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The Synthesis of 3-Methyl-5-(2-aminoalkyl)isoxazoles

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The reaction of 3,5-dimethylisoxazole with Schiff bases gave 3-methyl-5-(2-aminoalkyl)isoxazole derivatives in the presence of sodium amide in liquid ammonia. The *N*-alkylation on the anilino group of 3-methyl-5-(2-anilino-2-phenylethyl)isoxazole resulted in deamination, thus giving 3-methyl-5-styrylisoxazole. The reaction of 3,5-dimethylisoxazole with benzonitrile gave 3-methyl-5-(2-aminostyryl)isoxazole, which was then reduced to 3-methyl-5-(2-amino-2-phenylethyl)isoxazole.

It has been previously reported[1] that the 5-methyl group of 3,5-dimethylisoxazole (**1**) is metallated by the reaction of sodium amide in liquid ammonia, and that the sodium salt of **1** is alkylated by alkyl halides. Also, **1** reacts with some electrophilic reagents in the presence of butyllithium in anhydrous ether.[2] This paper will describe the reaction of **1** with Schiff bases or benzonitrile in the presence of sodium amide in liquid ammonia; we thus synthesized 3-methyl-5-(2-aminoalkyl)-isoxazole derivatives or 3-methyl-5-(2-aminostyryl)-isoxazole (**10**), which was subsequently reduced to 3-methyl-5-(2-amino-2-phenylethyl)isoxazole (**12**). It is very interesting to synthesize such aminoalkyl-isoxazole derivatives because of their antipyretic, analgetic, antiinflammatory, and antitussive activities.[3]

Results and Discussion

3,5-Dimethylisoxazole (**1**) was treated with an equimolar amount of *N*-benzylideneaniline, one of the Schiff bases, in the presence of an equimolar amount of sodium amide in liquid ammonia to give two products, A (mp 113 °C) and B(mp 236 °C). A was a 1 : 1 adduct of isoxazole and the Schiff base. From the IR and NMR spectra, the structure of A was deduced to be 3-methyl-5-(2-anilino-2-phenylethyl)isoxazole (**2**). For the confirmation of the structure, **2** was hydrogenated on platinum oxide in ethanol to give 1,2-diphenyl-6-methyl-2,3-dihydro-4-pyridone (**3**), which was identical with an authentic sample.[4] The product B was a 1 : 2 adduct of isoxazole and the Schiff base. From the IR and NMR spectra, the structure of B was found to be 3-methyl-5-[2-(1,3-dianilino-1,3-diphenyl)propyl]isoxazole (**4**). The yields of **2** and **4** based on the Schiff base, were 31 and 49% respectively. In the presence of butyllithium in dry THF, **1** and *N*-benzylideneaniline also gave **2** and **4** in yields of 15 and 9% respectively.

Similarly, **1** was treated with *N*-benzylidene-*p*-toluidine in the presence of sodium amide in liquid ammonia to give a 1 : 1 adduct (**5**) and a 1 : 2 adduct (**6**). However, the reaction of **1** with *N*,*N*′-bis(*p*-tolyl)-ethylenediimine[5] gave as the sole product a 2 : 1 adduct, 2,3-di(*p*-toluidino)-1,4-bis(3-methyl-5-isoxazolyl)butane (**7**). In the case of *N*-benzylidenebutylamine, **1** did not react under the condition of either butyllithium in THF or sodium amide in liquid ammonia.

In a previous paper,[1] it was described that 3-methyl-5-*sec*-butylisoxazole was synthesized by the reaction of **1** with an equimolar amount of methyl iodide, followed by a reaction with an equimolar amount of ethyl bromide in the presence of 2 molar amounts of sodium amide. In this reaction, it is suggested that 3-methyl-5-ethylisoxazole anion is formed by the excess sodium amide after the addition of methyl iodide. Therefore, the reaction of **1** with an equimolar amount of benzyl bromide, followed by a reaction with an equimolar amount of *N*-benzylideneaniline, was carried out in the presence of 2 molar amounts of sodium amide. By

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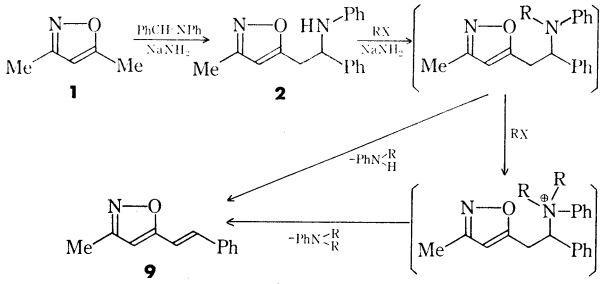
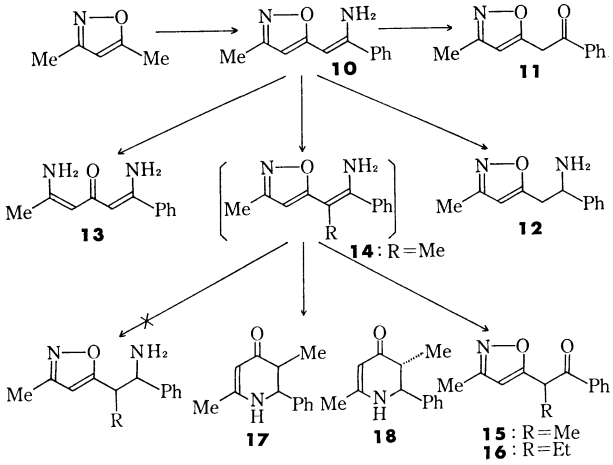


Scheme 1

this reaction, 3-methyl-5-[2-(1-anilino-1,3-diphenyl)-isoxazole (**8**) was obtained in a 25% yield. However the reaction of **1** with an equimolar amount of ethyl bromide, followed by a reaction with an equimolar amount of *N*-benzylideneaniline, gave only 3-methyl-5-*n*-propylisoxazole and no amino derivatives. When 3-methyl-5-*n*-propylisoxazole was treated with *N*-benzylideneaniline in the presence of an equimolar amount of sodium amide, the reaction did not occur and the starting materials were recovered. When **1** was treated with an equimolar amount of *N*-benzylideneaniline, followed by a reaction with an equimolar amount of benzyl bromide in the presence of 2 molar amounts of sodium amide, the expected product (**8**) was not obtained. From the NMR and IR spectra and the elemental analysis, the products were found to be **4**, *N*-benzylaniline, *N,N*-dibenzylaniline, and 3-methyl-5-styrylisoxazole (**9**). Similarly, the reaction products from **1**, *N*-benzylideneaniline and ethyl bromide were found to be **4**, *N*-ethylaniline, *N,N*-diethylaniline, and **9**. These results suggested that the alkylation of **2** occurred on the N atom to give trisubstituted amines and tetrasubstituted ammonium compounds. However, these alkylated compounds were unstable in a basic solution and easily eliminated the amines to produce **9**.

Since the reaction of **1** with benzonitrile catalyzed by butyllithium in ether has been reported to produce 3-methyl-5-benzoylmethylisoxazole (**11**) (mp 72 °C),[2] the reaction of **1** with benzonitrile was reexamined in the presence of sodium amide in liquid ammonia. The resulting residue was directly recrystallized from the *n*-hexane–benzene mixture. From the spectral data and the elemental analysis, the structure of the product



Scheme 2

was deduced to be 3-methyl-5-(2-aminostyryl)isoxazole (**10**). By passing through the silica gel column, **10** was easily hydrolyzed to give **11**, which was identified by a mixed-melting-point determination with an authentic sample and the spectral data. When **10** was reduced with sodium borohydride in methanol, the enamino group of **10** was selectively reduced to give 3-methyl-5-(2-amino-2-phenylethyl)isoxazole (**12**). By the hydrogenation on platinum oxide in ethanol, the isoxazole ring was cleaved, but the enamino group was not reduced. The product was deduced to be 1-phenyl-1,5-diaminohexa-1,4-dien-3-one (**13**), on the basis of the spectral data and the elemental analysis.

Furthermore, **10** was expected to alkylate on either the N atom or the C atom of the enamino group. For determining the alkylation site, **1** was treated with an equimolar amount of benzonitrile, followed by a reaction with an equimolar amount of methyl iodide in the presence of 2 molar amounts of sodium amide. Since the purification of the product (**14**) failed, the mixture was hydrolyzed by passing through a silica gel column. Thereby, 3-methyl-5-(1-benzoylethyl)-isoxazole (**15**), the C-alkylated product, was obtained. Similarly, 3-methyl-5-(1-benzoylpropyl)isoxazole (**16**) was obtained from **1**, benzonitrile, and ethyl bromide. However, it was impossible to detect the *N*-alkylated product by this method. Thus, the hydrogenation of **14** with palladium on charcoal was carried out to give two products. By a study of the IR and NMR spectra and the elemental analysis, the structures of these products were determined to be *cis*- (**17**) and *trans*-2-phenyl-3,6-dimethyl-2,3-dihydro-4(1*H*)pyridone (**18**): no *N*-alkylated products could be detected. These results showed that the *N*-alkylation of enamine (**10**) did not occur, and also that **14** was hydrogenated at the enamino group and then at the isoxazole ring.

In conclusion, the synthesis of 3-methyl-5-(2-amino-alkyl)isoxazoles was accomplished by the reaction of **1** with Schiff bases in the presence of sodium amide, or by the reaction of **1** with benzonitrile, followed with a hydride reduction.

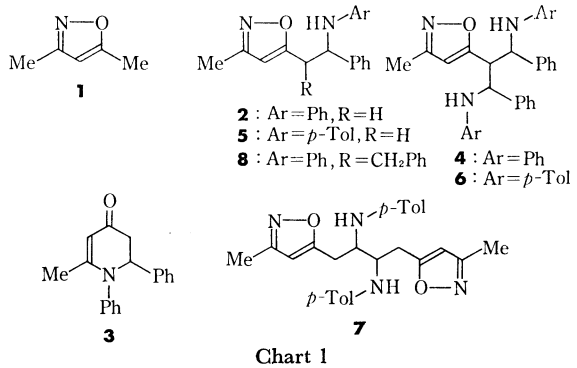


Chart 1

Experimental

The General Procedure. *a) By the Use of Sodium Amide in Liquid Ammonia*: To a sodium amide suspension, which has been prepared from sodium (0.01 mol) and liquid ammonia (*ca.* 50 ml) in the presence of ferric chloride, **1** (0.01 mol) in anhydrous ether (15 ml) was added. After stirring for 1 hr under a nitrogen stream at −50 °C, the Schiff base (0.01 mol)

was added; stirring was then continued for another 2 hr at −50 °C. The mixture was subsequently neutralized with ammonium chloride, and the ammonia was removed at room temperature. To the residual ether solution, dichloromethane was added. The dichloromethane solution was washed with aqueous sodium chloride and dried over anhydrous sodium sulfate. After the removal of the solvent, the residue was purified by recrystallization and/or silica gel column chromatography.

b) By the Use of Butyllithium: To a solution of **1** (0.01 mol) in dry THF (30 ml), an *n*-hexane solution (20%) of butyllithium (0.01 mol) was added at −40 °C. The mixture was stirred for 1 hr under nitrogen. After the addition of the Schiff base (0.01 mol), the stirring was continued for another 4 hr at −40 °C. The solution was then warmed to room temperature and washed with water. The aqueous layer was extracted with dichloromethane. The combined organic layer was dried over anhydrous sodium sulfate and concentrated. The residue was then purified as above.

3-Methyl-5-[2-(1,3-dianilino-1,3-diphenyl)propyl]isoxazole (4): Purified by recrystallization from chloroform; mp 236 °C; yield, 49%. IR (KBr): 3400, 1605, 1500, 745, 695, and 685 cm^{-1}. UV: λ_{max}^{EtOH} 246 (ε 25200) and 295 nm (3600). NMR δ_{CDCl_3} 2.14 (s, 3H), 3.3 (m, 1H), 4.55 (broad s, 2H), 5.07 (m, 2H), 5.63 (s, 1H) and 7.3—6.35 ppm (m, 10H). Found: C, 81.28; H, 6.35; N, 8.69%. Calcd for $C_{31}H_{29}N_3O$: C, 81.08; H, 6.36; N, 9.14%.

3-Methyl-5-(2-anilino-2-phenylethyl)isoxazole (2): The mother solution in the crystallization of **4** was concentrated and recrystallized from *n*-hexane; mp 113 °C; yield, 31%. IR (KBr): 3320, 1600, 1525, 1495, 745, 700, and 690 cm^{-1}. UV: λ_{max}^{EtOH} 247 (ε 14100) and 297 nm (2390). NMR: δ_{CDCl_3} 2.20 (s, 3H), 3.17 (d, J=7 Hz, 2H), 3.95 (broad s, 1H), 4.70 (t, J=7 Hz, 1H), 5.70 (s, 1H), 7.3—6.36 (m, 5H) and 7.27 ppm (s, 5H). Found: C, 77.46; H, 6.52; N, 10.10%. Calcd for $C_{18}H_{18}N_2O$: C, 77.67; H, 6.52; N, 10.07%.

*3-Methyl-5-(2-*p*-toluidino-2-phenylethyl)isoxazole (5)*: This was purified by silica gel column chromatography with a benzene ethyl acetate mixture, and the eluate was recrystallized from an *n*-hexane benzene mixture; mp 117 °C; yield, 13%. IR (KBr): 3300, 1615, 1600, 1525, 815 and 805 cm^{-1}. UV: λ_{max}^{EtOH} 249 (ε 14000) and 306 nm (2300). NMR: δ_{CDCl_3} 2.18 (s, 3H), 2.21 (s, 3H), 3.17 (d, J=7 Hz, 2H), 3.4 (broad s, 1H), 4.68 (t, J=7 Hz, 1H), 5.70 (s, 1H), 7.0—6.3 (AB-q, J=9 Hz, 4H) and 7.27 ppm (s, 5H). Found: C, 78.21; H, 7.13; N, 9.58%. Calcd for $C_{19}H_{20}N_2O$: C, 78.05; H, 6.90; N, 9.58%.

*3-Methyl-5-[2-(1,3-di-*p*-toluidino-1,3-diphenyl)propyl]isoxazole (6)*: This was purified by silica gel column chromatography with a benzene–ethyl acetate mixture, and the eluate was recrystallized from an ethyl acetate–ethanol mixture; mp 167 °C; yield, 56%. IR (KBr): 3350, 1610, 1510, 805, and 700 cm^{-1}. UV: λ_{max}^{EtOH} 249 (ε 27200) and 304 nm (3600). NMR: δ_{CDCl_3} 2.15 (s, 9H), 3.7 (m, 1H), 4.1 (broad s, 2H), 5.0 (m, 2H), 5.68 (s, 1H) and 7.3—6.3 ppm (m, 18H). Found: C, 81.05; H, 6.94; N, 8.45%. Calcd for $C_{33}H_{33}N_3O$: C, 81.28; H, 6.82; N, 8.62%.

*2,3-Di(*p*-toluidino)-1,4-bis(3-methyl-5-isoxazolyl)butane (7)*: This was purified by silica gel column chromatography with a benzene–ethyl acetate mixture, and the eluate was recrystallized from benzene; mp 153 °C; yield, 66%. IR (KBr): 3400, 1610, 1515, 810, and 790 cm^{-1}. UV: λ_{max}^{EtOH} 253 (ε 31700) and 304 nm (4170). NMR: δ_{CDCl_3} 2.22 (s, 6H), 2.25 (s, 6H), 3.1 (m, 6H), 3.85 (broad s, 2H), 5.80 (s, 2H) and 7.1—6.4 ppm (AB-q, J=9 Hz, 8H). Found: C, 72.51; H, 7.13; N, 12.81%. Calcd for $C_{26}H_{30}N_4O_2$: C, 72.53; H, 7.02; N, 13.01%.

*The Reaction of **1** with Alkyl Halide, Followed by the Reaction with* N*-Benzylideneaniline.* To a sodium amide (0.02 mol) suspension in liquid ammonia (50 ml) an ether (15 ml) solution of **1** (0.01 mol) was added. After stirring for 1 hr at −50 °C, alkyl halide (0.01 mol) in ether (10 ml) was added. The mixture was then stirred for another 2.5 hr. *N*-Benzylideneaniline (0.01 mol) was then added to the mixture, and it was stirred for another 2.5 hr. After neutralization with ammonium chloride, the reaction mixture was treated by the general method.

3-Methyl-5-[2-(1-anilino-1,3-diphenyl)propyl]isoxazole (8): The eluate of silica gel chromatography was concentrated and recrystallized from *n*-hexane; mp 133 °C; yield, 25%. IR (KBr): 3400, 1605, 1505, 1490, 790 and 695 cm^{-1}. UV: λ_{max}^{EtOH} 248 (ε 14700) and 296 nm (2300). NMR: δ_{CDCl_3} 2.10 (s, 3H), 3.13 (d, J=6 Hz, 2H), 3.44 (t, J=6 Hz, 1H), 4.3 (broad s, 1H), 4.68 (d, J=6 Hz, 1H), 5.41 (s, 1H) and 7.3—6.35 ppm (m, 15H). Found: C, 81.73; H, 6.80; N, 7.54%. Calcd for $C_{25}H_{24}N_2O$: C, 81.49; H, 6.57; N, 7.60%.

*The Reaction of **1** with* N*-Benzylideneaniline, Followed by Alkylation.* To a sodium amide (0.02 mol) suspension in liquid ammonia (50 ml) an ether solution of **1** (0.01 mol) was added. After the mixture had been stirred for 1 hr at −50 °C, *N*-benzylideneaniline (0.01 mol) was added to the mixture, after which it was stirred for another 2.5 hr. To the mixture alkyl halide (0.01 mol) in ether (10 ml) was then added. The stirring was continued for another 2.5 hr. After a usual work-up, the products were compared with authentic samples.

3-Methyl-5-styrylisoxazole (9): Mp 91.5 °C; yield 23%. IR (KBr): 1645, 1580, 1565, 1410, 965, 795, 760, and 695 cm^{-1}. UV: λ_{max}^{EtOH} 222 (ε 8900), 227 (9900), 234 (7600) and 301 nm (30100). NMR: δ_{CCl_4} 2.25 (s, 3H), 5.96 (s, 1H), 7.35—6.6 (AB-q, J=16 Hz, 2H) and 7.5—7.1 ppm (m, 5H). Found: C, 77.75; H, 6.18; N, 7.36%. Calcd for $C_{12}H_{11}NO$: C, 77.81; H, 5.99; N, 7.56%.

*The Hydrogenation of **2**.* An ethanol (30 ml) solution of **2** was hydrogenated with platinum oxide (6.0 mg) for 15 hr. After the subsequent removal of the catalyst and the solvent, the residue was chromatographed on silica gel with a benzene–ethyl acetate mixture. The products were identified by comparison with authentic samples.

*3-Methyl-5-(2-aminostyryl)isoxazole (**10**).* To a sodium amide (0.01 mol) suspension in liquid ammonia (*ca.* 50 ml) **1** (0.01 mol) in dry ether (15 ml) was added. After stirring for 1 hr at −60 °C, the ether solution (10 ml) of benzonitrile (0.01 mol) was added. The stirring was then continued for another 2 hr. After a usual work-up, the residue was recrystallized from an *n*-hexane–benzene mixture; mp 85 °C; yield, 49%. IR (KBr): 3500, 3400, 1630, 1610, 1580, 975, 810, 770, 745 and 695 cm^{-1}. UV: λ_{max}^{EtOH} 230 (ε 9600) and 331 nm (18800). NMR: δ_{CDCl_3} 2.25 (s, 3H), 5.15 (broad s, 2H), 5.34 (s, 1H), 5.79 (s, 1H) and 7.7—7.2 ppm (m, 5H). Found: C, 72.07; H, 6.23; N, 14.19%. Calcd for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04; N, 13.99%.

*3-Methyl-5-benzoylmethylisoxazole (**11**).* **10** was passed through a silica gel column with a benzene–ethyl acetate mixture; the eluate was then concentrated, and the residue was recrystallized from an *n*-hexane–benzene mixture; yield, 95%. The product was identified by comparison with an authentic sample.

*3-Methyl-5-(2-amino-2-phenylethyl)isoxazole (**12**).* To **10** (500 mg) in methanol (20 ml) was added sodium borohydride (136 mg) at room temperature. The mixture was then stirred for 20 hr. The resulting residue was distilled; bp 174—180 °C/6 mmHg; yield, 27%. IR (liquid film): 3350, 3300, 1605, 800, and 700 cm^{-1}. NMR: δ_{CCl_4} 1.6 (broad s, 2H),

2.17 (s, 3H), 2.90 (d, J=7 Hz, 2H), 4.22 (t, J=7 Hz, 1H), 5.65 (s, 1H) and 7.20 ppm (s, 5H). Found: C, 70.63; H, 7.27; N, 13.49%. Calcd for $C_{12}H_{14}N_2O$: C, 71.26; H, 6.98; H, 13.85%.

*1-Phenyl-1,5-diaminohexa-1,4-dien-3-one (**13**).* The ethanol (10 ml) solution of **10** (237 mg) was hydrogenated on platinum oxide (4.6 mg). After the removal of the catalyst and the solvent, the residue was recrystallized from an *n*-hexane–benzene mixture; mp 129 °C; yield, 56%. IR (KBr): 3400, 1630, 1535, 1305, 1150, 960, 800, 770 and 685 cm^{-1}. UV: λ_{max}^{EtOH} 240 (ε 10300), 265 (6200) and 375 nm (19700). NMR: δ_{CDCl_3} 1.89 (s, 3H), 4.90 (s, 1H), 5.18 (s, 1H), 8.0—6.0 (broad s, 4H, disappeared by D_2O exchange) and 7.6—7.1 ppm (m, 5H). Found: C, 71.30; H, 7.06; N, 13.82%. Calcd for $C_{12}H_{14}N_2O$: C, 71.26; H, 6.98; N, 13.85%.

*The Reaction of **1** with Benzonitrile, Followed by Alkylation.* To a sodium amide (0.015 mol) suspension in liquid ammonia (*ca.* 50 ml) **1** (0.01 mol) in dry ether (15 ml) added. After the mixture had been stirred for 1 hr at −60 °C, an ether solution (15 ml) of benzonitrile (0.01 mol) was added; the stirring was then continued for 1 more hr. After the addition of alkyl halide (0.01 mol) in ether (15 ml), the stirring was continued for another 2 hr at −60 °C. After a usual work-up, the resulting residue was passed through a silica gel column with benzene–ethyl acetate and the product was recrystallized from an *n*-hexane–benzene mixture.

*3-Methyl-5-(1-benzoylethyl)isoxazole (**15**)*: Yield, 7%; mp 48 °C. IR (liquid film): 1685, 1605, 980, 800, and 690 cm^{-1}. NMR: δ_{CCl_4} 1.49 (d, J=7 Hz, 3H), 2.11 (s, 3H), 4.84 (q, J=7 Hz, 1H), 5.81 (s, 1H) and 8.0—7.2 ppm (m, 5H). Found: C, 72.77; H, 6.14; N, 6.57%. Calcd for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51%.

*3-Methyl-5-(1-benzoylpropyl)isoxazole (**16**)*: Yield, 24%; mp 59 °C. IR (KBr): 1685, 1600, 1000, 810, 730, and 690 cm^{-1}. NMR: δ_{CCl_4} 0.96 (t, J=7 Hz, 3H), 2.4—1.7 (m, 2H), 2.20 (s, 3H), 4.65 (t, J=8 Hz, 1H), 5.83 (s, 1H) and 8.1—7.2 ppm (m, 5H). Found: C, 73.40; H, 6.70; N, 6.05%. Calcd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11%.

*The Hydrogenation of **14**.* The crude **14** (529 mg) was hydrogenated with palladium on charcoal (5%, 77 mg) in ethanol (25 ml) at room temperature for 15 hr. After the removal of the catalyst and the solvent, the residue was chromatographed on a silica gel column with a benzene–ethyl acetate mixture. The products were recrystallized from benzene.

cis-*2-Phenyl-3,6-dimethyl-2,3-dihydro-4(1H)pyridone (**17**)*: Mp 168 °C; yield, 14%. IR (KBr): 3220, 1600, 1580, 1525, 1250, 810, 760 and 700 cm^{-1}. NMR: δ_{CDCl_3} 0.85 (d, J=7 Hz, 3H), 2.05 (s, 3H), 2.8—2.0 (m, 1H), 4.80 (d, J=4 Hz, 1H), 4.97 (s, 1H), 5.2 (broad s, 1H) and 7.29 ppm (s, 5H). Found: C, 77.73; H, 7.54; N, 6.91%. Calcd for $C_{13}H_{15}NO$: C, 77.58; H, 7.51; N, 6.96%.

trans-*2-Phenyl-3,6-dimethyl-2,3-dihydro-4(1H)pyridone (**18**)*: Mp 166 °C; yield, 19%. IR (KBr): 3220, 1600, 1580, 1525, 1230, 805, 785, 750, and 690 cm^{-1}. NMR: δ_{CDCl_3} 0.89 (d, J=7 Hz, 3H), 2.00 (s, 3H), 2.52 (m, 1H), 4.21 (d, J=13 Hz, 1H), 4.96 (s, 1H), 5.3 (broad s, 1H) and 7.34 ppm (s, 5H). Found: C, 77.50; H, 7.56; N, 6.89%. Calcd for $C_{13}H_{15}NO$: C, 77.58; H, 7.51; N, 6.96%.