The Reaction of 5-Benzylidene-2,3,4,5-tetrahydropyridine with Some Nucleophiles

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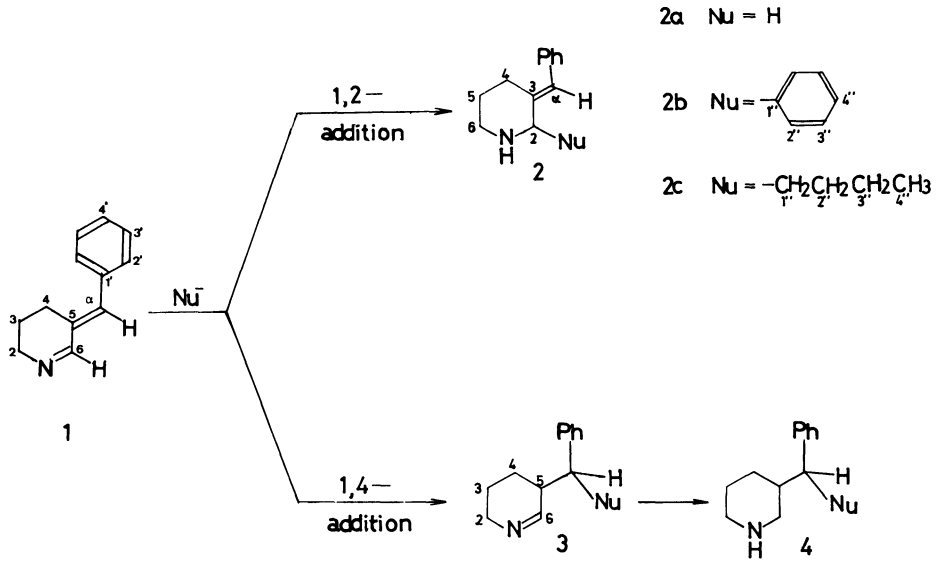
The reaction 5-benzylidene-2,3,4,5-tetrahydropyridine (**1**) with nucleophilic reagents, such as sodium tetrahydroborate, lithium tetrahydridoaluminate, organometallic reagents, pyrrole, or ethyl propiolate, has been studied. The reaction of **1** with sodium tetrahydroborate, lithium tetrahydridoaluminate, phenylmagnesium bromide, butyllithium gave exclusively respective 1,2-adducts. The reaction with pyrrole gave a tricyclic 1:1 adduct while **1** formed a 1:2 adduct with ethyl propiolate.

As an extension of our recent work directed toward the synthesis of 5-benzylidene-2,3,4,5-tetrahydropyridine (**1**)[1] which is featured with the α, β-unsaturated imine moiety fixed in *s-trans* conformation, we have investigated its reactivity toward nucleophiles. Two reaction modes are *a priori* expected: 1,2-addition of a nucleophile (Nu^-) to the C=N bond would provide a 2-substituted 3-benzylidenepiperidine (**2**), whereas conjugate addition (1,4-addition) of a nucleophile would afford 5-(α-substituted benzyl)-2,3,4,5-tetrahydropyridie (**3**) (Scheme 1). Compounds having the general structure **2** have recently attracted considerable attention in view of their potential clinical application as antihistamine and anticholine drugs.[2] On the other hand, the cyclic imine **3** may serve as a useful precursor to a variety of piperidine alkaloids and other natural alkaloids.[3] Herein we wish to report the results of such reactions of **1** with several nucleophiles which have been carried out in an attempt to synthesize these compounds (**2** and **3**).

Results and Discussion

Hydride Reduction of 1. Reduction of the C=N bond of **1** with a hydride reagent (1,2-addition) would produce 3-benzylidenepiperidine (**2a**, Nu=H), to which access has thus far been difficult using the conventional synthesis methodology.[1] On the other hand, 1,4-reduction would ultimately afford 3-benzylpiperidine (**4**) *via* partially reduced 5-benzyl-2,3,4,5-tetrahydropyridine (**3a**, Nu=H). It is generally accepted that in the reduction of α,β-unsaturated ketones 1,4-reduction tends to be more preferred with sodium tetrahydroborate than with lithium tetrahydridoaluminate.[4] In practice, however, the reduction of **1** with either reagent gave exclusively desired **2a** in 90% ($NaBH_4$, methanol, r.t.) or 85% ($LiAlH_4$, ether, 0 C). Structural identification of **2a** was based on spectral data (MS, IR, and ^1H and ^{13}C NMR). A molecular ion peak at *m/z* 173 in the mass spectrum was consistent with the molecular formula ($C_{12}H_{15}N$). ^1H NMR spectrum showed a characteristic singlet at δ 6.27 due to the benzylidene proton and one exchangeable proton at δ 2.13 (NH) in addition to eight methylene and five aromatic protons. The IR spectrum indicated a medium band at 1650 cm^{-1} due to the C=C bond conjugated with the phenyl group. In line with these data, its ^{13}C NMR spectrum exhibited ten peaks, six of which showed up in the sp^2-C region (δ 123.03—139.72), suggesting the presence of one C=C bond besides the aromatic ring.

Such a selective 1,2-hydride reduction of **1** is surprising for two reasons; (a) as described earlier, sodium



Scheme 1.

tetrahydroborate reduction of α,β-unsaturated ketones or aldehydes normally gives a mixture of 1,2- and 1,4-reduction products with the latter being predominant.[4] (b) lithium tetrahydridoaluminate reduction of 3-phenyl-2-propenal shows a discrete tendency depending on the reaction temperature; 3-phenyl-2-propen-1-ol is produced at −10 °C as a result of preferential 1,2-reduction,[5] whereas at 25 °C in diethyl ether 3-phenyl-1-propanol is obtained exclusively.[6] It should be noted here that in the case of **1** possessing an α,β-unsaturated imine structure with a phenyl group at the β-carbon, the reduction with lithium tetrahydridoaluminate at higher temperature (tetrahydrofuran, reflux, 0.5 h) resulted in the same product **2a** (79% yield); neither **3a** nor **4** was detected.

Reaction with Organometallic Compounds. The less reactive trend of the benzylidene C=C bond of **1** toward nucleophiles in comparison with α,β-unsaturate aldehyde was exposed more clearly by the reaction with organometallic compounds. Thus the reaction of **1** with excess phenylmagnesium bromide in diethyl ether at room temperature provided 3-benzylidene-2-phenylpiperidine (**2b**, Nu=Ph) exclusively in 56% yield. The structure of the product **2b** was confirmed by combustion analysis and spectral data (MS, IR, ^{1}H and ^{13}C NMR). The molecular formula ($C_{18}H_{19}N$) was established by elemental analysis (C, H, and N) and mass spectral molecular weight, m/z 249 (M^+). The assigned structure was compatible with the ^{1}H NMR spectrum which revealed characteristic signals at δ 1.93 (br s, 1H, NH, exchangeable with D_2O) and δ 5.90 (br s, 1 H, benzylidene proton) in addition to aromatic and alicyclic protons.

An analogous reaction mode was observed in the reaction of **1** with *n*-butyllithium at −78 °C in THF which resulted in the formation of 3-benzylidene-2-butylpiperidine (**2c**; Nu=*n*-Bu) in 95% yield. The structure of **2c** was characterized by the spectral data (MS, IR, ^{1}H and ^{13}C NMR). The ^{13}C NMR showed eight aliphatic carbons (δ 14.14—61.33) and six sp^2-carbons (δ 122.00—137.82); the peak due to the C=N bond was not detected, suggesting that the 1,2-adduct was the sole product. In agreement with this conclusion, the ^{1}H NMR indicated one benzylidene proton (δ 6.27). but no peak around δ 8 due to azomethine proton was detected.

It is noteworthy that both phenylmagnesium bromide and phenyllithium react with α,β-unsaturated imines, which can assume an *s-cis* conformation, to provide 1,4-adducts exclusively.[7] The above reaction therefore suggests an important synthetic approach for introduction of various alkyl or aryl substituent at C2 of the piperidine bearing exocyclic double bond at C3. Hence the present two-step sequence for preparation of such compounds (**2b**, **2c**) starting from 2,3,4,5-tetrahydropyridine[1,8] is much simpler and more economical than the previous methods.[9,10]

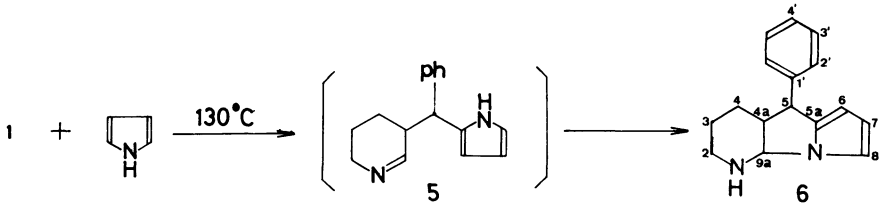
In order to prepare compounds of type **3**, we examined the reaction of organocuprates (I) (Li[R_2Cu], R=alkyl or aryl). However, desired 1,4-adducts could not be obtained under various conditions; only the starting material was recovered unchanged.

Reaction with Other Nucleophiles. The pronounced tendency of 1,2-addition of the above anionic nucleophiles could be reversed by the use of nonanionic nucleohiles, such as pyrrole. The reaction of **1** with excess pyrrole at 130 °C for 14 h gave 5-phenyl-1,3,4,4a, 5,9a-hexahydro-2*H*-pyrrolo[1',2':1,5]pyrrolo[2,3-*b*]pyridine(**6**) in 32% yield. Structural assignment was based on analytical and spectral data (MS, IR, ^{1}H and ^{13}C NMR). The presence of the fused pyrrole ring was evident by IR (1490 cm^{-1}, pyrrole ring skeletal vibration) as well as by ^{13}C NMR spectrum (four sp^2-carbons at δ 101.51(d), 111,85(d), 111.85(d)† and 142.32(s)). In its ^{1}H NMR spectrum, the three olefin protons absorbed at δ 5.83(d, J=3 Hz), 6.27(t, J=3 Hz) and 6.70(d, J=3 Hz) and two protons at δ 5.10(d, J=6 Hz) and 4.01(d, J=6 Hz) were assigned to the benzylic proton and the methine proton adjacent to the two nitrogen atoms, respectively. These NMR data were consistent with the tricyclic structrue **6**. This was also supported by analytical and mass spectral data.

Structure **6** suggested possible intervention of intermediate **5**, which may have been formed by 1,4-addition of pyrrole to the conjugated imine system of **1** (scheme 2). The reaction may be regarded as an electrophilic substitution of **1** with pyrrole which usually undergo such reactions preferentially at C2. This reaction therefore presents striking contrast to the previously mentioned examples of 1,2-addition of charged nucleophiles. It is very interesting that such a complex heterocyclic system can be constructed in one step by this reaction.

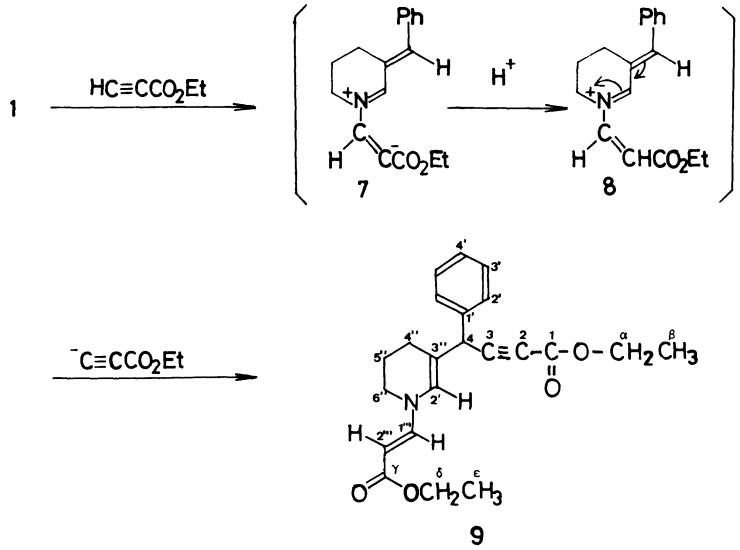
The other uncleophile examined was ethyl propiolate which is usually regarded as an electrophile because of its electron deficient triple bond. However, its conjugate base often functions as a nucleophile.[11]

Thus the reaction of **1** with ethyl propiolate (r.t., 13h, 73%; reflux, 0.5 h, 68%) afforded **9**. The structural elucidation of ethyl 4-[1-(2-ethoxycarbonylvinyl)-1,4,5,6-tetrahydro-3-pyridyl]-4-phenyl-2-butynoate (**9**) was based on spectroscopic data (MS, IR, ^{1}H and ^{13}C NMR). The mass spectral molecular ion peak (M^+=367) as well



Scheme 2.

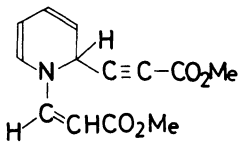
† Two signals are degenerated at the decoupling condition (see Experimental).



Scheme 3.

as ^{13}C NMR spectrum (a total of 20 peaks) established the molecular formula ($C_{22}H_{25}O_4N$). The presence of a *trans* C=C bond was suggested by ^{13}C NMR (δ 88.58 (d) and 150.33 (d)) and ^1H NMR (δ 4.85 (d, J=12 Hz) and 7.42 (d, J=12 Hz)).[12] The proton absorption at δ 4.85 disappeared upon addition of D_2O in agreement with the general behavior of the β-proton of an enamine system.[13] The other double bond was identified as a part of the endocyclic enamine segment on the basis of ^{13}C NMR (δ 127.42 or 127.96 (d) and 133.54 (s)) and ^1H NMR (δ 4.76(s)). The triple bond was evident by ^{13}C NMR (δ 77.47 (s) and 82.67 (s)) as well as by IR (2220 cm^{-1}).

The formation of **9** could be most simply rationalized by initial attack of one molecule of ethyl propiolate at the nitrogen of **1** to form the zwitter ion **7** and subsequent 1,6-addition of a second molecule of the acetylenic ester *via* the nitrilium ion intermediate **8**.[12] A similar reaction has previously been observed between pyridine and metyl propiolate to afford the 1,2-dihydropyridine **10**.[14]



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In summary, although our intention to synthesize both **2** and **3** could not entirely be satisfied in the present investigation, compounds **2** are potentially useful as anticholine or antihistamine drugs and the unanticipated formation of compounds **6** and **9** is intriguing not only because of the initial mechanism (1,4-addition) of their formation, but also because of their unique structural feature which is otherwise only difficultly accessible.

Experimental

All reactions were performed under dry inert conditions. Solvents used were purified by distillation over appropriate drying agent under dry nitrogen atmosphere. Mass spectra were measured on a Hitachi-Perkin Elmer RMU-6D spectrometer. Infrared spectra were recorded on a JASCO DS-403G spectrometer. ^1H NMR spectra were obtained with a JEOL MH-100 spectrometer. ^{13}C NMR spectra were recorded on a JEOL FX-90Q spectrometer operated at 22.5 MHz. Typical acquisition parameters were spectral width 5000 Hz, flip angle 30° and pulse delay 2s with 8192 data points. The ^{13}C NMR spectral data of the products (**2a**, **2b**, **2c**, **6**, and **9**) were collected in Table 1 and assignments were rationalized at the end of this section. All chemical shifts were reported in δ relative to internal tetramethylsilane.

5-Benzylidene-2,3,4,5-tetrahydropyridine (1).[1] A mixture of 2,3,4,5-tetrahydropyridine trimer (α-isomer) (32.5 g, 0.131 mol) and benzaldehyde (45.6 g, 0.430 mol) in absolute methanol (500 ml) was heated under reflux for 4 h. After removal of the solvent *in vacuo*, the residue was fractionally distilled to afford 28.0 g(42%) of 5-benzilidene-2,3,4,5-tetrahydropyridine (**1**): bp 108—110 °C (0.25 mmHg)

Reaction of 1 with Sodium Tetrahydroborate. Sodium tetrahydroborate (509 mg, 13.5 mmol) dissolved in methanol (20 ml) was added dropwise with stirring to a solution of **1** (1.085 g, 6.35 mmol) in methanol (30 ml) at ambient temperature. After additional 2 h stirring, concentrated hydrochloric acid (10 ml) was added to the reaction mixture. After removal of the solvent, water (15 ml) was added to the residue. The resultant solution, saturated with potassium carbonate, was extracted with diethyl ether. After drying the extract over anhydrous sodium sulfate and subsequent removal of ether *in vacuo*, 3-benzylidenepiperidine (**2a**) (984 mg, 90%) was obtained as colorless oil. ^1H NMR($CDCl_3$): δ 1.57(quintet, J=6 Hz, 2H), 2.13(s, 1H), 2.50(t, J=6 Hz, 2H), 2.90(t, J=6 Hz, 2H), 3.37(s, 2H), 6.27(s, 1H), and 7.00—7.40(m, 5H); IR(neat): 745 and 700 cm^{-1}; MS: M^+=173.

Reaction of 1 with Lithium Tetrahydroaluminate. A): A solution of **1** (983 mg, 5.75 mmol) in absolute ether (10 ml) was added dropwise with stirring to dry dietyl ether (15 ml) suspended with lithium tetrahydridoaluminate (500 mg, 13.2 mmol) at 0 °C. After additional 2 h stirring, ice-water was added to the reaction mixture. The organic layer was separated, dried with anhydrous sodium sulfate, and evapo-

TABLE 1. C-13 CHEMICAL SHIFTS (δ) FOR **1**, **2a**—**2c**, **6** AND **9**[a]

1		**2a**	**2b**	**2c**	**6**		**9**	
C6	163.64	C2	55.42	65.98	61.33	C9a	69.72	C2′	127.42[c]
C5	131.70	C3	139.72	142.48	142.37	C4a	50.66	C3″	133.54
C4	21.63	C4	27.85	27.41	26.11	C4	23.16	C4″	24.11
C3	25.03	C5	29.04	28.98	28.98	C3	25.35	C5″	25.02
C2	49.70	C6	47.02	45.24	43.39	C2	41.39	C6″	45.94
Cα	136.11	Cα	123.03	124.93	122.00	C5	47.00	C4	56.99
C1′	135.93	C1′	137.44	137.71	137.82	C1′	137.74	C1′	135.71
C2′	129.43[b]	C2′	128.83[b]	128.88[b]	128.94[b]	C2′	128.33[b]	C2′	128.88[b]
C3′	128.42[b]	C3′	128.07[b]	127.96[b]	128.01[b]	C3′	127.69[b]	C3′	128.34[b]
C4′	128.00	C4′	126.23	126.23	126.12	C4′	126.52	C4′	127.96[c]
		C1″		141.34	31.48	C5a	142.32	C3	82.67
		C2″		127.96[b]	29.36	C6	111.85	C2	77.47
		C3″		128.29[b]	22.81	C7	101.51	C1	153.04
		C4″		126.99	14.14	C8	111.85	Cα	62.19
								Cβ	13.98
								C1‴	150.33
								C2‴	88.58
								Cγ	169.08
								Cδ	59.21
								Cε	14.57

a) Measured in $CDCl_3$ on a JEOL FX-90Q spectrometer operated at 22.5 Hz (See Experimental section for acquisition conditions). b, c) Assignments may be reversed.

rated to afford **2a** (843 mg, 85%).

B): A solution of **1** (529 mg, 3.09 mmol) in dry tetrahydrofuran (10 ml) was added to dry tetrahydrofuran (15 ml) suspended with lithium tetrahydridoaluminate (494 mg, 13.0 mmol) under reflux. After continued reflux for 30 min, ice-water was added to the reaction mixture. The organic layer was separated, dried with anhydrous sodium sulfate, and evaporated to leave **2a** (421 mg, 79%).

Reaction of 1 with Phenylmagnesium Bromide. A solution of bromobenzene (2.5 ml, 23.9 mmol) in absolute dietyl ether (14 ml) was added under nitrogen atmosphere to magnesium powder (600 mg, 24.7 mmol) to form phenylmagnesium bromide. Subsequently, a solution of **1** (1.070 g, 6.26 mmol) dissolved in absolute ether (6 ml) was added to the Grignard reagent. The mixture was stirred for 14 h at ambient temperature and then poured into ice-cold 10% hydrochloric acid. The usual work-up followed by purification by silica-gel column chromatography using diethyl ether/dichloromethane (1:1) as an eluant afforded 3-benzylidene-2-phenylpiperidine (**2b**) (870 mg, 56%); mp 60.0—60.5 °C (sublimed, uncorrected); ^{1}H NMR ($CDCl_3$) δ 1.67 (quintet, J=6 Hz, 2H), 1.93 (broad s, 1H), 2.17—3.00 (m, 4H), 4.43 (broad s, 1H), 5.90 (broad s, 1H) and 7.00—7.56 (m, 10H); IR (KBr) 754, and 692 cm^{-1}; MS m/z 249 (M^+); Found: C. 86.71; H, 7.47; N, 5.85%. Calcd for $C_{18}H_{19}N$: C, 86.70; H, 7.68; N, 5.62%.

Reaction of 1 with Butyllithium. Butyllithium dissolved in hexane (1.51 mol/l, 4 ml) was added under nitrogen atmosphere to a cold (−78 °C) solution of **1** (500 mg, 2.92 mmol) in tetrahydrofuran (10 ml) and stirred for 45 min at −78 °C. The reaction was quenched with 10 ml of water and the resultant solution, saturated with potassium carbonate, was extracted with ether. The extract was dried over anhydrous sodium sulfate and the ether removed *in vacuo*. 3-Benzylidene-2-butylpiperidine (**2c**) was obtained as colorless oil. ^{1}H NMR ($CDCl_3$) δ 0.93 (t, 3H), 1.01—2.00 (m, 8H), 2.20 (broad, 1H), 2.33—3.33 (m, 4H), 3.60 (t, 1H), 6.27 (broad s, 1H) and 7.20 (m, 5H); IR (neat) 740 and 695 cm^{-1}; MS m/z 229 (M^+).

Reaction of 1 with Pyrrole. **1** (989 mg, 5.78 mmol) was dissolved in pyrrole (10 ml) and heated under reflux for 14 h. After removal of excess pyrrole *in vacuo*, the residue was purified by dry alumina column chromatography using hexane–dichloromethane–diethyl ether (1:1:1) as an eluent to afford 5-phenyl-1,3,4,4a,5,9a-hexahydro-2*H*-pyrrole[1′,2′:1,5]-pyrrolo[2,3-*b*]pyridine (**6**) (442 mg, 32%); mp 82.5—83.0 °C (sublimed, uncorrected); ^{1}H NMR ($CDCl_3$) δ 1.20—2.23 (m, 5H), 2.40—3.00 (m, 3H), 4.01 (d, J=6 Hz, 1H), 5.10 (d, J=6 Hz, 1H), 5.83 (d, J=3 Hz, 1H), 6.27 (t, J=3 Hz, 1H) 6.70 (d, J=3 Hz, 1H) and 7.00—7.57 (m, 5H); IR (KBr) 1490 (pyrrole ring), 748, 733, 720, 705 and 672 cm^{-1}; MS m/z 238 (M^+); Found (Calcd): C 80.63 (80.63), H 7.55 (7.61), N 11.91 (11.75).

Reaction of 1 with Ethyl Propiolate. A): A mixture of ethyl propiolate (9.77 mmol) and **1** (500 mg, 2.92 mmol) dissolved in benzene (20 ml) was heated under reflux for 30 min under nitrogen atmosphere. After removal of solvent *in vacuo*, the residue was purified by dry silica-gel column chromatography using hexane–dichloromethane–diethyl ether (2:1:1) as an eluant to afford ethyl 4-[1-(2-ethoxycarbonylvinyl)-1,4,5,6-tetrahydro-3-pyridyl]-4-phenyl-2-butynoate (**9**) (725 mg, 68%).

B): A mixture of ethyl propiolate (9.77 mmol) and **1** (456 mg, 2.67 mmol) dissolved in benzene (20 ml) was stirred under nitrogen atmosphere at ambient temperature for 13 h. After removal of solvent *in vacuo*, the residue was purified as described above to provide **9** (713 mg, 73%). ^{1}H NMR ($CDCl_3$) δ 1.20 (t, J=7 Hz, 3H), 1.25 (t, J=7 Hz, 3H), 1.43—2.00 (m, 2H), 2.20—2.60 (m, 1H), 2.70—3.00 (m, 1H), 3.33 (t, 2H), 4.12 (q, J=7 Hz, 2H), 4.20 (q, J=7 Hz, 2H), 4.76 (s, 1H), 4.85 (d, J=12 Hz, 1H exchangeable with D_2O), 6.50 (broad s, 1H), 7.00—7.47 (m, 5H) and 7.42 (d, J=12 Hz, 1H); IR (neat): 2220 (-C≡C-), 1710 (-C=C-CO-O-), 748, and 698 cm^{-1}; MS m/z 367(M^+).

^{13}C NMR Spectra. ^{13}C NMR chemical shift values are tabulated in Table 1. The assignment was made chiefly by the splitting pattern under off-resonance decoupling

conditions and by comparison with the compounds having similar (or partially similar) structures. The numbering of carbon atoms (see the structures in the schemes) is in some cases provided only for the sake of easy comparison.

5-Benzylidene-2,3,4,5-tetrahyropyridine (1): The low field signal of imine carbon atom was already described.[1] The assignment of C2′ and C3′ signals was based on the spin-lattice relaxation times (T_1). Thus, it is expected that C3′ relax faster than C2′. The chemical shift data for styrene[15] was also taken into consideration.

*3-Benzylidenepiperidines (**2a—c**)*: Comparison with the δ values for **2a—c** with those of **1** leaves little uncertainty in the assignment except that the assignment for C2′ and C3′ may be reversed. The differentiation of signals due to two aromatic rings of **2b** was made based on the assumption that C1′—C4′ resonances are in much the same field among three compounds **2a—c**.

*5-Phenyl-1,3,4,4a,5,9a-hexahydro-2H-pyrrolo[1′,2′:1,5]pyrrolo-2,3-b]pyridine (**6**)*: Of the two monoprotonated carbon resonances at δ 47.00 and δ 50.66, the latter can be assigned to C4a because of apparently shorter relaxation time due to the greater number of protons in the vicinity. Of the four sp^2-carbons of pyrrole moiety, two give a degenerate signal at δ 111.85, which should inevitably be assigned to C6 and C8 from chemical shift consideration. This assignment was confirmed by the observation that under weak decoupling condition the peak split into a pair of doublet with different splitting which reflects the distance between the carbon in question and the nitrogen atom. A high-field shift of unprotonated α-carbon resonance into protonated β-carbon region seems characteristic of α-carbons of 1,2-disubstituted pyrrole.[16]

*Ethyl-[1-(2-ethoxycarbonylvinyl)-1,4,5,6-tetrahydro-3-pyridyl]-4-phenyl-2-butynoate (**9**)*: There are in **9** four sp^2-hydridized enamine carbon atoms, of which the signal due to the unprotonated C3″ is assigned based on chemical shift consideration. Peaks at δ 88.58 and 150.33, are assigned to C2‴ and C1‴, respectively, since the corresponding carbon nuclei of enamino ester resonate at δ 84.0 and 160.6, respectively.[17] Hence, the peak at δ 127.42 or 127.96 is due to C2‴, an unsaturated α-carbon of 1,2,3,4-tetrahydropyridine moiety which resonates at δ 132—133.[18]

Of the two signals at δ 77.47 and 82.67 due to two *sp*-hybridized carbons, the latter which shows a small coupling with H4 is assigned to C3. Of the signals due to two sets of OCH_2-CH_3 moiety, peaks at δ 13.98 and 62.19 are assigned to Cβ and Cα, respectively, based on comparison with the δ values for ethyl propiolate.[19] Similarly, C=O signal in higher field as an ester carbonyl carbon (δ 153.04) was assigned to C1.[19] This is an additional support for the presence of -C≡CCOO- moiety.

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