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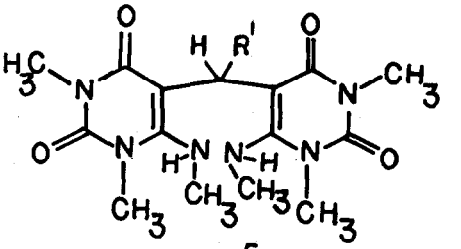

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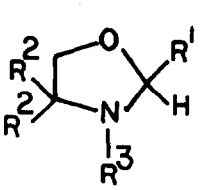

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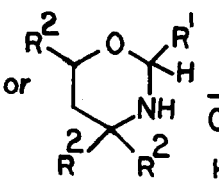

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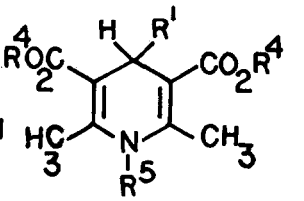
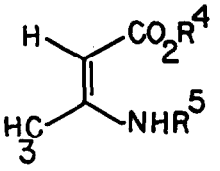


8

	R^1	R^2	R^3
a	C_6H_5	CH_3	CH_3
b	C_6H_5	CH_3	H
c	H	H	C_6H_5
d	CH_3	H	C_6H_5
e	C_6H_4-(o-NO_2)	CH_3	H



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	R^4	R^5
a	C_2H_5	H
b	C_2H_5	C_6H_5
c	CH_3	H

	R^1	R^2
a	C_6H_5	H
b	C_6H_5	CH_3
c	H	H
d	CH_3	CH_3
e	$CH_2C_6H_5$	CH_3
f	C_6H_4(o-NO_2)	H
g	C_6H_4(m-NO_2)	H
h	C_6H_4(p-NO_2)	H
i	CH_2OH	CH_3
j	CH_2OAc	CH_3
k	$CH_2COOC_2H_5$	CH_3

	R^1	R^4	R^5
a	C_6H_5	C_2H_5	H
b	H	C_2H_5	H
c	CH_3	C_2H_5	H
d	$CH_2C_6H_5$	C_2H_5	H
e	C_6H_5	C_2H_5	C_6H_5
f	H	C_2H_5	C_6H_5
g	CH_3	C_2H_5	C_6H_5
h	C_6H_4(o-NO_2)	CH_3	H
i	C_6H_4(m-NO_2)	CH_3	H
j	C_6H_4(p-NO_2)	CH_3	H
k	CH_2OH	C_2H_5	H
l	CH_2OAc	C_2H_5	H
m	$CH_2COOC_2H_5$	C_2H_5	H
n	$CH_2COOC_2H_5$	CH_3	H

(2H)-1,3-oxazine 2e, to furnish (i) 8c, (ii) 8b and (iii) 8d respectively (Table). In contrast to the slow and cumbersome reactions of benzaldehyde/acetaldehyde with ethyl-β-anilinocrotonate 7b[7], it has been found that 3a, 3b, 3c, 3d and 2a, 2c react with 7b to furnish corresponding 8e, 8f, 8g in much shorter time, better yields and without the formation of self condensation products of aliphatic aldehydes.

Table Reactions of 2/3 with 7

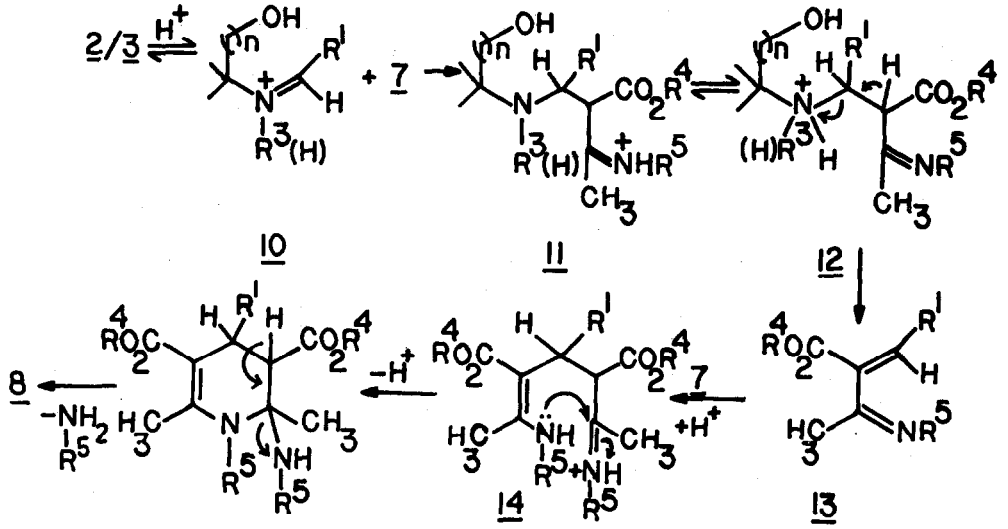
Reagents			Product[17]	Reaction time(h) using		Yield(%) using	
2	3	7	8	2	3	2	3
2a/2b	3a/3b	7a	8a	4[a]/5[a]	6[a]/4.5[a]	69/72	73/70
2c	3c	7a	8b	0.1[a]	3[a]	90	80
2d	3d	7a	8c	10[b]	13[b]	60	56
2e	-	7a	8d	36[a]	-	70-73	-
2a	3a/3b	7b	8e	0.25[a]	6[a]/8[a]	60	40/35
2c	3c	7b	8f	0.7[a]	2.5[a]	80	70
-	3d	7b	8g	-	12[a]	-	56
2f	3e	7c	8h	12[b]	10[b]	75	70
2g	-	7c	8i	6-7[b]	-	70	-
2h	-	7c	8j	0.5[b]	-	63	-
2i	-	7a	8k	15-16[a]	-	45-50	-
2j	-	7a	8l	15-20[a]	-	56	-
2k	-	7a	8m	11[b]	-	65	-
2k	-	7c	8n	12[b]	-	55	-

Reactions run in anhydrous acetonitrile in the presence of : a- AcOH (r.t.), b - TFA (r.t.).

2-(o-Nitro)phenyl-4,4-dimethyloxazolidine 3e[18] and 2-(o-nitro)phenyl-tetrahydro-(2H)-1,3-oxazine 2f[18] react with methyl-β-aminocrotonate in anhydrous acetonitrile : trifluoroacetic acid (10:1) to furnish nifedipine 8h in yields comparable to reported methods[19]. Likewise, 2-(m/p-nitro)phenyltetrahydro-(2H)-1,3-oxazines 2g/2h[18] react with methyl-β-aminocrotonate 7c to furnish 8i and 8j respectively. Since a myriad of transformations[20] are possible in C-2 aryl moiety of 1,3-oxazines/oxazolines, this approach could be used to procure a variety of analogs of nifedipine.

For procuring diethyl-2,6-dimethyl-4-hydroxymethyl-1,4-dihydropyridine-3,5-dicarboxylate 8k and dimethyl-2,6-dimethyl-4-acetoxymethyl-1,4-dihydropyridine-3,5-dicarboxylate, multistep, low yield synthetic approaches are reported[21,22]. Using 2-hydroxymethyl-4,4,6-trimethyltetrahydro-(2H)-1,3-oxazine 2i, 2-acetoxymethyl-4,4,6-trimethyltetrahydro-(2H)-1,3-oxazine 2j and 2-carbethoxymethyl-4,4,6-trimethyltetrahydro-(2H)-1,3-oxazine 2k, $-\overset{|}{C}H-CH_2OH$, $-\overset{|}{C}H-CH_2OAc$ and $-\overset{|}{C}H-CH_2COOC_2H_5$ have been transferred to ethyl and/or methyl-β-aminocrotonates and diethyl-2,6-dimethyl-4-hydroxymethyl/acetoxymethyl-1,4-dihydropyridine-3,5-dicarboxylates 8k/8l and diethyl/dimethyl-2,6-dimethyl-4-carbethoxymethyl-1,4-dihydropyridine-3,5-dicarboxylates 8m, m/z 339(M^+) and 8n, m/z 311(M^+) have been obtained (Table).

Like oxazolidines, tetrahydro-(2H)-1,3-oxazines exhibit ring-chain tautomerism[23] and in the presence of an acid, would generate, iminium cations 10,



(SCHEME)

which could react at nucleophilic α-carbon of alkyl-β-aminocrotonate to form an adduct iminium cation 11⇌12, and subsequently alkylidene imine 13. Further reaction with second molecule of nucleophile followed by cycloelimination could finally yield 8 (Scheme).

These few reactions demonstrate the utility of tetrahydro-(2H)-1,3-oxazine derivatives in the incorporation of functionalized groups at C-4 position of 1,4-dihydropyridine derivatives. Since many structural changes can be made at C-2 of 1,3-oxazines by using different acids/nitriles etc. for their formation, or by reactions at C-2 alkyl/alkenyl/aryl groups, syntheses of many more analogs of 1,4-dihydropyridines can be envisaged.

EXPERIMENTAL

General experimental details are given in reference 1.

Oxazolidines and oxazines - 2-Phenyl-3,4,4-trimethyloxazolidine 3a[24], 2-phenyl-4,4-dimethyloxazolidine 3b[25], 3-phenyloxazolidine 3c[26], 2-methyl-3-phenyloxazolidine 3d[27], 2-phenyl-tetrahydro-(2H)-1,3-oxazine 2a[28], 2-phenyl-4,4,6-trimethyltetrahydro-(2H)-1,3-oxazine 2b[14], tetrahydro-(2H)-1,3-oxazine 2c[29], 2,4,4,6-tetramethyltetrahydro-(2H)-1,3-oxazine 2d[14], 2-benzyl-4,4,6-trimethyltetrahydro-(2H)-1,3-oxazine 2e[14], 2-hydroxymethyl-4,4,6-trimethyltetrahydro-(2H)-1,3-oxazine 2i[1], 2-acetoxymethyl-4,4,6-trimethyltetrahydro-(2H)-1,3-oxazine 2j[1] and 2-carbethoxymethyl-4,4,6-trimethyltetrahydro-(2H)-1,3-oxazine[14] 2k[14] were obtained by reported methods. For procuring 2-(o-nitro)phenyl-4,4-dimethyloxazolidine 3e and 2-(o-/m-/p-nitro)phenyl tetrahydro-(2H)-1,3-oxazines 2f-h, appropriate nitrobenzaldehyde has been condensed with 2-amino-2-methyl-1-propanol/ γ-hydroxypropylamine by method of Agami[30] using anhydrous methanol as solvent. 3e : yield : 88%; IR(Neat) : 1700, 1543, 1330 cm^{-1}; ^1H NMR ($CDCl_3$)[31]: δ1.15, 1.3(6H, 2xCH_3, singlets), 2.35(1H, NH, D_2O exchangeable, br), 3.5, 3.57 (2H, CH_2, singlets), 6.0, 8.6 (1H, C(2)H and =C-H respectively, singlets), 7.15-8.0(4H, ArH, m); Mass : $M^{+\cdot}$ m/z 222.

2f : yield : 93%; IR(Neat): 1650, 1550, 1370 cm^{-1}; ^1H NMR ($CDCl_3$)[31]; δ 2.19

(2H, C(5)H, quintet, J = 6Hz), 3.40(1H, NH, D_2O exchangeable, br), 3.65(2H, C(4)H, t, J = 6Hz), 3.70(2H, C(6)H, t, J = 6Hz), 5.5 and 8.5(1H, C(2)H and =C-H, singlets), 7.0-8.0(4H, ArH, m); Mass: $M^{+\cdot}$ m/z 208.

2g : yield : 83%; IR(Neat): 1550, 1380 cm^{-1}; ^1H NMR($CDCl_3$): δ 1.95(2H, C(5)H, quintet, J = 6Hz), 3.2(1H, NH, D_2O exchangeable, br), 3.1-4.0(4H, C(4)H and C(6)H, m), 5.1(1H, C(2)H, s), 7.0-8.5(4H, ArH, m); Mass : $M^{+\cdot}$ m/z 208.

2h : yield : 60%; IR(Neat); 1570, 1360 cm^{-1}; ^1H NMR($CDCl_3$) : δ 1.97(2H, C(5)H, quintet, J = 6Hz), 2.8(1H, NH, D_2O exchangeable, br), 3.8(4H, C(4)H and C(6)H, m), 5.2(1H, C(2)H, br), 7.3-8.4(4H, ArH, m); Mass: $M^{+\cdot}$ m/z 208.

Reactions of oxazolidines 3 and tetrahydro-(2H)-1,3-oxazines 2 with alkyl β-aminocrotonates 7 : General Procedure :

A solution of alkyl-β-aminocrotonate (0.02 mole) and 3/2 (0.01 mole) in anhydrous acetonitrile (30-40 ml) containing an acid (10:1) (Table) was stirred till the reaction was completed (tlc). The reaction mixture was basified with cold aqueous sodium carbonate solution and extracted with chloroform (3x50 ml). Combined chloroform extract was washed with cold water (2x50 ml) and dried (anhydrous sodium sulphate). Solvent was removed and the residue was chromatographed over silica gel G(60-120 mesh) using hexane, benzene, chloroform, ethyl acetate and their mixtures as eluents.

Using the above procedure, following products have been obtained.

Diethyl 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate(8a): m.p. 156°C (Lit. 157°)[6]; λ_{max} (CH_3OH): 355, 235 nm; IR(KBr) : 1680 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.15(6H, 2xCH_3, t, J = 6Hz), 2.15(6H, 2xCH_3, s), 3.95(4H, 2xCH_2, q, J = 6Hz), 4.85(1H, CH, s), 5.70(1H, NH, D_2O exchangeable, br), 6.90-7.30 (5H, ArH, m).

Diethyl 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (8b) : m.p. 182-83°C (Lit. 184°)[6]; λ_{max}(CH_3OH) : 370, 230 nm; IR(KBr): 1670 cm^{-1}; ^1H NMR($CDCl_3$): δ1.2(6H,2xCH_3, t, J = 7Hz), 2.1(6H, 2xCH_3, s), 3.1(2H, CH_2, s), 4.05(4H, 2xCH_2, q, J = 7Hz), 5.25(1H, NH, D_2O exchangeable, br).

Diethyl 2,4,6-trimethyl-1,4-dihydropyridine-3,5-dicarboxylate (8c): m.p. 131°C (Lit. 131°)[6]; λ_{max}(CH_3OH): 350, 235 nm; IR(KBr): 1690 cm^{-1}; ^1H NMR($CDCl_3$) : δ1.05(3H, CH_3, d, J = 6Hz), 1.4(6H, 2xCH_3, t, J = 7Hz), 2.35(6H, 2xCH_3, s), 3.85(1H, CH, q, J = 6Hz), 4.25(4H, 2xCH_2, q, J = 7Hz), 4.95(1H, NH, D_2O exchangeable, br).

Diethyl 2,6-dimethyl-4-benzyl-1,4-dihydropyridine-3,5-dicarboxylate(8d): m.p. 115-17°C (Lit.115°)[6]; λ_{max}(CH_3OH): 350, 230 nm; IR(KBr): 1680 cm^{-1}; ^1H NMR($CDCl_3$): δ 1.2(6H, 2xCH_3, t, J = 7Hz), 2.1(6H, 2xCH_3, s), 2.51(2H, CH_2, d, J = 7Hz), 4.0(4H, 2xCH_2, q, J = 7Hz), 4.4(1H, CH, t, J = 7Hz), 5.65(1H, NH, D_2O exchangeable, br), 6.7-7.4(5H, ArH, m).

Diethyl 2,6-dimethyl-1,4-diphenyldihydropyridine-3,5-dicarboxylate (8e): m.p. 155°C (Lit. 155°)[7]; λ_{max}(CH_3OH): 350, 237 nm; IR(KBr): 1622 cm^{-1}; ^1H NMR ($CDCl_3$): δ1.4(6H, 2xCH_3, t, J = 6Hz), 2.65(6H, 2xCH_3, s), 4.25(4H, 2xCH_2, q, J = 6Hz), 4.95(1H, CH, s), 6.0-7.25(10H, ArH, m).

Diethyl 2,6-dimethyl-1-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (8f) : m.p. 99°C; λ_{max}(CH_3OH): 345, 235 nm; IR(KBr): 1670 cm^{-1}; ^1H NMR($CDCl_3$): δ 1.15(6H, 2xCH_3, t, J = 6Hz), 1.8(6H, 2xCH_3, s), 3.25(2H, CH_2, s), 4.05(4H, 2xCH_2, q, J = 6Hz), 6.8-7.4(5H, ArH, m); Mass : $M^{+\cdot}$ m/z 329.

Diethyl 2,4,6-trimethyl-1-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (8g): m.p. 99-101°C (Lit.104-105°)[7]; λ_{max} (CH_3OH): 347, 236 nm; IR(KBr): 1680 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.1(3H, CH_3, d, J = 6Hz), 1.3(6H, 2xCH_3, t, J = 7Hz), 2.0(6H, 2xCH_3, s), 3.7(1H, CH, q, J = 6Hz), 4.15(4H, 2xCH_2, q, J = 7Hz), 7.35(5H, ArH, m).

Dimethyl 2,6-dimethyl-4-(o-nitro)phenyl-1,4-dihydropyridine-3,5-dicarboxylate (nifedipine) (8h): m.p. 169°C (Lit. 172°)[19]; λ_{max} (CH_3OH): 340, 230 nm; IR(KBr): 1680, 1520, 1340 cm^{-1}; ^1H NMR($CDCl_3$): δ 2.23(6H, 2xCH_3, s), 3.45(6H, 2xOCH_3, s), 5.5(1H, CH, s), 5.7(1H, NH, D_2O exchangeable, br), 7.05-7.65(4H, ArH, m).

Dimethyl 2,6-dimethyl-4-(m-nitro)phenyl-1,4-dihydropyridine-3,5-dicarboxylate(8i): m.p. 200°C (Lit. 206°)[19]; λ_{max} (CH_3OH): 350, 230nm; IR(KBr): 1660, 1535, 1510, 1360 cm^{-1}; ^1H NMR($CDCl_3$): δ 2.4(6H, 2xCH_3,s), 3.6(6H, 2xOCH_3,s), 5.1(1H, CH, s), 7.0-8.5(4H, ArH, m), 6.1(1H, NH, D_2O exchangeable, br).

Dimethyl 2,6-dimethyl-4-(p-nitro)phenyl-1,4-dihydropyridine-3,5-dicarboxylate(8j): m.p. 196°C (Lit. 196°)[19]; λ_{max} (CH_3OH): 355, 232 nm; IR(KBr): 1650, 1530, 1360 cm^{-1}; ^1H NMR($CDCl_3$): δ 2.35(6H, 2xCH_3, s), 3.6(6H, 2xOCH_3, s), 5.2(1H, CH, s), 6.8(1H, NH, D_2O exchangeable, br), 7.3-8.2(4H, ArH, m).

Diethyl 2,6-dimethyl-4-hydroxymethyl-1,4-dihydropyridine-3,5-dicarboxylate(8k): m.p. 135°C (Lit. 135°)[21]; λ_{max} (CH_3OH): 355, 233 nm; IR(KBr): 1725, 1680 cm^{-1}; ^1H NMR($CDCl_3$): δ 1.35(6H, 2xCH_3, t, J = 6Hz), 2.3(6H, 2xCH_3, s), 3.65(2H, CH_2, m), 4.0(1H, CH, br), 4.25(4H, 2xCH_2, q, J = 6Hz), 6.0(1H, NH, D_2O exchangeable, br).

Diethyl 2,6-dimethyl-4-acetoxymethyl-1,4-dihydropyridine-3,5-dicarboxylate(8l): thick liquid; λ_{max} (CH_3OH): 345, 232 nm; IR($CHCl_3$): 1715, 1680, 1640 cm^{-1}; ^1H NMR($CDCl_3$): δ 1.3(6H, 2xCH_3, t, J = 6Hz), 1.19(3H, CH_3, s), 2.25(6H, 2xCH_3, s), 3.85(2H, CH_2, d, J = 6Hz), 4.1(4H, 2xCH_2, q, J = 6Hz), 4.22(1H, CH, t, J = 6Hz); Mass: $M^{+\cdot}$ m/z 325.

Diethyl 2,6-dimethyl-4-carbethoxymethyl-1,4-dihydropyridine-3,5-dicarboxylate(8m): m.p. 77°C (benzene : petr. ether (40-60°)); λ_{max} (CH_3OH): 340, 232 nm; IR(KBr): 1723, 1693 cm^{-1}; ^1H NMR($CDCl_3$): δ 1.30(9H, 3xCH_3, two fused triplets, J = 7Hz), 2.89(6H, 2xCH_3, s), 3.85(2H, CH_2, d, J = 6Hz), 4.14, 4.21(6H, 3xCH_2, two quartets, J = 7Hz), 4.43(1H, CH, t, J = 6Hz), 6.3(1H, NH, D_2O exchangeable, br); Mass : $M^{+\cdot}$ m/z 339; (Found : C, 57.58; H, 6.84. $C_{17}H_{25}NO_6$ requires: C,57.87; H,6.75%).

Dimethyl 2,6-dimethyl-4-carbethoxymethyl-1,4-dihydropyridine-3,5-dicarboxylate(8n): m.p. 115-17°C (benzene petr. ether (40-60°)); λ_{max} (CH_3OH) 340, 230 nm, IR(KBr); 1714, 1684, 1644 cm^{-1}; ^1H NMR($CDCl_3$): δ 1.22(3H, CH_3, t, J = 7Hz), 1.77(1H, NH, D_2O exchangeable, br), 2.30(6H, 2xCH_3, s), 3.72(6H, 2xOCH_3, s), 3.81(2H, CH_2, d, J = 7Hz, overlapping the singlet at 3.72), 4.01(2H, CH_2, q, J = 7Hz), 4.29 (1H, CH, t, J = 6Hz); Mass: $M^{+\cdot}$ m/z 311; (Found: C,60.65; H,7.33. $C_{15}H_{21}NO_6$ requires: C,60.10; H,7.38%).

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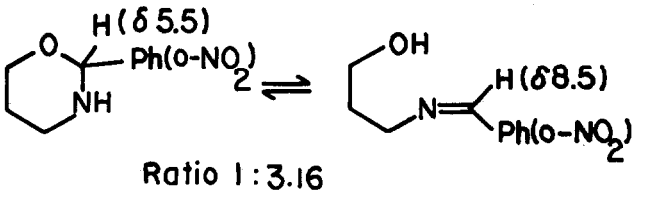

Ratio 1 : 3.16