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ADDITION REACTIONS UPON 1,4-DIHYDROPYRIDINES

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Introduction:

1,4-Dihydropyridines are still the largest and most widely studied class of "Calcium Channel Blockers". Some of them have been successfully introduced as commercial products for the treatment of cornary diseases or hypertension e.g. nifedipine, nimodipine and furnidipine[1]. Also, chemistry of dihydropyridines is an area of intense interests owing to the key role played by these compounds as an intermediate for the synthesis of natural products[2] and other heterocycles. Dihydropyridine, Tetrahydropyridines and piperidines are important and interesting compounds playing important role in synthetic, therapeutic and bioorganic chemistry. The reactivity of dihydropyridine mainly involved in selective reductions[3], electrophilic additions[4,5,6] and has allowed the completion of total synthesis of alkaloids[7,8,9].

A general drawback that severally restricts the use of 1,4-dihydropyridines in organic synthesis is their easy oxidation to the corresponding pyridinium salts (NADH is oxidized to NAD in many metabolic reactions). Rodolfo and coworkers have reported several oxidative electrophilic additions upon 1,4-dihydropyridines having electron withdrawing group at β- position, leading to corresponding 3-halo-2-substituted-1,2,3,4-tetrahydropyridines[10,11]. These transformations constitute general non biomimetic oxidation of 1,4-dihydropyridines, avoiding the natural oxidation pathway to pyridinium salts. It has been established that the oxidative addition upon 1,4-dihydropyridines with halonium ion and trapping the iminium ions (produced in the interaction of enamine moity with the halogenating agents) with nucleophiles resulted in the preparation of 3-halo-2-substituted-1,2,3,4-tetrahydropyridines. These tetrahydropyridines are valuable synthetic intermediates and can be elaborated to the pharmacologically interesting polysubstituted piperidines and polycyclic alkaloids[12].

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Nucleophilic trapping of iminium species formed by the attack of electrophile (I^+) on enamine moity of the dihydropyridine may result into 2-substituted – 3-halotetrahydropyridine or 2,3-disubstituted tetrahydropyridine derivatives **(Scheme-1)**.
It is also planned in this work to introduced oxygen based moity in 1,4-dihydropyridine ring system. Thus, 1,4-dihydropyridine on treatment with bromine at very low temperature followed by treatment with various nucleophiles (RO^-Na^+) resulted in the formation of 2,3-dialkoxytetrahydropyridines and some cyclic compounds **(Scheme-2)**.

Experimental

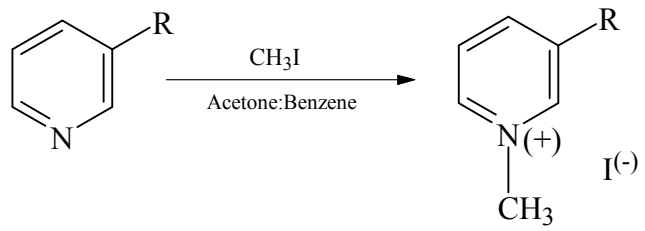
General: All solvents were purified and dried by standard methods. All reagents were of commercial quality from freshly opened containers. Organic extracts were dried over anhy. sodium sulphate. TLC and column chromatography were carried out by using silica gel. All reported ^1H NMR spectra were recorded with Bucker (300MHz) spectrometer. Chemical shifts are reported as δ values relative to TMS peak defined at δ = 0.00. Mass spectra were recorded on Geol GC-MS spectrometer by using electron ionization (*EI*) at 70 ev and only major peaks are quoted.

Methyl 1-methyl-1,4-dihydropyridine-3-carboxylate (3a)[13].

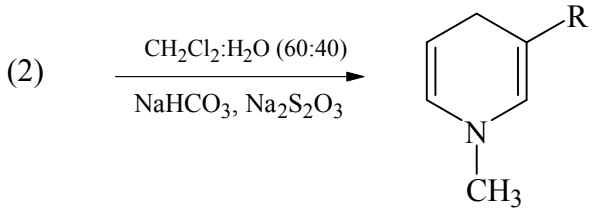
A solution of methyl iodide (7.3mmol, 10.36gm) in acetone (10ml) was added drop wise to a stirred solution of methyl nicotinate (72.26mmol, 10gm) in a mixture of acetone and benzene (1:1) at 0-5^oC and stirring was continued at room temperature for 12 hrs. The yellow coloured solid compound3-Methoxycarbonyl-1-methylpyridinium iodide (2a) thus obtained was filtered and washed with dry acetone: hexane (1:1), yield-88.45%, 16.52g M.P.-132^oC. Similarly (2b) was prepared.

To a two phase solution of dichloromethane (60ml) and water (40ml) containing pyridinium salt (2a, 10mmol, 2.79g) and sodium bicarbonate (4.20g), sodium dithionite (5.22g) in installments was added at 0^oC. The mixture was stirred at room temprature for 2 hrs under nitrogen atmosphere. Water (50ml) was added and the mixture was extracted with CH_2Cl_2 (3x15ml), the combined organic extract was dried over anhydrous sodium sulphate.

After the removal of solvent under reduced pressure at room temperature Methyl 1-methyl-1,4-dihydropyridine-3-carboxylate (3a) was obtained as a pale yellow oil. Similarly Methyl 1-methyl-1,4-dihydropyridine-3-carbonitrile (3b) was prepared. These compounds decompose on standing in air but was stored at –10^oC under nitrogen atmosphere.



(1) (2)

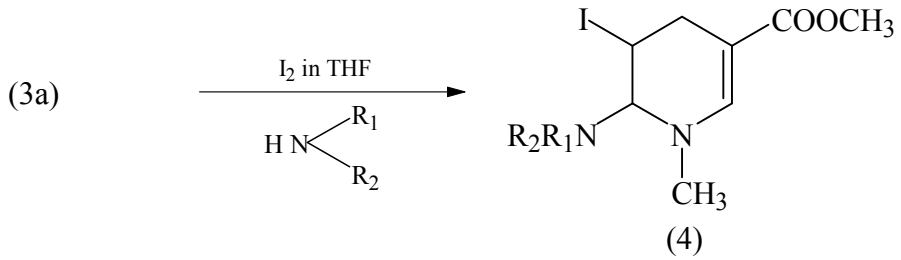


(3)

	R
(2a)	$COOCH_3$
(2b)	CN
(3a)	$COOCH_3$
(3b)	CN

Methyl 2-(diethylamino)-3-iodo-1-methyl-1,2,3,4-tetrahydropyridine-5-carboxylate (4a):

Thus as a test case a solution of iodine (3.5mmol , 0.9g) in THF (50ml) was added dropwise under nitrogen atmosphere to a stirred solution of Methyl 1-methyl-1,4-dihydropyridine-3-carboxylate (3a, 1mmol, 0.153g) and diethylamine (25mmol) in THF (50ml) kept at 0^oC, and stirring was continued at room temperature until no dihydropyridine was detected by TLC (usually 3hrs). Water (150ml) was added and the mixture was extracted with CH_2Cl_2. The combined organic extracts were washed with aqueous sodium thiosulphate solution (100ml, 0.5M) and brine solution (100ml). It was dried over anhy. sodium sulphate. The solvent was removed under reduced pressure and residue was purified by column chromatography over silica gel, elution with chloroform:ether yield pure Methyl 2-(diethylamino)-3-iodo-1-methyl-1,2,3,4-tetrahydropyridine-5-carboxylate (4a), yield 84% (0.295g) its structure was assigned on the basis of spectral data such as ^1H NMR, IR and Mass spectroscopy. Its ^1H NMR (300MHz, δ, $CDCl_3$) 4.10(m, 1H, H-2), 4.81(m, 1H, H-3), 2.26(m, 1H, H-4a), 2.61(m, 1H, H-4b), 7.35(s, 1H, H-6), 3.04(bs, 3H, $-NCH_3$), 3.70(m, 3H, OCH_3), 2.60(m, 4H, $-N-C\underline{H}_2CH_3$), 1.10(m, 6H, $N-CH_2C\underline{H}_3$). I.R. (film, cm^{-1}): 2342.0, 1734.0, 1675.0. and 1619.0. MS (EI) *m/z*: 352(M^+), 147, 125, 111, 85 and 43. Similarly compounds (4a-4e,5 & 6) were synthesized **(Scheme-1)** and their analytical data are given below.



	R_1	R_2
(4a)	CH_2CH_3	CH_2CH_3
(4b)	$CH_2CH_2CH_3$	$CH_2CH_2CH_3$
(4c)	$CH_2(CH_2)_2CH_3$	$CH_2(CH_2)_2CH_3$
(4d)	H	$CH_2(CH_2)_2CH_3$
(4e)	H	CH_2CH_2OH

(Scheme-1)

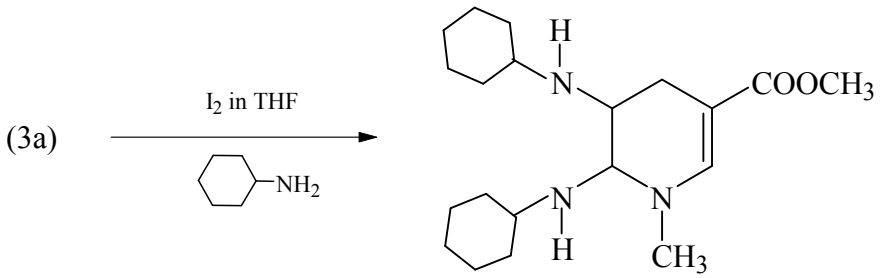
Methyl 3-iodo-1-methyl-2-(dipropylamino)-1,2,3,4-tetrahydropyridine-5-carboxylate (4b): yield-87% (0.33g), ^{1}H NMR (300MHz, δ, $CDCl_3$): 3.83(m, 1H, H-2), 4.27(m, 1H, H-3), 2.65(m, 1H, H-4a), 2.38(m, 1H, H-4b), 7.14(s, 1H, H-6), 2.87(m, 3H, N-CH_3), 3.58(m, 3H, OCH_3), 0.89(t, 6H, N-$CH_2CH_2C\underline{H}_3$), 2.59(m, 4H, N-$C\underline{H}_2CH_2CH_3$), 1.65(m, 4H, N-$CH_2C\underline{H}_2CH_3$). I.R. (film, cm^{-1}): 2363.0, 1770.0 and 1626.0. MS (EI) *m/z*: 380(M^+), 321, 281, 253, 101 and 43.

Methyl 2-(dibutylamino)-3-iodo-1-methyl-1,2,3,4-tetrahydropyridine-5-carboxylate (4c): yield-85% (0.34g), ^{1}H NMR (300MHz, δ, $CDCl_3$): 4.53(m, 1H, H-2), 3.83(m, 1H, H-3), 2.26(m, 1H, H-4a), 2.35(m, 1H, H-4b), 7.19(s, 1H, H-6), 2.86(m, 3H, N-CH_3), 3.59(m, 3H, OCH_3), 0.80(t, 6H, N-$CH_2CH_2CH_2C\underline{H}_3$), 1.41(m, 8H, N-$CH_2C\underline{H}_2C\underline{H}_2CH_3$), 2.86(m, 4H, N-$C\underline{H}_2CH_2CH_2CH_3$). I.R.(film, cm^{-1}): 2362.0, 1709.0, 1677.0. and 1621.0. MS (EI) *m/z*: 408(M^+), 349, 255, 128, 96, 64 and 43.

Methyl 2-(butylamino)-3-iodo-1-methyl-1,2,3,4-tetrahydropyridine-5-carboxylate (4d): Yield-81% (0.29g), ^{1}H NMR (300MHz, δ, $CDCl_3$): 4.57(m, 1H, H-2), 4.30(m, 1H, H-3), 2.60(m, 1H, H-4a), 2.45(m, 1H, H-4b), 7.21(s, 1H, H-6), 2.90(m, 3H, N-CH_3), 3.79(m, 3H, OCH_3), 0.89(t, 6H, N-$CH_2CH_2CH_2C\underline{H}_3$), 1.20(m, 8H, N-$CH_2C\underline{H}_2C\underline{H}_2CH_3$), 2.10(m, 4H, N-$C\underline{H}_2CH_2CH_2CH_3$). I.R. (film, cm^{-1}): 1679.0, 1626.0 and 1530.0. MS (EI) *m/z*: 352(M^+), 337, 281, 147, 128, 87 and 43.

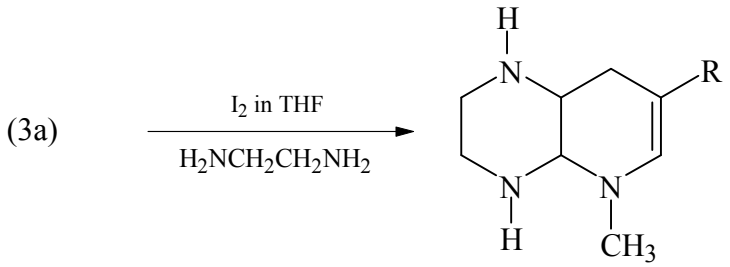
Methyl 2-(2-hydroxyethylamino)-3-iodo-1-methyl-1,2,3,4-tetrahydropyridine-5-carboxylate (4e): Yield-83% (0.28g), ^{1}H NMR (300MHz, δ, $CDCl_3$): 4.58(m, 1H, H-2), 4.30(m, 1H, H-3), 3.20(m, 1H, H-4a), 2.90(m, 1H, H-4b), 7.45(s, 1H, H-6), 2.75(m, 3H, N-CH_3), 3.81(m, 3H,OCH_3), 8.16(bs, 1H, OH), 2.75(m, 2H, N-$C\underline{H}_2CH_2OH$), 3.5(m, 2H, N-$C\underline{H}_2OH$). I.R. (film, cm^{-1}): 3410.0, 1655.0, 1460.0. and 1120.9. MS (EI) *m/z*: 340(M^+), 325, 269, 116, 74 and 43.

Methyl 2,3-bis(cyclohexylamino)-1-methyl-1,2,3,4-tetrahydropyridine-5-carboxylate (5): Yield-78% (0.27g), ^{1}H NMR (300MHz, δ, $CDCl_3$): 4.01(m, 1H, H-2), 7.35(s, 1H, H-6), 3.10(bs, 3H, N-CH_3), 3.50(m, 3H, OCH_3), 2.30-2.60(m, 5H), 1.55-1.90(m, 10H), 1.20-1.40(m, 10H). I.R. (film, cm^{-1}): 2348.0, 2360, 1659.8 and 1463.0 and 1123.0. MS (EI) *m/z*: 349 (M^+), , 291, 155, 141, and 59.



(5)

Methyl 5-methyl-1,2,3,4,4a,5,8,8a-octahydropyrido[2,3-b]pyrazine-7-carboxylate (6): Yield-88% (0.27g), ^{1}H NMR (300MHz, δ, $CDCl_3$): 4.01(m, 1H, H-2), 7.28(s, 1H, H-6), 3.13(m, 3H, N-CH_3), 3.56(s, 3H, OCH_3), 3.60-3.70(bs, 1H, H-4a), 2.90(m, 1H, H-8a), 2.09(m, 4H, methylene), 2.35(m,2H, H-8). I.R. (film, cm^{-1}): 1772.0, 1734.0 and 1699.0. MS (EI) *m/z*: 211 (M^+), 180, 152, and 30.



(6)

R = $COOCH_3$

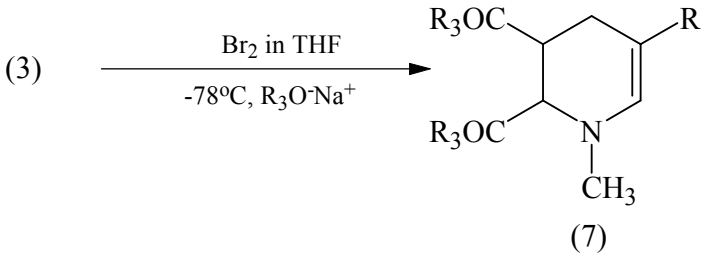
Further dihydropyridines on treatment with Br_2 at very low temperature followed by treatment with various nucleophiles (RO^-Na^+) resulted in the formation of 2,3-dialkoxytetrahydropyridines **(Scheme- 2)**.

Methyl 1-methyl-2,3-bis (methoxy)-1,2,3,4-tetrahydropyridine-5-carboxylate (7a)
Thus as a test case bromine (2.84mmol, 4.54mg) was added to a solution of Methyl 1-methyl-1,4-dihydropyridine-3-carboxylate(3a, 2.99mmol, 457mg) in anhydrous THF (25ml) kept under inert atmosphere at –78^{o}C. The resulting precipitate was removed by decantation of the solution, which was used immediately in subsequent reaction.

A solution of sodium methoxide (2.77mmol, 150mg) in anhydrous DMF (2ml) was added to a solution of dibromide (obtained above) in THF kept at –78^{o}C. The resulting mixture was stirred for 30 minutes at this temperature, and then cooling bath was removed. Stirring was continued for 12hrs at room temperature. Water (25ml) was added, and the mixture was extracted with ethyl acetate. The organic extracts were washed with an aquesh sodiumthiosulphate solution (0.5M, 30ml) brine solution (30ml) and dried over anhy.sodium sulphate. The solvent was removed under reduced pressure to yield an oil which was purified by column chromatography over silica gel. Elution with hexane/ethylacetoacetate afforded Methyl1-methyl-2,3-bis (methoxy)-1,2,3,4-tetrahydropyridine-5-carboxylate (7a) as an oil, 48% (0.30g). Its structure was identified on the basis of NMR, IR and Mass spectrometry. Its ^{1}H NMR (300MHz, δ, $CDCl_3$) show a singlet at 4.71(m, 1H, H-2), 4.29(m, 1H, H-3), 2.23-2.73(m, 2H, H-4), 3.09(s, 3H,

NCH_3), 3.64(m, 9H, 3xOCH_3), 7.24(s, 1H, H-6). I.R. (film, cm^{-1}): 2928.99, 1667.78, 1631.88, 1409.06 and 1182.83. MS (EI) *m/z*: 216 (M^+), 201, 184, 169, 110 and 83.

Similarly compounds (7b-7d,8a & 8b) were synthesized **(Scheme-2)** and their analytical data is given below.



(7)

	R	R_3
(7a)	$COOCH_3$	OCH_3
(7b)	CN	OCH_3
(7c)	$COOCH_3$	OC_2H_5
(7d)	CN	OC_2H_5

(Scheme-2)

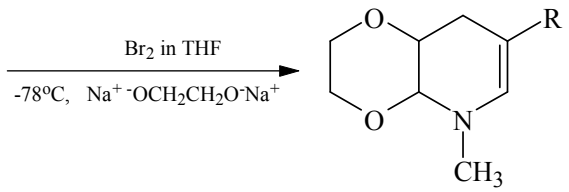
Methyl 1-methyl-2,3-bis (methoxy)-1,2,3,4-tetrahydropyridine-5-carbonitrile (7b): Yield-49% (0.26g), ^{1}HNMR (300MHz, δ, $CDCl_3$) show a singlet at 5.18(m, 1H, H-2), 4.68(m, 1H, H-3), 2.50-2.53(m, 2H, H-4), 3.07(s, 3H, NCH_3), 3.65(m, 9H, 3xOCH_3), 7.90(s, 1H, H-6). I.R. (film, cm^{-1}): 2926.71, 2253.99, 1658.03 and 1383.36. MS (EI) *m/z*: 167 (M^+), 152, 137, 134, 122 and 51.

Methyl 1-methyl-2,3-bis (ethoxy)-1,2,3,4-tetrahydropyridine-5-carboxylate (7c):
Yield-48% (0.34g), ^{1}H NMR (300MHz, δ, $CDCl_3$): 1.72(t, 6H, $OCH_2C\underline{H}_3$), 4.48(m, 1H, H-2), 4.81(m, 1H, H-3), 2.69-2.71(m, 2H, H-4), 3.00(s, 3H, NCH_3), 3.62(m, 9H, OCH_3), 7.15(s, 1H, H-6). I.R. (film, cm^{-1}): 1681.95, 1633.04, 1302.64 and 1182.82. MS (EI) *m/z*: 244(M^+), 229, 215, 186 and 83.

Methyl 1-methyl-2,3-bis (ethoxy)-1,2,3,4-tetrahydropyridine-5-carbonitrile (7d):
Yield-47% (0.29g), ^{1}H NMR (300MHz, δ, $CDCl_3$): 1.74(t, 6H, $OCH_2C\underline{H}_3$), 4.87(m, 1H, H-2), 4.46(m, 1H, H-3), 2.65-2.71(m, 2H, H-4), 3.07(s, 3H, NCH_3), 3.78(q, 4H, $OC\underline{H}_2CH_3$), 7.18(s, 1H, H-6). I.R. (film, cm^{-1}): 2925.67, 2263.09, 1407.6 and 1263.00. MS (EI) *m/z*: 211(M^+), 196, 182, 153 and 45.

Methyl 1-methyl-4a,5,8,8a-tetrahydropyrido[2,3-b]dioxane-7-carboxylate(7e):
Yield-49% (0.31g), ^{1}H NMR (300MHz, δ, $CDCl_3$): 5.30(m, 1H, H-4a), 5.10(m, 1H, H-8a), 3.17(s, 3H, N-CH_3), 3.60(s, 3H, OCH_3), 3.80(m, 4H, methylene), 7.24(s, 1H, H-6). I.R. (film, cm^{-1}): 1708.52, 1650.33, and 1036.50. MS (EI) *m/z*: 213(M^+), 198, 185, 153, 130 and 73.

Methyl 1-methyl-4a,5,8,8a-tetrahydropyrido[2,3-b]dioxane-7-carbonitrile (7f):
Yield-49% (0.26g), ^{1}H NMR (300MHz, δ, $CDCl_3$): 5.23(m, 1H, H-4a), 2.45-2.50(m, 2H, H-8), 4.92(m, 1H, H-8a), 2.98(s, 3H, N-CH_3), 3.74(m, 4H, methylene), 7.16(s, 1H, H-6). I.R. (film, cm^{-1}): 1766.77, 1659.2, 1285.20 and 1037.13. MS (EI) *m/z*: 180(M^+), 165, 152, 137, 105 and 41.

(3) 

(8)

	R
(8a)	COOCH3
(8b)	CN

Conclusion: Generally N-alkyl 1,4-dihydropyridines oxidises to pyridinium salts (natural oxidative pathway). But by this non-biomimetic oxidation we can synthesize some pharmacologically important tetrahydropyridines, piperidines and alkaloids.

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