HETEROCYCLES, Vol. 68, No. 2, 2006, pp. 387 - 393. © The Japan Institute of Heterocyclic Chemistry
Received, 5th December, 2005, Accepted, 12th January, 2006, Published online, 17th January, 2006. COM-05-10645

A SYNTHESIS OF *N*-FORMYLENAMIDES OF ISOQUINOLINE

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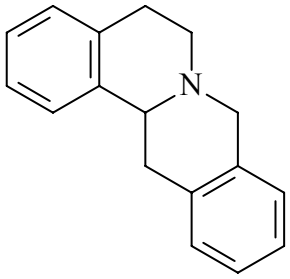
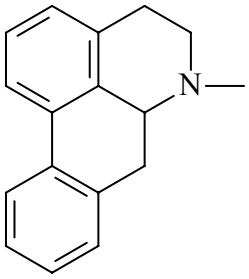
Abstract – *N*-Formylenamides of isoquinoline (**6**) were obtained from *N*-[2-(2-acyl-4,5-dimethoxyphenyl)ethyl]formamides (**5**) by cyclization in the presence of catalytic amount of *p*-toluensulfonic acid. The starting keto formamides (**5**) were obtained by acylation of a *N*-[2-(3,4-dimethoxyphenyl)ethyl]formamides (**1**) with carboxylic acids or their anhydrides in polyphosphoric acid (PPA).

INTRODUCTION

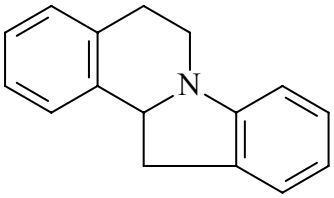
The enamides have proven to be versatile reagents in the contemporary organic synthesis.[1-6] Enamide derivatives of isoquinoline, in particular, have been utilized as starting compounds in numerous asymmetric,[7,8] cycloaddition[9-11] and photochemical reactions for synthesis of isoquinoline alkaloids or their analogs.[12-15] Some enamides of this type, like polycarpine, have also been isolated as natural products.[3] The enamides of isoquinoline are usually synthesized by acylation of 3,4-dihydroisoquinolines with acid chlorides or anhydrides.[1,2] A few years ago we demonstrated a different approach, in which *N*-[2-(2-acyl-4,5-dimethoxyphenyl)ethyl]amides were obtained by acylation of *N*-acyl-3,4-dimethoxyphenylethyl-amines with carboxylic acids in PPA and then cyclized in acidic media to provide various enamides of isoquinoline.[16] The success of this approach depends to an extent on the reaction conditions and on the nature of the *N*-acyl group in the starting compounds, since a cleavage of this group in the course of the reaction would lead to the formation 3,4-dihydroisoquinolines instead of enamides as end products. In this paper we report an extention of this method, allowing the synthesis of *N*-formyl-enamides of isoquinoline, which represent interest as intermediates in the synthesis of protoberberines, aporphines, dibenzopyrrocolines.[12-15] Until now these compounds have been synthesized only by acylation of 3,4-dihydroisoquinolines with formic, formic-acetic or formic-pivalic anhydrides[1,2,7-10] which are not commercially available.



Protoberberine



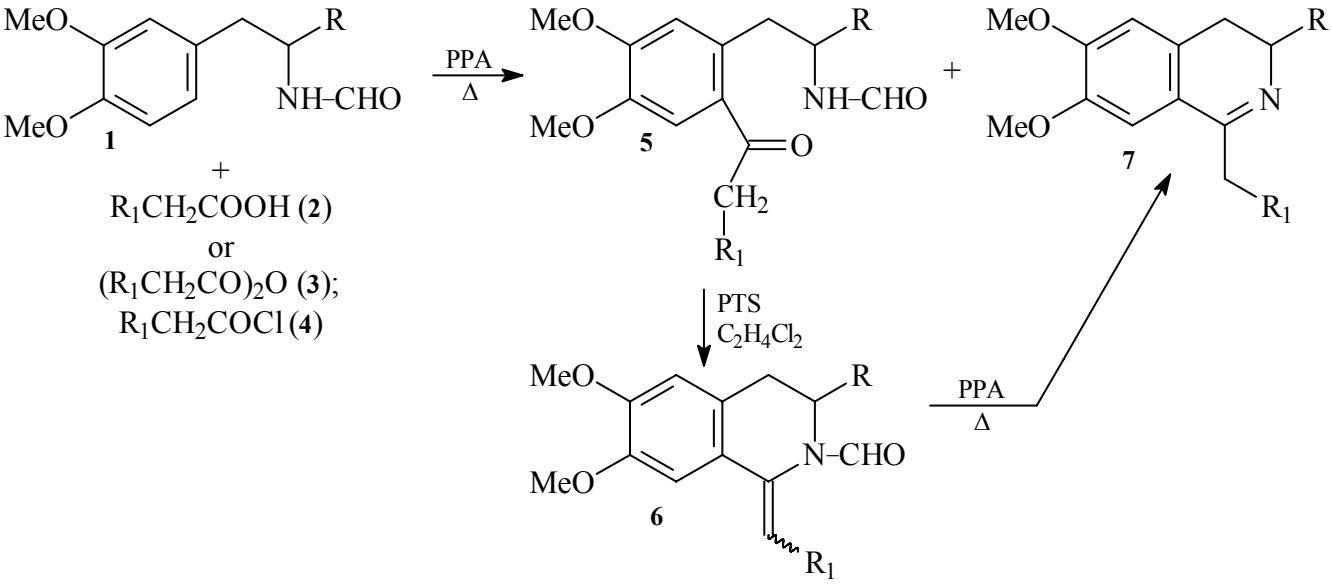
Aporphine



Dibenzopyrrocoline

RESULTS AND DISCUSSION

Our initial studies showed that the reaction of *N*-[2-(3,4-dimethoxyphenyl)ethyl]formamides (**1**)[17] and carboxylic acids in PPA for 2 h at 80°C leads to a mixture of *N*-[2-(2-acyl-4,5-dimethoxyphenyl)-ethyl]formamides (**5a-g**) and 3,4-dihydroisoquinolines (**7a-g**). Later we found that the ratio of **5** to **7** could be increased when the reaction was carried out at lower temperature (50°C), using the more reactive acid chlorides or anhydrides as acylating agents (Table 1).



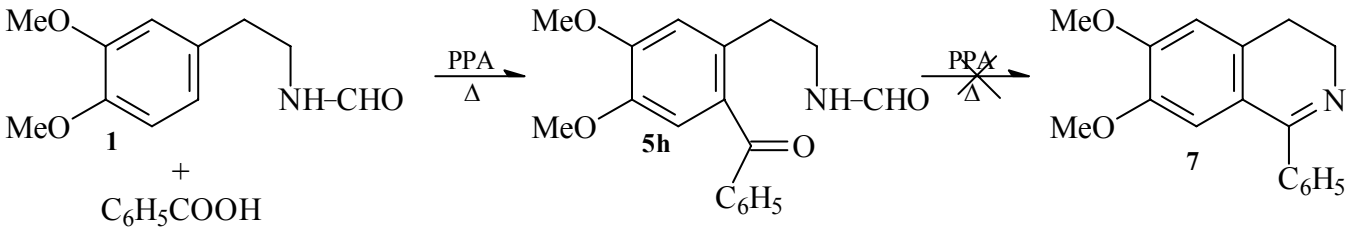
Scheme 1

Table 1

Compound	R	R_1	Yield [%]		
			5	**6**	**7**
a	H	H	60	80	13
b	H	CH_3	53	82	18
c	H	CH_2CH_3	59	65	17
d	H	$CH(CH_3)_2$	61	71	10
e	H	C_6H_5	60	85	13
f	CH_3	H	55	62	19
g	CH_3	C_6H_5	57	70	11

Practically, however, it is more convenient to be used carboxylic acids in this reaction instead of their anhydrides or chlorides. The reaction in this case depended on the order of mixing the reagents. Thus, two equivalents of the carboxylic acid should be mixed with excess of PPA and heated at 50°C for 30 min prior to addition of one equivalent of the formamide (**1**). The increase of **5** to **7** ratio under these conditions could be attributed to an initial formation of anhydride *in situ* from the carboxylic acid. When the reaction was carried out at higher temperatures (80~100°C), the 3,4-dihydroisoquinolines **7** are the predominant product.

We assume that under the reaction conditions enamides (**6**) are initially obtained from **5** and subsequent cleavage of the formyl group in **6** furnishes the 3,4-dihydroisoquinolines (**7**). In support of this assumption, we found that the reaction of formamide (**1**) with benzoic acid under the same conditions stoped at the first stage 3,4-dihydroisoquinoline, (Scheme 2) caused by to give no possibility for enamide formation in this case.



Scheme 2

Furthermore, the cyclization of **5a-g** could be stopped at the enamide stage when milder acidic conditions are applied. Their cyclization in less acidic medium as in the presence of catalytic amount of *p*-toluenesulfonic acid monohydrate (PTS) afforded the corresponding enamides (**5a-g**) to (**6a-g**) for 30 min in refluxing 1,2-dichloroethane solution. When the isolated in this way enamides (**6**) were treated with PPA at 80-100°C, the *N*-formyl group is cleaved and 3,4-dihydroisoquinolines (**7**) were obtained, which are known compounds.[10,16,18]

EXPERIMENTAL

Melting points were determined on a Boëtius hotstage apparatus and are uncorrected. Infrared spectra were recorded on a FT-IR Perkin-Elmer 1750. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker 250 MHz device by using $CDCl_3$ as solvent. Chemical shifts (δ, ppm) were referenced to the chemical shifts of either TMS as an internal standard and coupling constants are indicated in Hz. Unless otherwise noted, all the NMR spectra were taken at room temperature (*ca.* 295 K). MS spectra were recorded on a JEOL JMS-D300 spectrometer (70 eV). All new compounds had correct parent ion peaks by mass spectrometry. All experiments were monitored by TLC using DC Alufolien Kieselgel 60.

Polyphosphoric acid was obtained from 85% phosphoric acid and P_2O_5 (1:1 w/w).

Synthesis of *N*- [2-(2-acyl-4,5-dimethoxyphenyl)ethyl)]formamides (5a-h); Typical procedure:

N-[2-(3,4-dimethoxyphenyl)ethyl]formamides (3 mmol) and the corresponding anhydride (6 mmol) were dissolved in CH_2Cl_2 (5-10 mL) in an open flask and polyphosphoric acid (10 g) was added. (When carboxylic acid was used instead of anhydride then the carboxylic acid was initially mixed with the polyphosphoric acid and the mixture was heated for 30 min at 50°C. To this mixture then was added *N*-[2-(3,4-dimethoxyphenyl)ethyl]formamide). The reaction mixture was stirred carefully at 50ºC for 2 h, then poured on crushed ice and extracted with CH_2Cl_2 (3 x 20 mL). The organic phase was dried over Na_2SO_4, filtered on a short column with neutral Al_2O_3. The products, after evaporation of the solvent, were recrystallized from 2:1hexane-ethyl acetate.

***N*-[2-(2-Acetyl-4,5-dimethoxyphenyl)ethyl]formamide (5a)**: mp 90-92°C. IR (KBr): 3335, 1678, 1655. ^{1}H-NMR: 2.60 (s, 3H), 3.03 (t, 2H, J=6.6 Hz), 3.58 (q, 2H, J=5.5 Hz), 3.92 (s, 3H), 3.93 (s, 3H), 6.68 (s, 1H, br, NH), 6.77 (s, 1H), 7.28 (s, 1H), 8.10 (s, 1H, CHO). ^{13}C-NMR: 29.23, 32.51, 40.04, 55.88, 55.89, 112.79, 113.96, 129.63, 133.98, 146.74, 151.92, 161.33 (NH-CHO), 200.75 (CO). Anal. Calcd for $C_{13}H_{17}NO_4$: C 62.14, H 6.82, N 5.57. Found: C 62.12, H 6.98, N 5.64.

***N*-[2-(4,5-Dimethoxy-2-propionylphenyl)ethyl]formamide (5b)**: mp 101-103°C. IR (KBr): 3321, 1674, 1656. ^{1}H-NMR: 1.16 (t, 3H, J=7.2 Hz), 2.93 (t, 2H, J=6.5 Hz), 2.92 (q, 2H, J=7.2 Hz), 3.53 (q, 2H, J=5.3 Hz), 3.87 (s, 3H), 3.88 (s, 3H), 6.74 (s, 1H), 6.99 (s, 1H, br, NH), 7.13 (s, 1H), 8.06 (s, 1H, CHO). ^{13}C-NMR: 8.40, 32.26, 34.26, 40.27, 55.90, 56.03, 111.73, 113.82, 129.96, 133.42, 146.84, 151.69, 161.49 (NH-CHO), 204.24 (CO). Anal. Calcd for $C_{14}H_{19}NO_4$: C 63.38, H 7.22, N 5.28. Found: C 63.02, H 6.96, N 5.02.

***N*-[2-(2-Butyryl-4,5-dimethoxyphenyl)ethyl]formamide (5c)**: mp 93.5-95°C. IR (KBr): 3325, 1675, 1657. ^{1}H-NMR: 0.96 (t, 3H, J=7.5 Hz), 1.70 (sextet, 2H, J=7.4 Hz), 2.85 (t, 2H, J=7.3 Hz), 2.92 (t, 2H, J=6.8 Hz), 3.53 (q, 2H, J=6.4 Hz), 3.88 (s, 3H), 3.89 (s, 3H), 6.74 (s, 1H), 7.04 (s, 1H, br, NH), 7.11 (s, 1H), 8.07 (s, 1H, CHO). ^{13}C-NMR: 13.72, 17.90, 32.13, 40.35, 43.07, 55.92, 56.07, 111.74, 113.79, 130.30, 133.37, 146.85, 151.70, 161.51 (NH-CHO), 204.06 (CO). Anal. Calcd for $C_{15}H_{21}NO_4$: C 64.50, H 7.58, N 5.01. Found: C 64.21, H 7.45, N 4.96.

***N*-{2-[4,5-Dimethoxy-2-(3-methylbutyryl)phenyl]ethyl}formamide (5d)**: mp 79-82°C. IR (KBr): 3319, 1672, 1654. ^{1}H-NMR: 0.95 (d, 6H, J=6.6 Hz), 2.17-2.24 (m, 1H), 2.74 (d, 2H, J=6.9 Hz), 2.92 (t, 2H, J=6.8 Hz), 3.55 (q, 2H, J=5.2 Hz), 3.88 (s, 3H), 3.89 (s, 3H), 6.74 (s, 1H), 7.03 (s, 1H, br, NH), 7.63 (s, 1H), 8.07 (s, 1H, CHO). ^{13}C-NMR: 22.59, 25.37, 32.01, 40.37, 50.17, 55.91, 56.08, 111.78, 113.76, 130.67, 133.34, 146.83, 151.70, 161.49(NH-CHO), 204.03(CO). Anal. Calcd for $C_{16}H_{23}NO_4$: C 65.51, H 7.90, N 4.77. Found: C 65.21, H 7.85, N 4.74.

***N*-[2-(4,5-Dimethoxy-2-phenylacetylphenyl)ethyl]formamide (5e)**: mp 103-104°C. IR (KBr): 3324, 1672, 1648. ^{1}H-NMR: 2.91(t, 2H, J=6.7 Hz), 3.49 (q, 2H, J=5.5 Hz), 3.87 (s, 3H), 3.89 (s, 3H), 4.20 (s, 2H), 6.74 (s, 1H), 6.77 (s, 1H, br, NH), 7.24 (s, 1H), 7.17-7.35 (m, 5H), 8.03 (s, 1H, CHO). ^{13}C-NMR:

28.66, 38.50, 48.26, 55.83, 56.04, 111.44, 113.31, 127.19, 128.64, 128.85, 129.28, 133.77, 146.72, 152.90, 162.67 (NH-CHO), 200.07 (CO). Anal. Calcd for $C_{19}H_{21}NO_4$: C 69.71, H 6.47, N 4.28. Found: C 69.97, H 6.53, N 4.52.

***N*-[2-(2-Acetyl-4,5-dimethoxyphenyl)-1-methylethyl]formamide (5f)**: mp 124-125°C. IR (KBr): 3320, 1673, 1646. ^{1}H-NMR: 1.33 (d, 3H, J=6.4 Hz), 2.61 (s, 3H), 2.73 (dd, 1H, J=4.3, 14.3 Hz), 3.08 (dd, 1H, J=11.1, 14.3 Hz), 3.91 (s, 3H), 3.92 (s, 3H), 4.15-4.25 (m, 1H), 6.77 (s, 1H), 7.15 (s, 1H), 7.31 (s, 1H, br NH), 7.94 (s, 1H, CHO). ^{13}C-NMR: 21.59, 29.44, 38.60, 47.40, 55.87, 56.05, 112.38, 113.79, 130.18, 133.56, 146.78, 152.02, 160.77 (NH-CHO), 202.3(CO). Anal. Calcd for $C_{14}H_{19}NO_4$: C 63.38, H 7.22, N 5.28. Found: C 63.49, H 7.54, N 5.32.

***N*-{2-[4,5-Dimethoxy-2-(2-oxo-2-phenylethyl)phenyl]-1-methylethyl}formamide (5g)**: mp 122-123°C. IR (KBr): 3318, 1673, 1642. ^{1}H-NMR: 1.28 (d, 3H, J=6.4 Hz), 2.66 (dd, 1H, J=4.3, 11.3 Hz), 2.95 (dd, 1H, J=11.2, 2.2 Hz), 3.88 (s,3H), 3.90 (s, 3H), 4.14-4.30 (m, 1H), 4.20 (s, 2H), 6.76 (s, 1H), 7.19 (s, 1H, br, NH), 7.21 (s, 1H), 7.22-7.35 (m, 5H), 7.90 (s, 1H, CHO). ^{13}C-NMR: 21.6, 38.5, 47.4, 48.4, 55.9, 56.1, 111.8, 113.7, 127.1, 128.7, 129.3, 129.9, 133.8, 146.8, 152.0, 160.8 (NH-CHO), 201.8(CO). Anal. Calcd for $C_{20}H_{23}NO_4$: C 70.36, H 6.79, N 4.10. Found: C 70.44, H 6.53, N 4.25.

***N*-[2-(2-Benzoyl-4,5-dimethoxyphenyl)ethyl]formamide (5h)**: mp 73-75°C from ether. IR (KBr): 3322, 1659, 1648. ^{1}H-NMR: 2.83 (t, 2H, J=8 Hz), 3.40-3.65 (m, 2H), 3.75 (s, 3H), 3.95 (s, 3H), 6.85 (s, 1H), 6.91 (s, 1H), 7.20 (s, 1H, br, NH), 7.45-7.95 (m, 5H), 8.18 (s, 1H, CHO). Anal. Calcd for $C_{18}H_{19}NO_4$: C 68.99, H 6.11, N 4.47. Found: C 68.74, H 6.23, N 4.23.

Synthesis of 1-alkylidene-, 1-phenylmethylidene-3,4-dihydro-1*H*-isoquinoline-2-carbaldehyde (6a-g); Typical procedure: Solution of *N*-[2-(2-acyl-4,5-dimethoxyphenyl)ethyl)]formamides (3 mmol) and a catalytic amount of *p*-toluenesulfonic acid (20 mg) in 20 mL of 1,2-dichloroethane was refluxed for 30 min. The solvent was removed under reduced pressure and the remainder was taken with CH_2Cl_2 and washed with 5% aq. Na_2CO_3. The organic phase was dried over Na_2SO_4. The products, after evaporation of the solvent, were purified by column chromatography on neutral Al_2O_3 with ether as eluent.

6,7-Dimethoxy-1-methylene-3,4-dihydro-1*H*-isoquinoline-2-carbaldehyde (6a): mp 135-137°C (lit.,[8] mp 136.5-138°C). IR (KBr): 1662, 1622. ^{1}H-NMR: 2.75 (t, 2H, J=6 Hz), 3.85 (s, 3H), 3.87 (s, 3H), 3.90 (t, 2H, J=6 Hz), 4.78 (d, 1H, J=2 Hz, C=CH_2), 5.13 (d, 1H, J=2 Hz, C=CH_2), 6.58 (s, 1H), 7.03 (s, 1H), 8.53 (s, 1H, CHO). ^{13}C-NMR: 28.68, 38.59, 55.78, 55.93, 94.60, 106.50, 110.95, 121.84, 127.27, 140.67, 147.88, 149.90, 160.41 (CHO). Anal. Calcd for $C_{13}H_{15}NO_3$: C 66.94, H 6.48, N 6.00. Found: C 66.89, H 6.41, N 6.03.

1-Ethylidene-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinoline-2-carbaldehyde (6b): mp 117-118°C. IR (KBr): 1661, 1620. ^{1}H-NMR ($CDCl_3$): 1.89 (d, 3H, J=7.1 Hz), 2.84 (t, 2H, J=6.1 Hz), 3.86 (t, 2H, J=6.1 Hz), 3.87 (s, 3H), 3.90 (s, 3H), 6.02 (q, 1H, J=7.1 Hz, C=C<u>H</u>-CH_3), 6.58 (s, 1H), 7.03 (s, 1H), 8.21 (s, 1H,

CHO). ^{13}C-NMR: 13.43, 28.41, 38.88, 55.77, 55.91, 105.60, 111.99, 111.34, 123.94, 126.18, 134.52, 147.78, 149.09, 162.07 (CHO). Anal. Calcd for $C_{14}H_{17}NO_3$: C 68.00, H 6.93, N 5.66. Found: C 67.92, H 6.74, N 5.53.

6,7-Dimethoxy-1-propylidene-3,4-dihydro-1*H*-isoquinoline-2-carbaldehyde (6c): mp 110-112°C. IR (KBr): 1663, 1618. ^{1}H-NMR: 1.11 (t, 3H, J=7.5 Hz), 2.29 (pentet, 2H, J=7.4 Hz), 2.84 (t, 2H, J=6.2 Hz), 3.89 (t, 2H, J=6.2 Hz), 3.87 (s, 3H), 3.92 (s, 3H), 5.88 (t, 1H, J=7.4 Hz, C=C<u>H</u>-CH_2-CH_3), 6.58 (s, 1H), 7.30 (s, 1H), 8.22 (s, 1H, CHO). ^{13}C-NMR: 14.59, 21.07, 28.38, 38.99, 55.76, 55.94, 105.66, 111.34, 118.68, 123.89, 126.34, 133.03, 147.77, 149.11, 161.91 (CHO). Anal. Calcd for $C_{15}H_{19}NO_3$: C 68.94, H 7.33, N 5.36. Found: C 68.88, H 7.44, N 5.30.

1-Isobutylidene-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinoline-2-carbaldehyde (6d): mp 153-154°C. IR (KBr): 1661, 1616. ^{1}H-NMR: 1.10 (d, 6H, J=6.5 Hz), 2.65-2.77 (m, 1H), 2.85 (t, 2H, J=6.1 Hz), 3.87 (s, 3H), 3.90 (t, 2H, J=6.1 Hz), 3.93 (s, 3H), 5.71 (d, 1H, J=10.3 Hz, C=CH-), 6.57 (s, 1H), 7.02 (s, 1H), 8.24 (s, 1H). ^{13}C-NMR: 23.5, 26.8, 28.4, 39.2, 55.8, 56.0, 105.7, 111.4, 124.1, 125.1, 126.5, 131.6, 147.8, 149.2, 161.9 (CHO). Anal. Calcd for $C_{16}H_{21}NO_3$: C 69.79, H 7.69, N 5.09. Found: C 69.70, H 7.72, N 5.14.

1-Benzylidene-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinoline-2-carbaldehyde (6e): mp 151-152°C. IR (KBr): 1666, 1635. ^{1}H-NMR: 2.89 (t, 2H, J=6.1 Hz), 3.89 (s, 3H), 3.95 (s, 3H), 3.99 (t, 2H, J=6.1 Hz), 6.61 (s, 1H, C=C<u>H</u>-Ph), 6.81 (s, 1H), 7.22 (s, 1H), 7.19-7.40 (m, 5H), 8.12 (s, 1H, CHO). ^{13}C-NMR: 28.72, 38.53, 55.86, 56.09, 105.75, 111.52, 113.31, 123.28, 126.98, 127.69, 128.68, 128.88, 133.85, 135.24, 147.98, 149.78, 162.66. Anal. Calcd for $C_{19}H_{19}NO_3$: C 73.77, H 6.19, N 4.53. Found: C 73.57, H 6.08, N 4.48.

6,7-Dimethoxy-3-methyl-1-methylene-3,4-dihydro-1*H*-isoquinoline-2-carbaldehyde (6f): mp 98-99°C. IR (KBr): 1664, 1620. ^{1}H-NMR: 1.17 (d, 3H, J=6.8 Hz), 2.59 (dd, 1H, J=15.3, 1.9 Hz), 3.23 (dd, 1H, J=15.3, 5.9 Hz), 3.98 (s, 3H), 4.00 (s, 3H), 4.94 (d, 1H, J=2 Hz, C=CH_2), 5.15 (m, 1H), 5.39 (d, 1H, J=2 Hz, C=CH_2), 6.69 (s, 1H), 7.25 (s, 1H), 8.71 (s, 1H, CHO). ^{13}C-NMR: 17.22, 34.70, 42.66, 55.83, 56.10, 94.22, 112.24, 114.99, 122.70, 125.51, 135.24, 144.8, 147.85, 162.49. Anal. Calcd for $C_{14}H_{17}NO_3$: C 68.00, H 6.93, N 5.66; Found: C 68.20, H 6.87, N 5.70.

1-Benzylidene-6,7-dimethoxy-3-methyl-3,4-dihydro-1*H*-isoquinoline-2-carbaldehyde (6g): mp 42-44°C IR (KBr): 1660, 1618. ^{1}H-NMR: 1.37 (d, 3H, J=6.9 Hz), 2.66 (dd, 1H, J=16.2, 1.2 Hz), 3.33 (dd, 1H, J=16.2, 6.1 Hz), 3.89 (s, 3H), 3.99 (s, 3H), 5.10-5.20 (m, 1H), 6.59 (s, 1H, C=CH-), 6.91 (s, 1H), 7.16-7.45 (m, 6H), 8.09 (s, 1H, CHO). ^{13}C-NMR: 17.23, 34.73, 42.70, 55.86, 56.12, 105.53, 112.21, 114.97, 127.10, 128.58, 128.92, 131.91, 135.24, 147.87, 150.03, 162.59 (CHO). Anal. Calcd for $C_{20}H_{21}NO_3$: C 74.28, H 6.55, N 4.33. Found: C 74.30, H 6.50, N 4.30.

All of the obtained 3,4-dihydroisoquinoline derivatives (**7**) were characterized by their mp, IR and NMR spectra and compared with the data known from the literature.[10,16,18]

ACKNOWLEDGEMENTS

We acknowledge financial support from the Fund for scientific research of the University of Plovdiv.

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