Chemistry of Natural Compounds, Vol. 48, No. 2, May, 2012 [Russian original No. 2, March-April, 2012]

SYNTHESIS OF ISOQUINOLINE ALKALOID DERIVATIVES FROM EUGENOL

A. G. Mikhailovskii,* O. V. Surikova, E. S. Limanskii, and M. I. Vakhrin

UDC 547.913+547.94+547.833.3

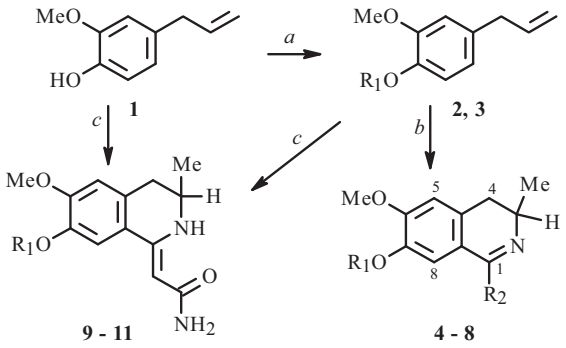
Alkylation under phase-transfer catalysis conditions (18-crown-6/KOH) of eugenol was used for cyclocondensation with nitriles (Ritter reaction), the products of which were isoquinoline derivatives.

Keywords: eugenol, phase-transfer catalysis (18-crown-6/KOH), alkylation, nitriles, Ritter reaction, isoquinoline derivatives, imines and enamines, dioxyline and papaverine analogs.

Eugenol (**1**, 4-allyl-2-methoxyphenol) is the main constituent of essential oil from *Syzygium aromaticum* (*Eugenia caryophyllata*) (Myrtaceae), *Camelia sasanqua* (Theaceae), certain basil species (*Ocimum*) (Lamiaceae), and other plants [1, 2].

Various isoquinoline derivatives, many of which can be viewed as synthetic alkaloid analogs, were prepared earlier by cyclocondensation of nitriles with dialkylbenzylcarbinols (Ritter reaction) [3]. The capability for this type of cyclocondensation involving instead of a carbinol 3,4-dimethoxy- and 3,4-methylenedioxyallylbenzenes, which are very similar to eugenol, was demonstrated in classical seminal studies [4, 5]. The goal of the present study was to use in analogous syntheses eugenol derivatives and nitriles that were verified by us earlier in reactions with carbinols.

Syntheses with a protected phenol hydroxyl were carried out first. The studies showed that the eugenol hydroxyl can be alkylated practically quantitatively under phase-transfer catalysis conditions using 18-crown-6/KOH. Alkylation of **1** by iodomethane or iodoethane formed the corresponding ethers **2** and **3**, which were used without further purification in the next step of the Ritter cyclocondensation. Use of hydrogen cyanide [6], acetonitrile [7], and homoveratryl nitrile instead of benzylcyanide [8], chloroacetonitrile [9], and 3-cyanocoumarin [10] as the nitrile component formed the corresponding 3,4-dihydroisoquinolines **4**–**8**. By analogy, reaction of allylbenzenes **2** and **3** with cyanoacetic acid amide produced amides **9** and **10** [11]. The fact that the cyclization occurred without protecting the phenol hydroxyl was interesting. The reaction of eugenol with cyanoacetamide gave enaminoamide **11**.



4: R_1 = Et, R_2 = H; **5:** R_1 = R_2 = Me
6: R_1 = Me, R_2 = 3,4-dimethoxybenzyl; **7:** R_1 = Me, R_2 = CH_2Cl
8: R_1 = Me, R_2 = 3-coumarinyl; **2, 9:** R_1 = Me; **3, 10:** R_1 = Et; **11:** R_1 = H

a. R_1I, 18-crown-6/KOH; *b*. R_2CN; *c*. $NCCH_2C(O)NH_2$

Perm State Pharmaceutical Academy, 614990, Perm, Ul. Polevaya, 2; e-mail: neorghim@pfa.ru. Translated from *Khimiya Prirodnykh Soedinenii*, No. 2, March–April, 2012, pp. 254–256. Original article submitted September 8, 2011.

0009-3130/12/4802-0285 ©2012 Springer Science+Business Media, Inc.

The principal structural feature of the prepared isoquinolines **4**–**11** was the presence in the 3-position of a methyl, which related them to dioxyline [12], which exhibits spasmolytic activity. Compound **6** was 3-methyl-3,4-dihydropapaverine. Compound **8** combined simultaneously two natural and biologically active moieties, isoquinoline and coumarin. Isoquinoline derivatives, e.g., compounds with methoxy- and hydroxyls in the 6,7-positions are related structurally to corypalline and isosalsoline, respectively [13].

Isoquinoline derivatives **8–11** were identified as the bases; all others, as the hydrochlorides.

IR spectra of all compounds as the bases were recorded from $CHCl_3$ solutions at concentration 0.01 mol/L. Bases **4–7** were prepared by treating solutions of the corresponding hydrochlorides with NH_4OH with subsequent extraction of the base by Et_2O, drying, and distillation of the solvent. Spectra of azomethine bases **4–8** contained an absorption band for the imine in the range 1630–640 cm^{-1}. The spectrum of coumarin derivative **8** had an absorption band for the lactone carbonyl (1720 cm^{-1}). The spectrum of **11** showed a phenol hydroxyl band (3210 cm^{-1}). Spectra of amide bases **9–11** exhibited absorption bands for chelated carbonyl (1610–1620 cm^{-1}) and NH (3100–3150 cm^{-1}). This was consistent with the *Z*-configuration of the base that was stabilized by an intramolecular H-bond.

All PMR spectra contained a doublet for the 3-CH_3 in the range 1.12–1.56 ppm and a multiplet for the 3-H proton in the range 3.20–3.59 ppm (4.26 in the spectrum of the salt of **7**). A set of resonances characteristic of a CH_AH_B system (4-CH_2) was also observed in the range 2.70–3.07 ppm. Spectra of bases **4**–**8**, which existed in the imine form, differed from those of enamines **9**–**11**. Spectra of the last ones had singlets for the vinyl proton (~5 ppm) and the ring NH proton (~9.5 ppm). The position of the NH singlet at weak field in addition to data from IR spectra indicated that an H-chelate ring was present.

EXPERIMENTAL

PMR spectra of **7** and **11** were recorded in DMSO-d_6; of all others, in $CDCl_3$. PMR spectra were recorded with HMDS internal standard on a Bruker DRX 300 instrument (300 MHz). IR spectra were recorded on a Specord-80 spectrometer. The purity of the products was checked by TLC on Silufol UV-254 plates using Me_2CO:EtOH:$CHCl_3$ (1:3:6) with detection by Br_2 vapor. All compounds were recrystallized from *i*-PrOH. Elemental analyses for C, H, N, and Cl agreed with those calculated.

3,4-Dimethoxyallylbenzene (2) and 3-Methoxy-4-ethoxyallylbenzene (3). A mixture of eugenol (21.6 mL, 0.12 mol), the appropriate alkyl iodide (0.15 mol), and 18-crown-6 (0.5 g, 0.019 mol) in the presence of KOH (20 g, 0.36 mol) in benzene (150 mL) was stirred vigorously at 40-50°C for 2 h, cooled to 20°C, and filtered. The solid was rinsed with benzene (2 × 50 mL). The filtrate was concentrated to a volume of ~70 mL. The resulting solution was used without further purification.

6-Methoxy-7-ethoxy-3-methyl-3,4-dihydroisoquinoline (4). The benzene solution of **3** was treated with KCN (6.5 g, 0.1 mol) and glacial acetic acid (15 mL) and dropwise with conc. H_2SO_4 (30 mL). The mixture was stirred vigorously at 50–60°C for 30 min and poured into icewater (30 mL). The benzene layer was separated. The aqueous phase was neutralized by ammonia solution. The base crystallized upon cooling to 5–7°C. It was filtered off, dried, and dissolved in EtOAc (250 mL). Purging with dry HCl produced the hydrochloride that was filtered off, dried, and recrystallized. Yield 70% calculated per KCN. $C_{13}H_{17}NO_2 \cdot HCl$, mp 117–118°C.

PMR spectrum (δ, ppm, J/Hz): 1.34 (3H, t, J = 8, $C\underline{H}_3CH_2$); 1.45 (3H, d, J = 8, 3-CH_3); 3.07 (1H, m, 3-H); 3.02 (2H, dd, J_{AB} = 8, 4-CH_AH_B); 3.72 (3H, s, CH_3O); 3.83 (2H, q, J = 8, $CH_3C\underline{H}_2$); 7.05 (1H, s, H-5); 7.46 (1H, s, H-8); 8.86 (1H, s, HC=N); 13.52 (1H, s, NH^+).

1,3-Dimethyl-6,7-dimethoxy-3,4-dihydroisoquinoline hydrochloride (5) was synthesized analogously using methyliodide instead of iodoethane. Yield 82%, $C_{13}H_{17}NO_2 \cdot HCl$, mp 220–222°C.

PMR spectrum (δ, ppm, J/Hz): 1.56 (3H, d, J = 8, 3-CH_3); 3.27 (1H, m, 3-H); 3.02 (2H, dd, J_{AB} = 8, 4-CH_AH_B); 3.85 (3H, s, 1-CH_3); 3.92 (3H, s, CH_3O); 3.97 (3H, s, CH_3O); 6.80 (1H, s, H-5); 7.15 (1H, s, H-8); 14.26 (1H, s, NH^+).

1-(3,4-Dimethoxybenzyl)-3-methyl-6,7-dimethoxy-3,4-dihydroisoquinoline hydrochloride (6) was prepared analogously using iodomethane and 3,4-dimethoxyphenylacetic (homoveratryl) acid nitrile (17.7 g, 0.1 mol). Yield 52%, $C_{21}H_{25}NO_4 \cdot HCl$, mp 176–178°C.

PMR spectrum (δ, ppm, J/Hz): 1.62 (3H, d, J = 7, 3-CH_3); 2.82 (2H, dd, J_{AB} = 8, 4-CH_AH_B); 3.40 (1H, m, 3-H); 3.80, 3.85, 3.95, 3.97 (12H, 4 singlets, 4CH_3O); 4.01 [2H, d, J = 8, $C\underline{H}_2C_6H_3(MeO)_2$]; 6.74–7.65 (5H, m, Ar); 12.83 (1H, s, NH^+).

1-Chloromethyl-3-methyl-6,7-dimethoxy-3,4-dihydroisoquinoline hydrochloride (7) was prepared analogously using iodomethane and chloroacetonitrile (6.3 mL, 0.1 mol). Yield 67%, $C_{13}H_{16}NO_2Cl \cdot HCl$, mp 208–210°C.

PMR spectrum (δ, ppm, J/Hz): 1.40 (3H, d, J = 7, 3-CH_3); 3.07 (2H, dd, J_{AB} = 8, 4-CH_AH_B); 3.83, 3.93 (6H, 2 singlets, 2CH_3O); 4.21 (1H, m, 3-H); 5.36 (2H, d, J = 6, CH_2Cl); 7.18 (1H, s, H-5); 7.50 (1H, s, H-8); 14.05 (1H, s, NH^+).

1-(3-Coumarinyl)-3-methyl-6,7-dimethoxy-3,4-dihydroisoquinoline (8) was prepared analogously using 3-cyanocoumarin (17.1 g, 0.1 mol). The crystalline precipitate forming after neutralization of the solution by ammonia was filtered off, dried and recrystallized. Yield 57%, $C_{21}H_{19}NO_2$, mp 130–132°C.

PMR spectrum (δ, ppm, J/Hz): 1.20 (3H, d, J = 8, 3-CH_3); 3.27 (1H, m, 3-H); 2.76 (2H, dd, J_{AB} = 8, 4-CH_AH_B); 3.50 (1H, s, 3-H); 3.75 (3H, s, CH_3O); 3.92 (3H, s, CH_3O); 7.26–7.41 (6H, m, Ar); 8.15 (1H, s, coumarin HC=).

(3-Methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-1-idene)acetamide (9) was synthesized analogously to **8** using cyanoacetamide (8.4 g, 0.1 mol). Yield 77%, $C_{14}H_{18}N_2O_3$, mp 115–117°C.

PMR spectrum (δ, ppm, J/Hz): 1.12 (3H, d, J = 8, 3-CH_3); 2.70 (2H, dd, J_{AB} = 8, 4-CH_AH_B); 3.60 (1H, m, 3-H); 3.92 (6H, s, 2CH_3O); 4.87 (2H, s, NH_2CO); 5.02 (1H, s, HC=); 7.20 (1H, s, 5-H); 7.06 (1H, s, 5-H); 7.20 (1H, s, 8-H); 9.43 (1H, s, NH-ring).

(3-Methyl-6-methoxy-7-ethoxy-1,2,3,4-tetrahydroisoquinolin-1-idene)acetamide (10) was prepared by the method for synthesizing **8** and **9** with the difference that iodoethane was used instead of iodomethane. Yield 73%, $C_{15}H_{20}N_2O_3$, mp 50–52°C.

PMR spectrum (δ, ppm, J/Hz): 1.32 (3H, t, J = 7, $C\underline{H}_3CH_2$); 1.47 (3H, d, J = 7, 3-CH_3); 2.83 (2H, dd, J_{AB} = 9, 4-CH_AH_B); 3.59 (1H, m, 3-H); 3.90 (3H, s, CH_3O); 4.03 (2H, q, J = 7, $CH_3C\underline{H}_2O$); 4.87 (2H, s, NH_2CO); 4.90 (1H, s, HC=); 6.62 (1H, s, 5-H); 7.08 (1H, s, 8-H); 9.50 (1H, s, NH-ring).

(3-Methyl-6-methoxy-7-hydroxy-1,2,3,4-tetrahydroisoquinolin-1-idene)acetamide (11). A mixture of eugenol (18 mL, 0.1 mol) and cyanoacetamide (8.4 g, 0.1 mol) in benzene (150 mL) was treated successively with glacial acetic acid (15 mL) and dropwise with conc. H_2SO_4 (30 mL). Then the reaction was carried out analogously as for **8–10** with the exception that the aqueous phase was neutralized by anhydrous $NaHCO_3$, adding it in small portions to avoid foaming. Yield 54%, $C_{13}H_{16}N_2O_3$, mp 218–220°C.

PMR spectrum (δ, ppm, J/Hz): 1.16 (3H, d, J = 8, 3-CH_3); 2.78 (2H, dd, J_{AB} = 8, 4-CH_AH_B); 3.30 (1H, m, 3-H); 3.83 (3H, s, CH_3O); 4.86 (1H, s, HC=); 6.18 (2H, s, NH_2CO); 6.64 (1H, s, 5-H); 6.88 (1H, s, 8-H); 8.81 (1H, s, OH); 9.26 (1H, s, NH-ring).

REFERENCES

1. L. G. Dudchenko, A. S. Koz′yakov, and V. V. Krivenko, *Aromatic and Gustatory Plants* [in Russian], Naukova Dumka, Kiev, 1989.
2. D. A. Murav′eva, *Tropical and Subtropical Medicinal Plants* [in Russian], Meditsina, Moscow, 1983.
3. A. G. Mikhailovskii, B. Ya. Syropyatov, V. S. Shklyaev, and A. V. Dolzhenko, *Nitrogen-containing Heterocycles and Alkaloids*, Vol. 1, V. G. Kartsev (ed.), Iridium Press, Moscow (2001), p. 393.
4. J. J. Ritter and F. X. Murphy, *J. Am. Chem. Soc.*, **74**, 763 (1952).
5. M. Lora-Tamayo, G. G. Munoz, and R. Mandronero, *Bull. Soc. Chim. Fr.*, **11–12**, 1334 (1958).
6. A. G. Mikhailovskii, V. S. Shklyaev, and E. V. Feshina, *Khim. Geterotsikl. Soedin.*, 236 (1998).
7. R. Z. Dautova, V. S. Shklyaev, B. Ya. Syropyatov, B. B. Aleksandrov A. G. Mikhailovskii, and M. I. Vakhrin, *Khim.-farm. Zh.*, **23**, No. 2, 172 (1989).
8. V. S. Shklyaev, B. B. Aleksandrov, A. G. Mikhailovskii, and M. I. Vakhrin, *Khim. Geterotsikl. Soedin.*, 963 (1987).
9. A. G. Mikhailovskii, A. V. Dolzhenko, B. Ya. Syropyatov, Yu. V. Shklyaev, and M. I. Vakhrin, *Khim.-farm. Zh.*, **36**, No. 6, 8 (2002).
10. A. G. Mikhailovskii and M. I. Vakhrin, *Khim. Geterotsikl. Soedin.*, 1198 (2004).
11. V. S. Shklyaev, B. B. Aleksandrov, A. G. Mikhailovskii, and M. I. Vakhrin, *Khim. Geterotsikl. Soedin.*, 1239 (1989).
12. V. G. Brovchenko, N. V. Shibaeva, A. I. Pyshchev, and E. V. Kuznetsov, *Khim. Geterotsikl. Soedin.*, 363 (1992).
13. V. G. Kartsev, B. N. Zhitar′, O. N. Denisenko, and M. S. Yunusov, *Selected Methods for the Synthesis and Modification of Heterocycles. Natural Isoquinolines: Chemistry and Biological Activity* [in Russian], Vol. 8, V. G. Kartsev (ed.), ICSPF, Moscow (2011), pp. 22–23.