8.10 ppm showed no other coupling (especially $J_{4,8}$). It is concluded from these data that the methoxy and chloro substituents are found in the 5 and 8 positions, respectively.

The second component, 5-chloro-1,6-naphthyridine, was identified by its melting point and nmr[9] and ir spectra.[10]

The third component, 8-chloro-6-methyl-1,6-naphthyridin-5(6*H*)-one, was identified by its ir spectrum and chemical conversion to (2). The spectrum of (4) indicated a carbonyl absorption at 1650, the same wavelength as found in the starting material. When (4) was reacted with $POCl_3$ in a sealed tube at 160°, the product was found to be identical to (2) by mixture melting point and nmr and ir spectra.

Since PCl_5 is a highly active chlorinating agent, reactions were attempted with $POCl_3$ under different conditions. The starting material was quantitatively isolated after a 12-hr reflux period. However, a 62.5% yield of 5-chloro-1,6-naphthyridine was obtained when the reaction took place in a sealed tube at 170° for 20 hr.

In the case of $POCl_3$ at an elevated temperature, only 3 is isolated. However, when a mixture of $POCl_3$ and PCl_5 is used, chlorination at the 8 position also occurs.

Experimental Section

1,6-Naphthyridine-6-methiodide.[4] 1,6-Naphthyridine (4.7 g, 0.036 mol) was dissolved in 40 ml of anhydrous methanol. To this was added 10.03 g (0.0724 mol) of methyl iodide, whereupon the mixture was refluxed 24 hr. The reaction mixture was cooled and 50 ml of ethyl acetate was added. A yellow precipitate was removed by filtration: yield 3.28 g; mp 154–156° (lit.[4] 153–155°). An additional 200 ml of ethyl acetate was added to the filtrate and cooled, and 2.43 g of yellow precipitate was removed: total yield 5.73 g (64%).

6-Methyl-1,6-naphthyridin-5(6*H*)-one.[4] 1,6-Naphthyridine-6-methiodide (5.50 g, 0.0202 mol) was dissolved in 50 ml of water and cooled to 0° in an ice bath. With stirring, 14.2 g (0.0435 mol) of potassium ferricyanide in 50 ml of water and 4.3 g (0.358 mol) of sodium hydroxide in 7.25 ml of water were added simultaneously. The base addition was complete in 10 min and the oxidizing agent addition was complete in 30 min. The solution was stirred at 0° for 90 min, then at room temperature for 27 hr. After continuously extracting the aqueous solution with chloroform for 24 hr, the chloroform was removed *in vacuo*. The residue was sublimed at 90°: yield 2.44 g (75.3%); mp 98–99° (lit.[4] 97–98°).

Chlorination Procedure. To a cold solution of 4.00 g (0.0192 mol) of PCl_5 and 20 ml of $POCl_3$ was added 2.25 g (0.0141 mol) of 6-methyl-1,6-naphthyridin-5(6*H*)-one. The mixture was refluxed with stirring for 24 hr. The excess $POCl_3$ was removed at reduced pressure and ice was added to the residue. After basifying with a saturated solution of sodium carbonate to pH 8, the solution was extracted with chloroform (4 × 50 ml). The chloroform extracts were dried overnight with anhydrous sodium sulfate and the chloroform was removed *in vacuo* at 20°. The residue was placed on an alumina column (Brockman Grade II, 150 g, 2.5 cm diameter) and chromatographed with 5% dichloromethane–carbon tetrachloride (50 ml in 450 ml) until the first band was isolated. Then elution was completed with ethyl acetate.

Fraction A: 5,8-dichloro-1,6-naphthyridine; yield 550 mg (23.9%); mp 113–115°; exact mass ($C_8H_4Cl_2N_2$) 197.969 (calcd 197.975); nmr 9.26 (m, 2-H), 8.67 (m, 4-H), 8.60 (s, 7-H), 7.68 (m, 3-H), $J_{2,4}$ = 1.6 Hz, $J_{2,3}$ = 4.4 Hz, $J_{3,4}$ = 8.8 Hz; ir 2970, 1600, 792, 610 cm^{-1}.

Fraction B: 5-chloro-1,6-naphthyridine; yield 38 mg (2.00%); mp 106–107° (lit.[9] 107°) (after sublimation at 60°).

Fraction C: 8-chloro-6-methyl-1,6-naphthyridin-5(6*H*)-one; yield 320 mg (14.3%); mp 199–200° (after sublimation at 155°); exact mass ($C_9H_7ClN_2O$) 194.025 (calcd 194.025); nmr 9.01 (m, 2-H), 8.68 (m, 4-H), 7.52 (s, 7-H), 7.38 (m, 3-H), 3.60 (s, -NCH_3) ($J_{2,3}$ = 4.6 Hz, $J_{2,4}$ = 1.7 Hz, $J_{3,4}$ = 8.0 Hz); ir 3150, 1650, 1570 cm^{-1}.

Fraction D: 6-methyl-1,6-naphthyridin-5(6*H*)-one; yield 400 mg; mp 98–99° (after sublimation at 60°); nmr and ir superimposable with starting material.

5-Methoxy-8-chloro-1,6-naphthyridine. 5,8-Dichloro-1,6-naphthyridine (100 mg, 0.502 mmol, from fraction A) and 200 mg of sodium methoxide were dissolved in 50 ml of anhydrous methanol and heated at reflux for 4 hr. The methanol was evaporated away with a stream of nitrogen and the residue was taken up in 20 ml of a saturated aqueous solution of sodium carbonate. The basic solution was extracted with chloroform (4 × 10 ml) and the extracts were dried overnight with anhydrous sodium sulfate. The chloroform was removed under a stream of nitrogen: yield 85.7 mg (88%); mp 80–82°; exact mass ($C_9H_7ClN_2O$) 194.019 (calcd 194.025); nmr (CCl_4) 8.92 (m, 2-H), 8.32 (m, 4-H), 8.10 (s, 7-H), 7.33 (m, 3-H), 3.98 (s, OCH_3) ($J_{2,3}$ = 4.8 Hz, $J_{2,4}$ = 1.6 Hz, $J_{3,4}$ = 9.4 Hz).

Conversion of 4 into 2. 8-Chloro-6-methyl-1,6-naphthyridin-5(6*H*)-one (4, 256 mg, 1.32 mmol) was combined with 25 ml of $POCl_3$ and heated for 16 hr in a sealed tube at 160°. The excess $POCl_3$ was removed at reduced pressure and the residue was taken up in 20 ml of an ice-cold, saturated, aqueous solution of sodium carbonate. The basic solution was extracted with chloroform (3 × 25 ml) which was dried overnight with anhydrous sodium sulfate. The chloroform was removed and the product was sublimed at 95°: yield 227 mg (88%); mp 112–114°; mp with 2 112–113°.

Phosphorus Oxychloride with 6-Methyl-1,6-naphthyridin-5(6*H*)-one. A. 6-Methyl-1,6-naphthyridin-5(6*H*)-one was heated at reflux with 10 ml of phosphorous oxychloride for 12 hr. The isolation and work-up as described above was used. The starting material was isolated quantitatively and was identical in mp, and ir and nmr spectra.

B. Phosphorus oxychloride (5 ml) and 100 mg (0.625 mmol) of 6-methyl-1,6-naphthyridin-5(6*H*)-one were combined in a sealed tube and heated at 170° for 20 hr. The residue (81.4 mg), isolated as indicated above, was sublimed at 60–70°: yield 64 mg (62.5%); mp 106.5–107° (lit.[9] 107°); ir and nmr spectra were superimposable with that isolated earlier.

Registry No.—1, 19693-54-0; 2, 53731-30-9; 3, 23616-32-2; 4, 53731-31-0; 1,6-naphthyridine-6-methiodide, 37960-58-0; 1,6-naphthyridine, 253-72-5; 5-methoxy-8-chloro-1,6-naphthyridine, 53731-32-1.

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Condensation of 2-Benzoyl-1,2-dihydroisoquinaldonitrile Hydrofluoroborate with Ethyl Cinnamate and Related Compounds

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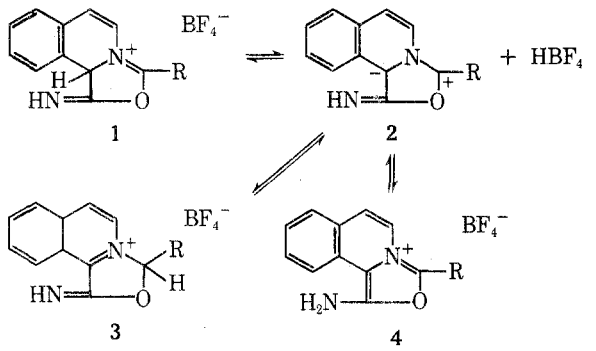
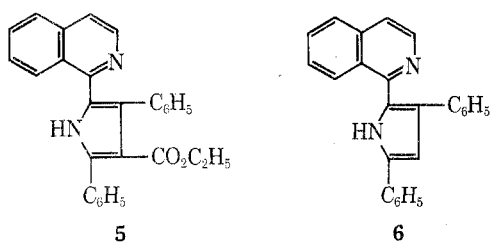
Evidence has been presented[1] that freshly prepared hydrofluoroborate salts of 2-acyl-1,2-dihydroisoquinaldonitriles (Reissert compounds[2]) have the structure 1, but, in solution, an equilibrium mixture of 1, 3, and 4 results. These salts are also presumed to be in equilibrium with the 1,3-dipolar compound 2 (a mesoionic compound) and fluoroboric acid. Several studies of 1,3-dipolar addition reactions of hydrofluoroborate salts of Reissert compounds



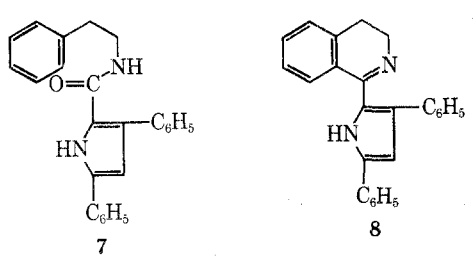
have been reported.[3-6] Numerous examples of complex, acid-catalyzed condensation–rearrangement reactions of Reissert compounds with olefins have also been reported.[7-10] It is believed that these condensation–rearrangement reactions involve an initial Diels–Alder type of condensation of the olefin with the isomeric form 4 of the Reissert salt, and detailed mechanisms of reaction have beer suggested.[9,10] We now wish to report, as a useful synthetic procedure, the condensation of 2-benzoyl-1,2-dihydroisoquinaldonitrile hydrofluoroborate (1, R = C_6H_5) with ethyl cinnamate and related compounds.

Ethyl 3,5-diphenyl-2-(1-isoquinolyl)pyrrole-4-carboxylate (5) has been obtained in 64% yield by treatment of 2-



benzoyl-1,2-dihydroisoquinaldonitrile hydrofluoroborate (1, R = C_6H_5) with ethyl cinnamate in dimethylformamide solution for 20 hr at room temperature. The reaction was regiospecific, and no isomeric product could be found in the reaction mixture.

The first step in the proof of structure of 5 (apart from routine spectral and elemental analyses) was its acid-catalyzed hydrolysis and decarboxylation to give 2-(1-isoquinolyl)-3,5-diphenylpyrrole (6). The known[11] 2,4-diphenylpyrrole was the principal starting material for an unambiguous synthesis of 6. An exchange reaction with ethylmagnesium bromide and subsequent treatment with ethyl chloroformate provided ethyl 2,4-diphenylpyrrole-5-carboxylate. Condensation of the ester with β-phenethylamine gave *N*-(2-phenethyl)-3,5-diphenylpyrrole-2-carboxamide (7). Bischler–Napieralski cyclization of the amide provided 2-(3,4-dihydro-1-isoquinolyl)-3,5-diphenylpyrrole (8), which afforded 6 by catalytic dehydrogenation.



The condensation of 1 (R = C_6H_5) with ethyl *p*-nitrocinnamate gave, in 62% yield, a single product which, on the basis of analogy and spectral comparisons, is assigned the structure of ethyl 2-(1-isoquinolyl)-3-(*p*-nitrophenyl)-5-phenylpyrrole-4-carboxylate. The condensation of 1 (R = C_6H_5) with ethyl acrylate, methylene chloride–ethanol being used as cosolvents in this case, also proceeded smoothly to give, in 67% yield, the known[10] ethyl 2-(1-isoquinolyl)-5-phenylpyrrole-3-carboxylate. Once again, no isomeric product was detected.

The herein described method for the preparation of highly substituted pyrroles appears to be reasonably general and regiospecific, and therefore it can serve as a useful synthetic procedure. Detailed kinetics studies are being initiated, and these plus other approaches should provide additional insights into the general mechanism proposed previously.[3,10,12]

Experimental Section[13]

2-Benzoyl-1,2-dihydroisoquinaldonitrile Hydrofluoroborate (1, R = C_6H_5). This compound, mp 196–198° dec, was prepared as described previously.[5]

Condensation of 1 (R = C_6H_5) with Ethyl Cinnamate. A mixture of 2.28 g (6.55 mmol) of 2-benzoyl-1,2-dihydroisoquinaldonitrile hydrofluoroborate (1, R = C_6H_5), 1.16 g (6.58 mmol) of ethyl cinnamate, and 20 ml of dimethylformamide was stirred at room temperature for 20 hr, and the mixture was then poured into 500 ml of water. The aqueous suspension was extracted five times with benzene (1 l. total). The benzene extract was dried over anhydrous magnesium sulfate, filtered, and concentrated to a small volume. This was chromatographed on neutral alumina, benzene–chloroform (1:1) being used as the eluent. Ethyl 3,5-diphenyl-2-(1-isoquinolyl)pyrrole-4-carboxylate (5) was obtained by evaporation of the eluent of the first light yellow band. After crystallization from 95% ethanol, this compound weighed 1.75 g (64%): mp 169–170°; ir ($CHCl_3$) 3440 (NH) and 1700 cm^{-1} (ester C=O); nmr ($CDCl_3$) δ 0.96 (t, 3 H, *J* = 10 Hz), 4.04 (q, 2 H, *J* = 10 Hz), 6.8–7.8 (m, 16 H), 13.50 (s, 1 H).

Anal. Calcd for $C_{28}H_{22}N_2O_2$: C, 80.36; H, 5.30; N, 6.69; O, 7.65. Found: C, 80.16; H, 5.38; N, 6.50; O, 7.82.

A somewhat higher yield (70%) of 5 was obtained when methylene chloride–ethanol was used as the solvent at the reflux temperature. The detailed procedure is the same as that described below for the preparation of ethyl 2-(1-isoquinolyl)-5-phenylpyrrole-3-carboxylate.

Decarbethoxylation of 5. A mixture of 0.60 g (1.4 mmol) of 5 and 6 ml of 85% phosphoric acid was refluxed for 30 min under a nitrogen atmosphere. The reaction mixture was poured onto ice and neutralized with concentrated ammonia water. A yellow solid which precipitated was collected by filtration and crystallized twice from 95% ethanol. There was obtained 0.20 g (25%) of 2-(1-isoquinolyl)-3,5-diphenylpyrrole (6): mp 226–228°; ir ($CHCl_3$) 3460 (NH), 3080, 3025, 1605, 1587, 1552, 1500, 1470, 1405, 1354, 830, 700 cm^{-1} (the peaks of medium intensity); nmr ($CDCl_3$) δ 6.90 (d, 1 H, *J* = 3 Hz), 7.0–8.3 (m, 16 H), 12.15 (s, broad, 1 H).

Anal. Calcd for $C_{25}H_{18}N_2$: C, 86.67; H, 5.24; N, 8.09. Found: C, 86.50; H, 5.32; N, 7.68.

Ethyl 2,4-Diphenylpyrrole-5-carboxylate. The method employed was a modification of the procedure used for the preparation of ethyl 2,3,4-trimethylpyrrole-5-carboxylate.[14]

Ethylmagnesium bromide was prepared from 14.50 g (0.134 mol) of ethyl bromide and 3.23 g (0.132 mol) of magnesium turnings in 180 ml of absolute ether. To this solution was added as rapidly as possible, consistent with frothing due to evolution of ethane, a solution of 18.0 g (0.082 mol) of 2,4-diphenylpyrrole in 400 ml of anhydrous ether, and the mixture was refluxed for 30 min. The mixture was cooled to room temperature, and a solution of 12.00 g (0.110 mol) of ethyl chloroformate in 30 ml of anhydrous ether was added dropwise. The mixture was refluxed with stirring for 2.5 hr and then allowed to stand at room temperature for 10 hr. To the cooled mixture was added 120 ml of saturated ammonium chloride solution and then 120 ml of water. The ether layer was separated from the aqueous layer and washed twice with 200 ml of water. Concentration of the ether solution, which had been dried over anhydrous sodium sulfate, led to crystallization of the product. This was washed with cold alcohol and crystallized from 95% ethanol to give 7.30 g (31%) of colorless ethyl 2,4-diphenylpyrrole-5-carboxylate: mp 140–144°; ir ($CHCl_3$) 3440 (NH), 1670 (ester C=O) cm^{-1}; nmr ($CDCl_3$) δ 1.21 (t, 3 H, *J* = 6.7 Hz), 4.24 (q, 2 H, *J* = 6.7 Hz), 6.63 (d, 1 H, *J* = 3 Hz), 7.1–7.8 (m, 10 H), 9.67 (s, broad, 1 H).

Anal. Calcd for $C_{19}H_{17}NO_2$: C, 78.33; H, 5.88; N, 4.81. Found: C, 78.14; H, 5.70; N, 4.63.

***N*-(2-Phenethyl)-3,5-diphenylpyrrole-2-carboxamide (7).** A mixture of 6.30 g (0.022 mol) of ethyl 2,4-diphenylpyrrole-5-carboxylate and 8.47 g (0.070 mol) of β-phenethylamine was heated at 240–250° for 8 hr. The dark brown liquid was cooled to room temperature and then induced to deposit crystals by addition of small amounts of ether and Skelly B solvent. The solid was washed with ether and crystallized from 95% ethanol to give 2.80 g (35%) of **7**: mp 177–179°; ir ($CHCl_3$) 3435 (NH), 1627 (amide C=O) cm^{-1}; nmr ($CDCl_3$) δ 2.68 (t, 2 H, J = 6.7 Hz), 3.52 (q, 2 H, J = 6.7 Hz), 5.85 (t, broad, 1 H), 6.49 (d, 1 H, J = 3 Hz), 6.9–7.8 (m, 15 H), 10.55 (s, broad, 1 H).

Anal. Calcd for $C_{25}H_{22}N_2O$: C, 81.93; H, 6.05; N, 7.65. Found: C, 82.14; H, 6.04; N, 7.60.

2-(3,4-Dihydro-1-isoquinolyl)-3,5-diphenylpyrrole (8). A mixture of 1.0 g (2.7 mmol) of **7** and 10 g of phosphorus pentoxide in 15 ml of anhydrous *p*-xylene was heated under reflux for 6 hr. The hot *p*-xylene layer was decanted from a black, insoluble residue. The residue was added to 600 ml of ice-cold water with stirring, and a brown solid which formed was collected by filtration, washed with water, and suspended in concentrated sodium hydroxide solution. The suspension was diluted with water and then neutralized with 6 *N* sulfuric acid. The mixture was extracted with benzene, and the benzene extract was washed with water and dried over anhydrous magnesium sulfate. The solvent was evaporated, and the residue was chromatographed on alumina by the dry column technique.[15] Elution with benzene produced a yellow band near the top of the column, and this was cut out and extracted with benzene. Evaporation of the benzene gave a brown solid, which was crystallized from 95% ethanol–Skelly B solvent. A crystalline product of mp 209–211° was recrystallized from acetone to give 0.20 g (21%) of **8**: mp 214–216°; ir ($CHCl_3$) 3440 (NH), 1601 (C=N) cm^{-1}; nmr ($CDCl_3$) δ 2.70 (t, 2 H, J = 7 Hz), 3.60 (t, 2 H, J = 7 Hz), 6.76 (s, 1 H), 6.8–7.8 (m, 14 H), 10.26 (s, broad, 1 H).

Anal. Calcd for $C_{25}H_{20}N_2$: C, 86.17; H, 5.79. Found: C, 86.14; H, 5.85.

2-(1-Isoquinolyl)-3,5-diphenylpyrrole (6). A mixture of 0.15 g (0.43 mmol) of **8** and 0.08 g of 10% palladium-on-carbon catalyst was suspended in 6 ml of decalin and refluxed in a nitrogen atmosphere, with stirring, for 5 hr. The mixture was filtered, and the filtrate was evaporated to dryness by application of a jet of air. The residue was triturated in petroleum ether, then crystallized from benzene–Skelly B solvent. The product, mp 221–223°, was chromatographed on alumina by the dry column technique.[14] Two yellow bands were developed by elution with benzene. The eluent of the first yellow band gave 0.06 g (40%) of **6** on evaporation, mp 226–228° (after recrystallization from 95% ethanol), also in admixture with the sample prepared by decarbethoxylation of **5**. The ir and nmr spectra of the two samples were identical.

Condensation of 1 (R = C_6H_5) with Ethyl *p*-Nitrocinnamate. The reaction of 2.32 g (6.66 mmol) of **1** (R = C_6H_5) with 1.45 g (6.55 mmol) of ethyl *p*-nitrocinnamate in 20 ml of dimethylformamide was carried out in the same manner as described previously for the corresponding ethyl cinnamate reaction. There was obtained 1.88 g (62%) of yellow crystals of ethyl 2-(1-isoquinolyl)-3-(*p*-nitrophenyl)-5-phenylpyrrole-4-carboxylate: mp 224–225°; ir ($CHCl_3$) 3440 (NH), 1700 (ester C=O), 1345 (NO_2), 1510 (NO_2) cm^{-1}; nmr ($CDCl_3$) δ 1.00 (t, 3 H, J = 7 Hz), 4.10 (q, 2 H, J = 7 Hz), 7.0–8.1 (m, 15 H), 13.80 (s, 1 H).

Anal. Calcd for $C_{28}H_{21}N_3O_4$: C, 72.56; H, 4.57; N, 9.07. Found: C, 72.72; H, 4.45; N, 8.89.

Condensation of 1 (R = C_6H_5) with Ethyl Acrylate. A mixture of 1.5 g (4.31 mmol) of **1** (R = C_6H_5), 3 ml of ethyl acrylate, and 30 ml of methylene chloride was heated under reflux as 95% ethanol was added slowly until the solution became clear, 70 ml being required. The solution was refluxed for another hr, and the solvents were removed by evaporation in a rotary evaporator. The reddish residue was extracted with 300 ml of benzene and chromatographed on neutral alumina to give a yellow, gummy material. This was induced to crystallize from a mixture of ethyl acetate and Skelly B solvent. There was obtained 0.99 g (67%) of ethyl 2-(1-isoquinolyl)-5-phenylpyrrole-3-carboxylate, mp 149–150°, also in admixture with a sample of the known[10] compound. The ir and nmr spectra of the two samples, taken in chloroform and deuteriochloroform, respectively, were identical.

Acknowledgment. This work was supported in part by a grant from the National Science Foundation.

Registry No.—**1** (R = C_6H_5), 33969-32-3; **5**, 53778-22-6; **6**, 53778-23-7; **7**, 53778-24-8; **8**, 53778-25-9; ethyl cinnamate, 103-36-6; ethyl 2,4-diphenylpyrrole-5-carboxylate, 53778-26-0; ethyl bromide, 74-96-4; 2,4-diphenylpyrrole, 3274-56-4; β-phenethylamine, 64-04-0; ethyl *p*-nitrocinnamate, 953-26-4; ethyl 2-(1-isoquinolyl)-3-(*p*-nitrophenyl)-5-phenylpyrrole-4-carboxylate, 53778-27-1; ethyl acrylate, 140-88-5.

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Synthesis of 2-Methylpiperidine-*2-d*. Choice of Reductive Methods from Azomethine Precursors[1]

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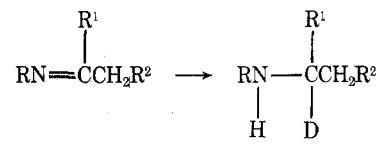
The synthesis of *2-d* 2-alkylamines by reductive methods from azomethine precursors (eq 1) is attended with some



(1)

difficulties. We wish to report a simple method avoiding these problems.

Thus, catalytic deuteration (PtO_2) of 2-methyl-Δ^1-piperideine[2] in methyl acetate gave a product showing two signals of equal intensity for the methyl group in its NMR spectrum: a doublet (J = 6 Hz) at 1.05 ppm and a singlet at 1.05 ppm. From the ratio of methyl protons:methylene protons at C-3, 4, and 5 (m, 1.15–2.05 ppm):methylene protons at C-2 and 6 (m, 2.4–3.4 ppm), the composition of the mixture was 20% each of **2a** and **2b** and 30% each of **2c** and **2d**; mass spectral data confirmed *m/e* 99, 100, and 101.

This result may be explained by the possibility of rearrangement of the azomethine **1** to the tautomeric enamine **3**,[3] allowing hydrogen from position 3 to enter the pool. Olefins are known to isomerize on catalytic hydrogenation,[4] leading to a mixture of reduction products.[5] Alternatively, the known[4] reversibility of the hydrogenation step could result in the introduction of hydrogen (as DH) into the