Research on Heterocyclic Compounds. XLIII. Synthetic Studies on 1,4-Dihydropyridine Derivatives

Maria Grazia Rimoli[1]*, Lucia Avallone[1], Serena Zanarone[1], Enrico Abignente[1], Alfonso Mangoni[2]

[1]Dipartimento di Chimica Farmaceutica e Tossicologica,
[2]Dipartimento di Chimica delle Sostanze Naturali,
Facoltà di Farmacia, Università di Napoli Federico II,
Via Domenico Montesano 49, 80131 Napoli, Italy

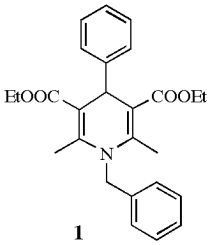
Received September 21, 2000
Received Revised May 29, 2002

In order to obtain *N*-benzyl-3,5-dicarbethoxy-2,6-dimethyl-4-phenyl-1,4-dihydropyridine **1** as a lead compound of pharmacological interest, the classical Hantzsch synthetic method and the modified Collie procedure were used. However, only a very low yield of **1** was obtained in a mixture with larger amounts of some by-products (**2**, **3**, **4**). Compound **1** was then synthesized in satisfactory yield *via* a different method, together with another by-product (**9**). The structures of all by-products were elucidated and possible mechanisms leading to the formation of such compounds are described.

J. Heterocyclic Chem., **39**, 1117(2002).

Introduction.

As part of a research program directed towards the design and synthesis of lead compounds potentially interesting as drugs, we have taken into consideration compound **1** (Figure 1) as a possible starting point to obtain new substances with pharmacological activity in the cardiovascular field.



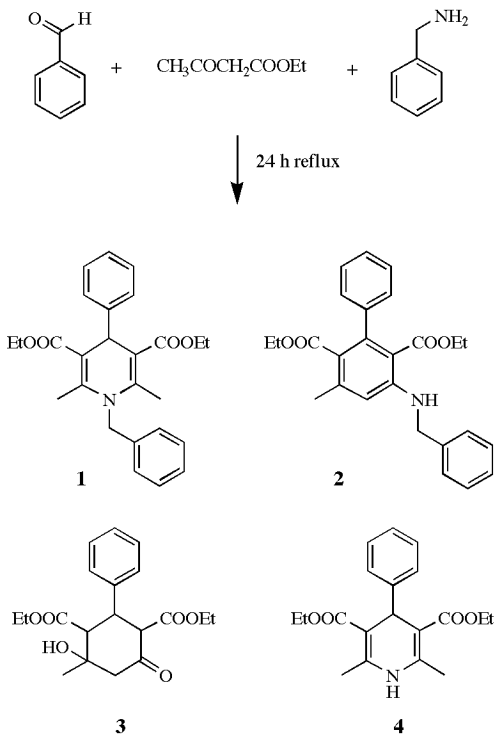
1

Figure 1

Compound **1**, namely *N*-benzyl-3,5-dicarbethoxy-2,6-dimethyl-4-phenyl-1,4-dihydropyridine, was prepared by Sausins *et al.* [1] together with a series of analogues and later by Vanden Eynde *et al.* [2] using different synthetic methods. Sausins *et al.* employed the classical cyclocondensation procedure first described by Hantzsch [3], which involved the one-pot reaction of an aldehyde, an acetoacetic ester and ammonium hydroxide, without isolation of intermediates. In order to obtain **1**, the starting compounds must be benzaldehyde, ethyl acetoacetate and benzylamine (in place of ammonium hydroxide), respectively. We have adopted this method, starting from a 1:2:1 mixture of the above compounds (Scheme I) which was stirred at reflux for 24 hours.

In our hands this procedure gave disappointing results: after the work-up and column chromatography of the crude reaction product, only a small amount of the required compound **1** was isolated, together with larger quantities of three other products (**2**, **3**, **4**; Scheme I). The first product eluted was *N*-benzyl-2,4-dicarbethoxy-5-methyl-3-phenylaniline **2** (5% yield), followed by compound **1** (1% yield) and then by 3,5-dicarbethoxy-2,6-dimethyl-4-phenyl-1,4-dihydropyridine **4** (3%) and 2,4-dicarbethoxy-5-hydroxy-5-methyl-3-phenylcyclohexanone **3** (48%). The structures of these four compounds were elucidated by ^{1}H- and ^{13}C-nmr spectra and mass spectra. Two-dimensional nmr experiments (HMQC and HMBC) were also acquired for compounds **2** and **3**.

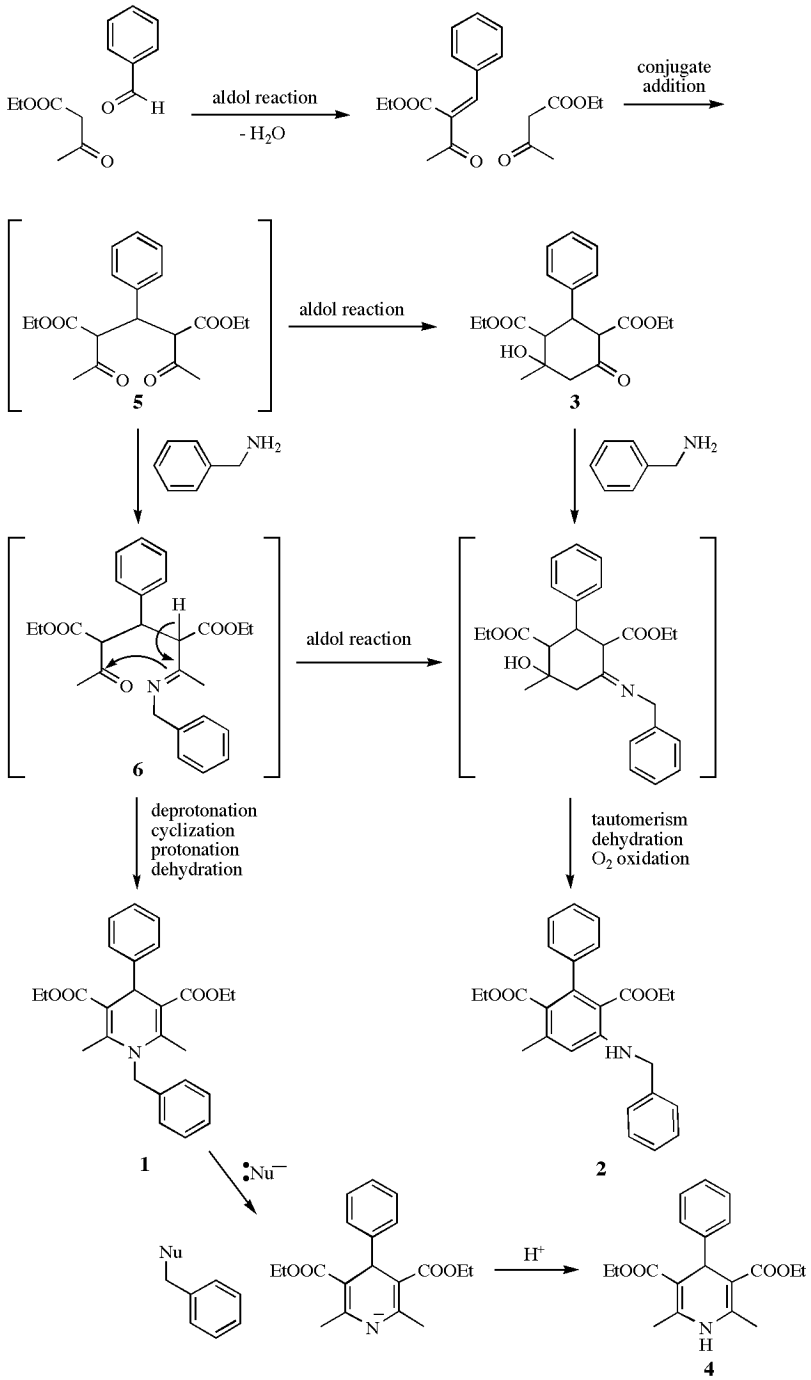
Scheme I



It should be noted that compound **4** is well known and cited in a number of literature references, starting from the ancient papers published by Hantzsch [3], Schiff [4] and Knoevenagel [5] up to recent reports [6-8]. Also cyclohexanone **3** is already known [9-15]. The only compound unknown is **2**.

A possible reaction mechanism leading to the formation of compounds **1**-**4** is depicted in Scheme II. The bis-adduct of ethyl acetoacetate to benzaldehyde (**5**) may undergo an intramolecular aldol reaction yielding the cyclohexanone **3**. This side-reaction of the Hantzsch synthesis has already been described for similar compounds [16]. Compound **3** could in turn react with benzylamine to give an imine, that after dehydration, tautomerism and oxidation (presumably by atmospheric O_2) would lead to the aniline **2**. Alternatively, the addition of benzylamine (giv-

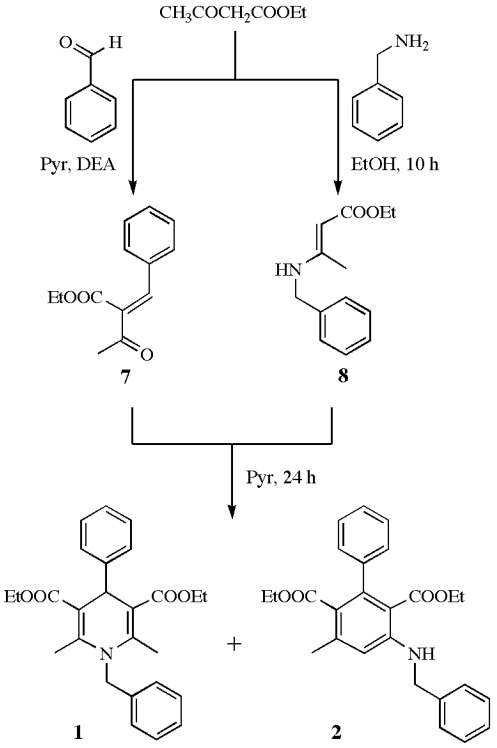
Scheme II



ing the intermediate **6**) could precede the intramolecular aldol reaction. The origin of the dihydropyridine **4** is more difficult to explain. The most probable hypothesis involves the nucleophilic attack of any of the nucleophiles present in the reaction mixture on the benzylic methylene, with subsequent loss of the resonance-stabilized anion of compound **4** as the leaving group.

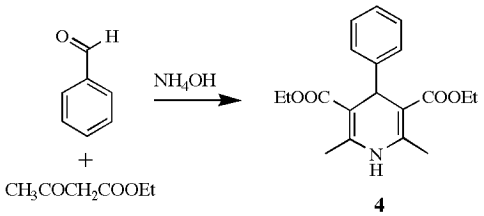
These results showed that the Hantzsch reaction was inadequate to reach the objective of our research: consequently, we attempted a variation of the Hantzsch procedure, developed by Collie [17]. This method involves preliminary preparation of two intermediate compounds (Scheme III), namely ethyl 2-benzylideneacetoacetate **7** and ethyl 3-benzylaminocrotonate **8**: both products were obtained by reaction of ethyl acetoacetate either with benzaldehyde in pyridine or with benzylamine in ethanol, respectively. The cyclocondensation of **7** and **8** was performed in pyridine at room temperature. The required product **1** was obtained together with compound **2** as the only by-product, but this result was not yet satisfactory, because the yield of compound **1** was still very low.

Scheme III

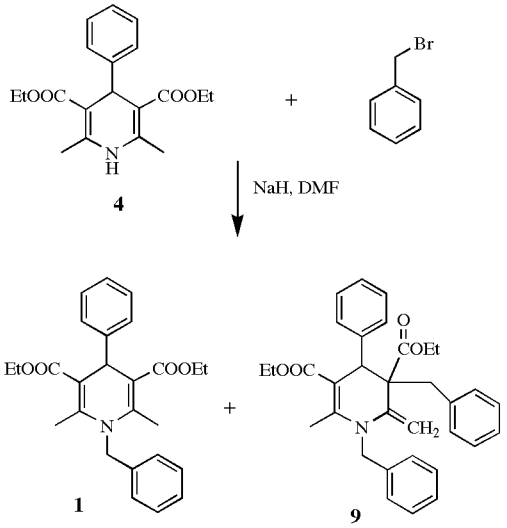


Consequently, we shifted to a different synthetic strategy, involving preparation of 3,5-dicarbethoxy-2,6-dimethyl-4-phenyl-1,4-dihydropyridine **4** and its subsequent *N*-benzylation to give **1**. The best method to prepare **4** turned out to be the classical Hantzsch procedure (Scheme IV), namely the reaction of a mixture of ethyl acetoacetate, benzaldehyde and ammonium hydroxide, which gave **4** in quantitative yield in absence of by-products. The *N*-benzylation of **4** was then performed (Scheme V) by reaction with benzyl bromide and sodium hydride in anhydrous dimethylformamide, giving the target compound **1** in reasonable yield (40%) together with small amounts of unreacted **4**, which was not recovered, and of a by-product. This one was identified as *N*,3-dibenzyl-3,5-dicarbethoxy-6-methyl-2-methylene-4-phenyl-1,2,3,4-tetrahydropyridine **9**, on the basis of its ^{1}H- and ^{13}C-nmr, DEPT and HMQC spectra. The formation of this compound can be reasonably explained by deprotonation of one of the methyl groups in compound **1** using sodium hydride to form the resonance-stabilized anion **10**, which can then react with benzyl bromide at C-3 to give the dibenzyl derivative **9** (Scheme VI). As a consequence, even though the transformation of the starting compound **4** is incomplete, this side-reaction prevents the possibility to increase the reaction yield by forcing the reaction conditions. For example, when we tried to use excess sodium hydride and benzyl bromide, we only obtained increased amounts of the by-product **9**.

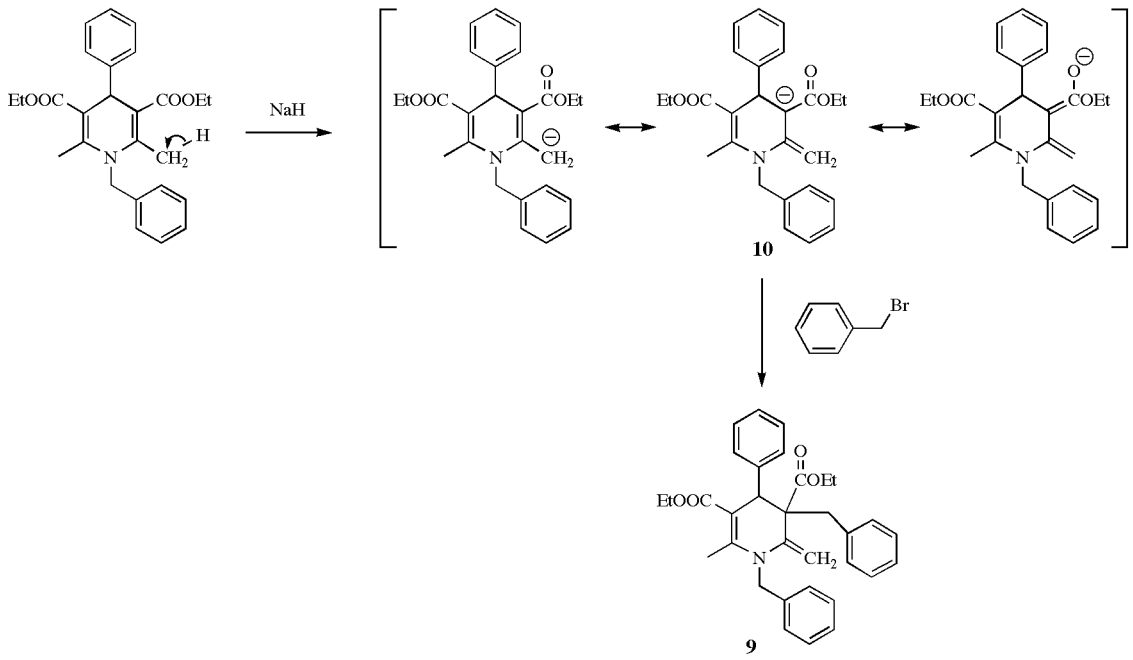
Scheme IV



Scheme V



Scheme VI



In spite of the relatively low yield of the last step, the synthetic procedure described appears reasonably satisfactory for further use of **1** as lead compound of pharmacological interest. However, such *N*-benzyl-1,4-dihydropyridine could undergo *N*-debenzylation *in vivo*: in this case, it would be inadequate for pharmacological purposes. Nevertheless, some reports showed that several similar compounds proved to be stable *in vivo* and to have interesting pharmacological activity. For example, Ohsumi *et al*. [18] synthesized a series of *N*-arylalkyl-4-aryl-3,5-dicarbomethoxy-2,6-dimethyl-1,4-dihydropyridines (including the *N*-benzyl derivative) which showed high antitumor activity *in vitro* and *in vivo* in combination with vincristine and were more potent than verapamil in potentiating the cytoxicity of vincristine. Donkor *et al*. [19] described a series of analogous *N*-adamantyl substituted compounds with radioprotective activity, whereas another series of *N*-substituted (also with benzyl moiety) 1,4-dihydropyrines were described by Lusis and Duburs [20].

EXPERIMENTAL

Analytical thin layer chromatography (tlc) was carried out on precoated (0.25 mm) Merck silica gel 60 F254 plates; detection of compounds was made by uv light and/or treatment with iodine vapours. Preparative chromatography was performed using columns packed with Farmitalia Carlo Erba silica gel RS (0.05-0.20 mm). Melting points were determined by a Kofler hot-stage microscope and are uncorrected. ^{1}H- and ^{13}C-nmr spectra were recorded on a Bruker AMX-500 spectrometer equipped with a Bruker X-32 computer, using deuterated solvents and tetramethylsilane as internal standard (δ scale). Mass spectra were recorded at 70 eV on a VG Prospec-Autospec (Fisons) mass spectrometer. Elemental analyses were within ±0.4% of the theoretical values.

Hantzsch Procedure for Preparation of Compound **1**.

A mixture of 20 ml (0.2 mol) of benzaldehyde, 50 ml (0.4 mol) of ethyl acetoacetate and 22 ml (0.2 mol) of benzylamine was stirred at reflux for 24 hours. The crude reaction product was partitioned between diethyl ether and water. The ethereal phase was dried over anhydrous sodium sulfate, evaporated and purified by column chromatography on silica gel, using chloroform as eluent. The first product eluted was the fluorescent compound **2** (5% yield), followed by the required compound **1** (1% yield) and then by the dihydropyridine **4** (3% yield) and the phenylcyclohexanone **3** (48% yield).

N-Benzyl-3,5-dicarbethoxy-2,6-dimethyl-4-phenyl-1,4-dihydropyridine (**1**).

This compound was obtained as a white powder, mp 157-158° (*n*-hexane); ^{1}H nmr (deuteriochloroform): δ 7.20-7.10 (several overlapping signals, 10H, phenyl protons), 5.12 (s, 1H, 4-H), 4.79 (s, 2H, NCH_2), 4.05 (q, J = 7 Hz, 4H, 3,5-$COOCH_2CH_3$), 2.04 (s, 6H, 2,6-CH_3), 1.20 (t, J = 7 Hz, 6H, 3,5-$COOCH_2CH_3$); ^{13}C nmr (deuteriochloroform): δ 167.9 (two CO), 148.4 (2,6-C), 146.2 (phenyl 1-C), 137.5 (benzyl 1-C), 128.5-125.7 (10 benzyl and phenyl CH), 106.7 (3,5-C), 59.7 (two ethyl CH_2), 49.3 (NCH_2), 38.0 (4-CH), 16.5 (2,6-CH_3), 14.0 (two ethyl CH_3).

Anal. Calcd. for $C_{26}H_{29}NO_4$: C, 74.44; H, 6.97; N, 3.34. Found: C, 74.24; H, 6.79; N, 3.15.

N-Benzyl-2,4-dicarbethoxy-5-methyl-3-phenylaniline (**2**).

This compound was obtained as a white powder, mp 86-87° (*n*-hexane); ^{1}H nmr (deuteriochloroform): δ 7.40−7.15 (several over-

lapping signals, 10H, 3-phenyl and benzyl aromatic protons), 6.90 (br, 1H, NH), 6.40 (s, 1H, 6-H), 4.39 (br, 2H, NCH_2), 3.79, 3.70 (2q, each, 2H, ethyl CH_2, J = 7 Hz), 2.21 (s, 3H, 5-CH_3), 0.79, 0.58 (2t, each, 3H, ethyl CH_3, J = 7 Hz); ^{13}C nmr (deuteriochloroform): δ 168.0 (two CO), 148.0 (5-C), 142.9 (3-C), 140.2 (phenyl 1-C), 139.0 (benzyl 1-C), 138.0 (1-C), 129.0-126.0 (10 benzyl and phenyl CH), 122.9 (2-C), 111.8 (4-C), 111.0 (6-CH), 60.0, 60.1 (two ethyl CH_2), 46.5 (NCH_2), 20.0 (5-CH_3), 12.8, 12.2 (two ethyl CH_3); eims: *m/z* 417 (100), 370 (78), 342 (71), 314 (35), 91 (72).

Anal. Calcd. for $C_{26}H_{27}NO_4$: C, 74.80; H, 6.52; N, 3.35. Found: C, 74.58; H, 6.35; N, 3.23.

2,4-Dicarbethoxy-5-hydroxy-5-methyl-3-phenylcyclohexanone (**3**).

This compound was obtained as an amorphous solid; mp 156-157° (*n*-hexane); ^{1}H nmr (deuteriochloroform): δ 7.25-7.15 (some overlapping signals, 5H, phenyl protons), 3.97 (q, 2H, 2-COOC*H*$_2$CH$_3$), 3.92 (m, 1H, 3-H), 3.78 (q, 2H, 4-COOC*H*$_2$CH$_3$), 3.69 (s, 1H, 5-OH), 3.64 (d, J = 10 Hz, 1H, 2-H), 2.99 (d, J = 10 Hz, 1H, 4-H), 2.66 (d, J = 12 Hz, 1H, 6-H), 2.47 (br d, J = 12 Hz, 1H, 6-H), 1.30 (s, 3H, 5-CH_3), 0.98 (t, J = 7 Hz, 3H, 2-COOCH$_2$C*H*$_3$), 0.75 (t, J = 7 Hz, 3H, 4-COOCH$_2$C*H*$_3$); ^{13}C nmr (deuteriochloroform): δ 201.1 (1-CO), 173.6 (2-COOEt), 167.4 (4-COOEt), 137.8 (phenyl 1-C), 128.4-127.5 (five phenyl CH), 72.8 (5-C), 62.2 (2-CH), 60.8 (two ethyl CH_2), 56.7 (4-CH), 52.4 (6-CH_2), 45.0 (3-CH), 28.4 (5-CH_3), 13.6-13.2 (two ethyl CH_3); fabms (glycerol, positive ion mode): *m/z* 349 (100).

Anal. Calcd. for $C_{19}H_{24}O_6$: C, 65.50; H, 6.94. Found: C, 65.22; H, 6.74.

3,5-Dicarbethoxy-2,6-dimethyl-4-phenyl-1,4-dihydropyridine (**4**).

This compound was obtained as a white powder, mp 156-157° (*n*-hexane); ^{1}H nmr (deuteriochloroform): δ 7.30-7.10 (some overlapping signals, 5H, phenyl protons), 6.10 (s, 1H, NH), 5.02 (s, 1H, 4-H), 4.10 (q, J = 7 Hz, 4H, 3,5-COOC*H*$_2$CH$_3$), 2.30 (s, 6H, 2,6-CH_3), 1.25 (t, J = 7 Hz, 6H, 3,5-COOCH$_2$C*H*$_3$); ^{13}C nmr (deuteriochloroform): δ 167.5 (two CO), 147.5 (2,6-C), 144.0 (phenyl 1-C), 128.5-126.1 (five phenyl CH), 104.1 (3,5-C), 60.0 (two ethyl CH_2), 40.0 (4-CH), 19.8 (2,6-CH_3), 14.0 (two ethyl CH_3).

Anal. Calcd. for $C_{19}H_{23}NO_4$: C, 69.28; H, 7.04; N, 4,25. Found: C, 69.04; H, 6.84; N, 4.16.

Collie Procedure for Preparation of Compound **1**.

To a solution of 2 ml (0.02 mol) of benzaldehyde in pyridine, cooled at 0°, 2.5 ml (0.02 mol) of ethyl acetoacetate and some drops of diethylamine were added. The solution was stirred at room temperature for 10 hours and then evaporated obtaining the first intermediate product, namely ethyl 2-benzylideneacetoacetate **7**. At the same time, a mixture of 2.7 ml (0.02 mol) of benzylamine and 2.5 ml (0.02 mol) of ethyl acetoacetate in ethanol was stirred and refluxed for 10 hours. The solution was then evaporated in order to obtain the second intermediate product, namely ethyl 3-benzylaminocrotonate **8**, which was dissolved in pyridine and added to the first compound **7**. The mixture was stirred at room temperature for 24 hours, then evaporated and extracted with chloroform. The extract was washed with water, dried over sodium sulfate, concentrated and purified by column chromatography on silica gel, using ethyl acetate/*n*-hexane as eluent. The first product eluted was **2**, followed by the required compound **1** (2% yield).

Hantzsch Procedure for Preparation of Compound **4**.

A mixture of 10 ml (0.08 mol) of ethyl acetoacetate, 4 ml (0.04 mol) of benzaldehyde and 4 ml of concentrated ammonia was stirred and refluxed for 3 hours. The crude reaction product was partitioned in dichloromethane/water mixture. The organic phase was dried on anhydrous sodium sulfate and then evaporated to give 13 g of compound **4** (100% yield).

Preparation of Compound **1** by *N*-Benzylation of Compound **4**.

The reaction was carried out under a nitrogen atmosphere. A solution of 1 g of **4** (3 mmol) in dry dimethylformamide was stirred at room temperature and added dropwise with 100 mg of sodium hydride (60% dispersion in mineral oil). After 30 min the reaction mixture was cooled at 0° and 375 mg (1.5 mmol) of benzyl bromide were added. After 30 min cooling was stopped and the same amounts of sodium hydride and benzyl bromide were added again. The reaction was run at 0° for 30 min and then at room temperature for 60 min. The mixture was evaporated and extracted with diethyl ether. The organic phase was washed with water, dried over sodium sulfate, concentrated and purified by column chromatography on silica gel, using dichloromethane as eluent. The first product eluted in small amount was compound **9**, followed by the required compound **1** (40% yield).

N,3-Dibenzyl-3,5-dicarbethoxy-6-methyl-2-methylene-4-phenyl-1,2,3,4-tetrahydropyridine (**9**).

This compound was obtained as an amorphous solid. ^{1}H nmr (deuteriochloroform): δ 7.40-7.15 (several overlapping signals, 15H, aromatic protons), 5.19 (d, J = 12 Hz, 1H, *N*-CH_2Ph), 4.82 (br s, 1H, 2-CH_2), 4.65 (d, J = 12 Hz, 1H, *N*-CH_2Ph), 4.58 (br s, 1H, 2-CH_2), 4.28 (s, 1H, 4-H), 4.02 (q, J = 7 Hz, 2H, 5-COOC*H*$_2$CH$_3$), 3.84 (q, J = 7 Hz, 2H, 3-COOC*H*$_2$CH$_3$), 3.50 (d, J = 11 Hz, 1H, 3-CH_2Ph), 3.08 (d, J = 11 Hz, 1H, 3-CH_2Ph), 2.63 (s, 3H, 6-CH_3), 1.15 (t, J = 7 Hz, 3H, 5-COOCH$_2$C*H*$_3$), 1.03 (t, J = 7 Hz, 3H, 3-COOCH$_2$C*H*$_3$); ^{13}C nmr (deuteriochloroform): δ 171.1 (3-CO), 168.2 (5-CO), 149.0 (6-C), 142.5 (2-C), 138.2 (phenyl 1-C), 137.2 (3-benzyl 1-C), 130.2-125.6 (15 benzyl and phenyl CH), 101.5 (5-C), 99.2 (exocyclic =CH_2), 60.4 (3-COO*C*H$_2$CH$_3$), 59.5 (5-COO*C*H$_2$CH$_3$), 55.4 (3-C), 53.6 (*N*-benzyl CH_2), 48.7 (4-CH), 43.4 (3-benzyl CH_2), 17.2 (6-CH_3), 14.2 (3-COOCH$_2$*C*H$_3$), 13.7 (5-COOCH$_2$*C*H$_3$).

Anal. Calcd. for $C_{33}H_{35}NO_4$: C, 77.77; H, 6.92; N, 2.75. Found: C, 77.65; H, 6.78; N, 2.55.

Acknowledgements.

The NMR spectra were performed at "Centro di Ricerca Interdipartimentale di Analisi Strumentale", Università di Napoli Federico II. The assistance of the staff is gratefully appreciated.

REFERENCES AND NOTES

* Corresponding author; E-mail: rimoli@unina.it; Telephone: 01139-081-678612; Telefax: 01139-081-678609.

[1] A. Sausins, B. Cekavicius, V. Lusis and G. Duburs, *Khim. Geterotsikl. Soedin.*, **16**, 493 (1980); *Chem. Heterocycl. Comp. (Eng. Transl.)*, **16**, 377 (1980).

[2] J. J. Vanden Eynde, A. Mayence, A. Maquestiau and E. Anders, *Synth. Commun.*, **22**, 3291 (1992).

[3] A. Hantzsch, *Justus Liebig's Ann. Chem.*, **215**, 1 (1882).

[4] R. Schiff and J. Puliti, *Ber.*, **16**, 1607 (1883).

[5] E. Knoevenagel, *Ber.*, **31**, 738 (1898).

[6] J. J. Vanden Eynde, P. D'Orazio, A. Mayence, A. Maquestiau and E. Anders, *Tetrahedron*, **48**, 1263 (1992).

[7] R. Martines, H. M. Mendoza and E. Angeles, *Synth. Commun.*, **28**, 2813 (1998).

[8] J. S. Yadav, B. V. S. Reddy, G. Sabitha and S. K. K. Garudammagari, *Synthesis*, **11**, 1532 (2000).

[9] E. Knoevenagel and H. Vieth, *Justus Liebig's Ann. Chem.*, **281**, 59 (1894).

[10] E. Knoevenagel and E. Reinecke, *Ber*., **32**, 418 (1899).

[11] P. Rabe and F. Elze, *Justus Liebig's Ann.Chem.*, **323**, 83 (1902).

[12] E. Knoevenagel, *Ber*., **36**, 2180 (1903).

[13] P. Rabe and D. Spence, *Justus Liebig's Ann.Chem.*, **342**, 328 (1905).

[14] M. A. Metwally, M. S. El-Hussiny, F. Z. El-Ablak and A. M. Khalil, *Pharmazie*, **44**, 261 (1989)

[15] M. A. Metwally, M. S. El-Hussiny, F. Z. El-Ablak and A. M. Khalil, *Pharmazie*, **47**, 336 (1992).

[16] B. Loev, M. M. Goodman, K. M. Snader, R. Tedeschi and E. Macko, *J. Med. Chem.*, **17**, 956 (1974).

[17] J. N. Collie, *Justus Liebig's Ann.Chem.*, **226**, 294 (1884).

[18] K. Ohsumi, K. Ohishi, Y. Morinaga, R. Nakagawa, Y. Suga, T. Sekiyama, Y. Akiyama, T. Tsuji and T. Tsuruo, *Chem. Pharm. Bull.*, **43**, 818 (1995).

[19] I. O. Donkor, X. Zhou, J. Schmidt, K. C. Agrawal and V. Kishore, *Bioorg. Med. Chem*., **6**, 563 (1998).

[20] V. Lusis and G. Duburs, *Khim. Geterotsikl. Soedin.*, **18**, 1067 (1982).