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Three-Component Condensation of *o*- and *p*-Methoxytoluenes with Isobutyraldehyde and α-Substituted Benzyl Cyanides. Synthetic Approach to Analogs of Natural Alkaloids

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Abstract—Three-component condensation of *o*(*p*)-methoxytoluene with isobutyraldehyde and α-substiituted benzyl cyanides gave 8-acetyl-3,6,6-trimethyl-5,6,7,12b-tetrahydrodibenzo[*d*,*f*]indol-2(1*H*)-one or 8-acetyl-1,6,6-trimethyl-3,4,5,6,7,12b-hexahydrodibenzo[*d*,*f*]indol-3-one. Analogous reaction of *p*-methoxytoluene with isobutyraldehyde and 1-phenylcyclopentane-1-carbonitrile afforded 1′,6′,6′-trimethyl-3′,4′,5′,6′,7′,12b′-hexahydrospiro[cyclopentane-1′,8-dibenzo[*d*,*f*]indol]-3′-one.

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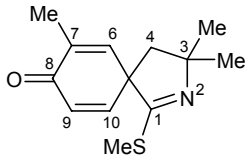
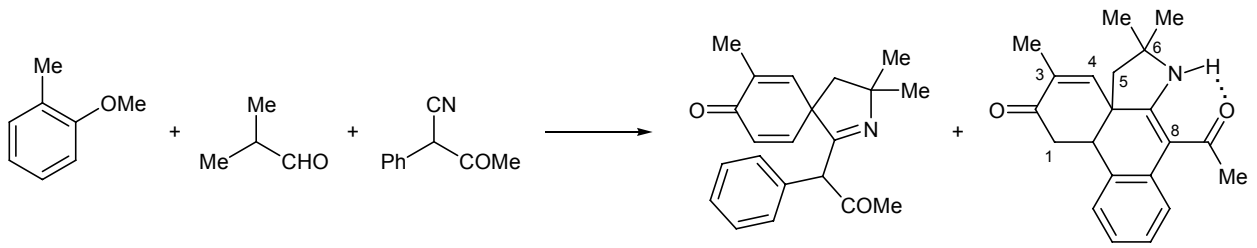
We reported previously that three-component condensation of anisole with isobutyraldehyde and phenylacetoacetonitrile yields 3,3-dimethyl-1-(2-oxo-1-phenylpropylidene)-2-azaspiro[4.5]deca-6,9-dien-8-one [1]. Analogous spiro heterocycle **A** was obtained by reaction of *o*-methoxytoluene with isobutyraldehyde and methyl thiocyanate [2].



A

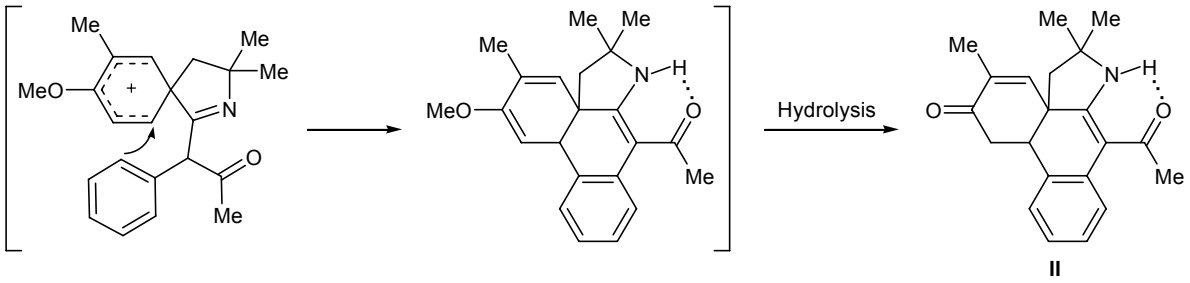
The reaction of *o*-methoxytoluene with isobutyraldehyde and 3-oxo-2-phenylbutanenitrile also gave 3,3,7-trimethyl-1-(2-oxo-1-phenylpropyl)-2-azaspiro-[4.5]deca-1,6,9-trien-8-one (**I**) as the major product; in addition, we isolated minor compound **II** with the same molecular weight but different ^{1}H NMR spectrum (Scheme 1). The ^{1}H NMR spectrum of **I** contained a singlet at δ 1.41 ppm from protons in the methyl group on C^7, a singlet at δ 6.64 ppm from 6-H, and a doublet at δ 5.58 ppm (J = 9.9 Hz) from 10-H. The 9-H signal was overlapped by aromatic multiplet at δ 6.91–7.03 ppm. In the ^{1}H NMR spectrum of **II** we observed only one singlet at δ 6.43 ppm from the 4-H proton, and three protons gave rise to an *ABM* pattern in the aliphatic region. Signals from two carbon atoms in the dienone fragment were displaced to aliphatic region of the ^{13}C NMR spectrum. Methylene protons on C^5 resonated as an *AB* spin system at δ 1.90 ppm (J = 12.8 Hz), and those on C^1 also appeared as an *AB* pattern centered at δ 2.74 ppm (J = 16.5 Hz). These findings, in combination with the data of elemental analysis, allowed us to assign the structures of 3,3,7-trimethyl-1-(2-oxo-1-phenylpropyl)-2-azaspiro[4.5]-

Scheme 1.



I **II**

Scheme 2.



II

deca-1,6,9-trien-8-one and 8-acetyl-3,6,6-trimethyl-5,6,7,12b-tetrahydrodibenzo[*d*,*f*]indol-2(1*H*)-one to compounds **I** and **II**, respectively. The minor product is likely to be formed via intramolecular attack by the *ortho*-carbon atom in the phenyl ring on intermediate σ-complex, followed by hydrolysis of the vinyl ether moiety (Scheme 2).

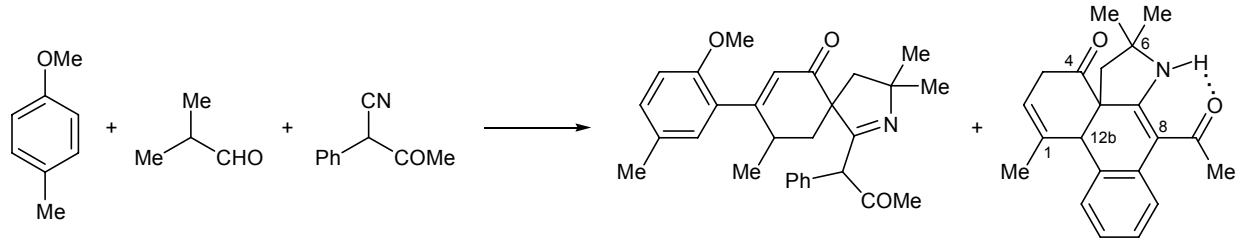
A heterocyclic system analogous to **II** but having a double bond at C^1 and no substituents on C^6 and C^8 was reported previously as intermediate in the synthesis and biosynthesis of morphinane alkaloids [3–5].

As we showed previously [6], three-component condensation of *p*-methoxytoluene with isobutyraldehyde and nitriles is accompanied by additional alkylation. However, in the reaction of *p*-methoxytoluene with isobutyraldehyde and 3-oxo-2-phenylbutanenitrile, apart from the expected product, 3,3,9-trimethyl-8-(2-methoxy-5-methylphenyl)-1-(2-oxo-1-phenylpropyl)-2-azaspiro[4.5]deca-1,7-dien-6-one (**III**, 17%)), we succeeded in isolating 2% of 8-acetyl-1,6,6-trimethyl-3,4,5,6,7,12b-hexahydrodibenzo[*d*,*f*]indol-4-one (**IV**) formed as a result of intramolecular alkylation of the aromatic ring (Scheme 3). Compound **IV** characteristically displayed in the ^{1}H NMR spectrum an *ABM* pattern due to two aliphatic protons on C^3 (δ 2.70 ppm, J = 23.1 Hz) and vinylic proton on C^2 (δ 5.68 ppm). The 12b-H proton resonated as a singlet at δ 3.36 ppm. In the ^{13}C NMR spectrum of **IV**, all carbon atoms in the fused benzene ring were nonequivalent (each gave a separate signal), whereas the C^2/C^6 and C^3/C^5 atoms in the unsubstituted phenyl group in **III** were equivalent in pairs. The spiro carbon atom in **IV** gives a signal at δ_C 60.8 ppm.

The formation of structure **IV** is possible only via intramolecular attack by the phenyl group on the σ-complex and subsequent hydrolysis of vinyl ether, as shown in Scheme 2 for compound **II**.

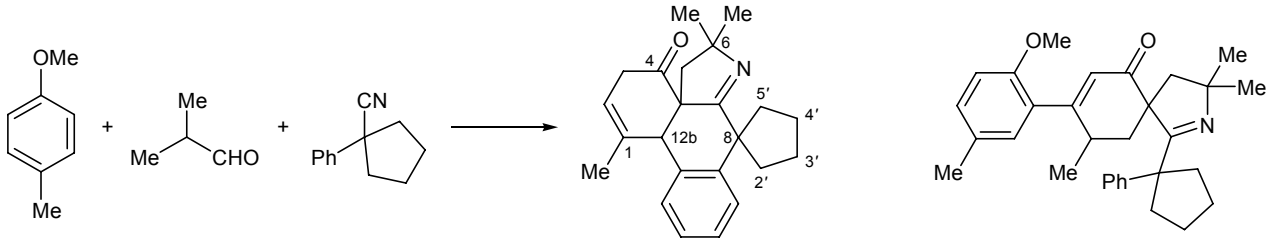
We presumed that the low yields of compounds **II** and **IV** are largely determined by electron-withdrawing effect of the acetyl group. Taking into account that the

Scheme 3.



III, 17% **IV**, 2%

Scheme 4.



V, 18% **VI**

condensation with unsubstituted benzyl cyanide leads to the corresponding 1-benzoyl-substituted heterocycles [7], as nitrile component we used 1-phenylcyclopentane-1-carbonitrile. Even in the reaction with 3 equiv of *p*-methoxytoluene, no compound **VI** was detected in the reaction mixture, and the only isolated product was 1′,6′,6′-trimethyl-4′,5′,6′,12b′-tetrahydrospiro[cyclopentane-1′,8-dibenzo[*d*,*f*]indol]-4′(3′*H*)-one (**V**, yield 18%). In the ^{1}H NMR spectrum of **V**, the *AB* pattern belonging to methylene protons on C^3 was overlapped by multiplet signal from protons in the tetramethylene bridge on C^8. The 2-H signal was located at δ 5.80 ppm, and the 12b-H proton resonated as a singlet at δ 3.51 ppm. Protons in the geminal methyl groups on C^6 gave two three-proton singlets at δ 1.47 and 1.74 ppm, indicating nonplanar structure of the dihydropyrrole fragment. The C^8 signal appeared in the ^{13}C NMR spectrum at δ_C 64.9 ppm.

EXPERIMENTAL

The IR spectra were recorded on a UR-20 spectrometer from samples dispersed in mineral oil. The ^{1}H NMR spectra were measured on a Varian Mercury Plus-300 spectrometer (300 MHz) from solutions in DMSO-d_6 using hexamethyldisiloxane as internal reference. The mass spectra (electron impact, 70 eV) were obtained on an Agilent GC 6890N–MSD 5975B GC–MS instrument. The progress of reactions and the purity of products were monitored by TLC on Silufol plates using chloroform–acetone (9:1) as eluent; spots were detected by treatment with a 5% solution of chloranil in toluene. The elemental compositions were determined on a Leco CHNS-932 analyzer (USA).

3,3,7-Trimethyl-1-(2-oxo-1-phenylpropyl)-2-azaspiro[4.5]deca-1,6,9-trien-8-one (I). A mixture of 6.1 g (50 mmol) of *o*-methoxytoluene, 3.6 g (50 mmol) of isobutyraldehyde, and 7.95 g (50 mmol) of phenylacetoacetonitrile in 40 ml of methylene chloride was added dropwise under stirring to 40 ml of concentrated sulfuric acid cooled with an ice–water mixture. The reaction mixture was stirred for 15 min, poured onto 150 g of crushed ice, and extracted with hexane. The aqueous phase was neutralized to pH 7–8 with aqueous ammonia and extracted with methylene chloride (3× 30 ml), the extract was dried over anhydrous magnesium sulfate and filtered, the solvent was distilled off, and the residue was recrystallized from propan-2-ol. Yield 3.05 g (19%), colorless crystals, mp 171–173°C. IR spectrum, ν, cm^{-1}: 3370, 3200, 1660, 1630, 1610, 1550. ^{1}H NMR spectrum, δ, ppm: 1.38 s (6H, 3-CH_3), 1.42 s (3H, 7-CH_3), 1.56 s ($COCH_3$), 1.94 d (2H, 4-H, J = 4.2 Hz), 5.58 d (1H, 2-H, J = 9.6 Hz), 6.64 m (1H, 6-H), 6.88 d (1H, 10-H, J = 2.7 Hz), 6.91–7.03 m (5H, H_{arom}), 10.92 br.s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 13.8 (7-CH_3), 26.5 (CO**C**H_3), 29.0 and 29.2 (3-CH_3), 46.2 (C^4), 52.2 (C^3), 58.5 (C^5), 105.0 (C^α), 130.9 (C^{10}), 131.0 (C^6), 125.0, 125.1, 125.7, 125.8, 131.6, 134.7 (C_{arom}), 143.4 (C^7), 147.0 (C^9), 158.4 (C^1), 183.0 (C^8), 194.5 (**C**OCH$_3$). Found, %: C 78.42; H 7.18; N 4.38. $C_{21}H_{23}NO_2$. Calculated, %: C 78.47; H 7.21; N 4.36.

8-Acetyl-3,6,6-trimethyl-5,6,7,12b-tetrahydrodibenzo[*d*,*f*]indol-2(1*H*)-one (II) was synthesized in a similar way, but the reaction mixture was stirred for 1.5 h. Compound **I** was isolated first, the mother liquor was evaporated, and the residue was recrystallized from hexane. Yield 0.5 g (3%), colorless crystals, mp 165–167°C. IR spectrum, ν, cm^{-1}: 3370, 3200, 1660, 1630, 1610. ^{1}H NMR spectrum, δ, ppm: 1.28 s (6H, 6-CH_3), 1.75 s (3H, 3-CH_3), 1.78 s ($COCH_3$), 1.90 (2H, 5-H, *AB* system, J = 12.8 Hz), 2.74 (2H, 1-H, *AB* part of *ABM* system, J = 16.5, 3.3, 1.6 Hz), 4.38 m (1H, 12b-H), 6.43 s (1H, 4-H), 7.14–7.28 m (5H, NH, H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 14.0 (3-CH_3), 16.5 (CO**C**H_3), 28.0 and 29.0 (6-CH_3), 45.9 (C^1), 50.5 (C^5), 58.4 (C^2), 69.8 (C^{12b}), 78.5 (C^{3a}), 109.6 (C^8); 124.8, 126.1, 128.0, 128.8, 133.2, 140.0 (C_{arom}); 141.0 (C^2), 158.6 (C^{12a}), 163.7 (C^{7a}), 180.9 (C^{8a}), 192.6 (**C**OCH$_3$). Found, %: C 78.48; H 7.24; N 4.36. $C_{21}H_{23}NO_2$. Calculated, %: C 78.47; H 7.21; N 4.36.

8-(2-Methoxy-5-methylphenyl)-3,3,9-trimethyl-1-(2-oxo-1-phenylpropyl)-2-azaspiro[4.5]deca-1,7-dien-6-one (III). A mixture of 12.20 g (100 mmol) of *p*-methoxytoluene, 3.60 g (50 mmol) of isobutyraldehyde, and 7.95 g (50 mmol) of 3-oxo-2-phenylbutanenitrile in 40 ml of methylene chloride was added dropwise under stirring to 40 ml of concentrated sulfuric acid cooled with an ice–water mixture. The reaction mixture was stirred for 15 min, poured onto 150 g of crushed ice, and extracted with hexane. The aqueous phase was neutralized to pH 7–8 with aqueous ammonia and extracted with methylene chloride (3×30 ml), the extract was dried over anhydrous magnesium sulfate and filtered, the solvent was distilled off, and the residue was recrystallized from ethyl acetate. Yield 3.76 g (17%), colorless crystals, mp 234–237°C. IR spectrum, ν, cm^{-1}: 3220, 1710, 1660, 1630. ^{1}H NMR spectrum, δ, ppm: 0.90 d (3H, 9-CH_3), 1.09 s and 1.28 s (3H each, 3-CH_3), 1.76 m (1H, 9-H), 1.81 s (3H, $COCH_3$), 2.23 s (3H, C_6H_3C**H**$_3$), 2.40 d.d (2H, 10-H), 3.73 s (3H, OCH_3), 4.15 s (1H, 7-H), 6.73 d (1H,

3′-H), 6.90 s (1H, 6′-H), 6.97 d (1H, 5′-H), 7.14–7.28 m (5H, C_6H_5). ^{13}C NMR spectrum, δ_C, ppm: 13.1 (9-CH_3), 18.6 (CO**C**H_3), 26.2 (3-CH_3), 29.2 (C^9), 36.4 (C^{10}), 43.6 (C^4), 53.5 (OCH_3), 63.1 (C^3), 70.0 (C^5), 85.7 (1-CH), 109.1 ($C^{3'}$), 124.8 (C^7), 125.0 ($C^{1'}$), 126.1 ($C^{3''}$, $C^{5''}$), 126.2 ($C^{4''}$), 128.0 ($C^{6'}$), 128.2 ($C^{5'}$), 128.8 ($C^{2''}$, $C^{6''}$), 128.8 ($C^{4'}$), 134.2 ($C^{1''}$), 153.6 ($C^{2'}$), 157.4 (C^1), 162.6 (C^8), 190.2 (C^6), 207.7 (**C**OCH_3). Found, %: C 78.73; H 7.75; N 3.32. $C_{29}H_{33}NO_3$. Calculated, %: C 78.52; H 7.50; N 3.16.

8-Acetyl-1,6,6-trimethyl-3,4,5,6,7,12b-hexahydrodibenzo[*d*,*f*]indol-4-one (IV). After separation of compound **III**, the mother liquor was evaporated, and the residue was recrystallized from alcohol. Yield 0.64 g (2%), mp 205–206°C. IR spectrum, ν, cm^{-1}: 3220, 1660, 1630, 1600. ^1H NMR spectrum, δ, ppm: 1.21 s and 1.34 s (3H each, 6-CH_3), 1.99 d.d (2H, 5-H), 2.05 s (3H, 1-CH_3), 2.29 s (3H, $COCH_3$), 2.70 d.d (2H, 3-H, J = 23.1 Hz), 3.56 s (1H, 12b-H), 5.68 m (1H, 2-H), 6.90–7.20 m (4H, H_{arom}), 10.01 br.s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 22.7 (1-CH_3), 26.6 (6-CH_3), 29.2 (CO**C**H_3), 35.8 (C^3), 44.2 (C^5), 49.5 (C^6), 60.4 (C^{12b}), 60.8 (C^{4a}), 100.6 (C^8), 118.4 (C^2); 122.0, 123.1, 124.6, 125.1 (C_{arom}); 129.9 (C^{12a}), 133.5 (C^{8a}), 134.5 (C^1), 161.5 (C^9), 192.3 (**C**OCH_3), 205.6 (C^4). Found, %: C 78.73; H 7.75; N 3.32. $C_{21}H_{23}NO_2$. Calculated, %: C 78.47; H 7.21; N 4.36.

1′,6′,6′-Trimethyl-4′,5′,6′,12b′-tetrahydrospiro[cyclopentane-1.8′-dibenzo[*d*,*f*]indol]-4′(3′*H*)-one hydrochloride (V). A mixture of 1.22 g (10 mmol) of *o*-methoxytoluene, 0.72 g (10 mmol) of isobutyraldehyde, and 1.6 g (10 mmol) of 1-phenylcyclopentane-1-carbonitrile in 40 ml of methylene chloride was added dropwise under stirring to 10 ml of concentrated sulfuric acid cooled with an ace–water mixture. The reaction mixture was stirred for 15 min, poured onto 150 g of crushed ice, and extracted with hexane, the aqueous phase was neutralized to pH 7–8 with aqueous ammonia and extracted with methylene chloride (3× 30 ml), the extract was dried over anhydrous magnesium sulfate under stirring in an argon atmosphere and filtered, and dry hydrogen chloride was passed through the filtrate. When the mixture became transparent, the precipitate was filtered off and recrystallized from propan-2-ol. Yield 0.64 g (18%), colorless crystals, mp 208–212°C. ^1H NMR spectrum, δ, ppm: 1.47 s and 1.74 s (3H each, 6-CH_3), 1.74–1.84 m (2H, 3′-H), 2.14 d.d (2H, 3-H, J = 13.8 Hz), 2.16 s (3H, 1-CH_3), 2.37–2.63 m (5H, 4′-H, 5-H, 5′-H), 2.89–2.99 m (3H, 2′-H, 5-H), 3.51 s (1H, 12b-H), 5.80 m (1H, 2-H), 7.06–7.28 m (4H, H_{arom}), 16.26 s (1H, HCl). ^{13}C NMR spectrum, δ_C, ppm: 23.4 (1-CH_3), 24.9 (6-CH_3), 25.0 ($C^{3'}$), 27.4 ($C^{4'}$), 35.1 (C^3), 40.6 ($C^{2'}$), 42.6 ($C^{5'}$), 46.3 (C^5), 47.7 (C^{12b}), 50.2 (C^6), 64.9 (C^8), 69.1 (C^{4a}), 119.1 (C^2), 124.1 (C^{12}), 124.5 (C^9), 125.8 (C^{11}), 126.8 (C^{10}), 130.2 (C^{12a}), 133.8 (C^{8a}), 140.0 (C^1), 195.9 (C^{7a}), 202.2 (C=O). Found, %: C 78.87; H 7.85; Cl 9.50; N 3.52. $C_{23}H_{27}NO \cdot HCl$. Calculated, %: C 74.68; H 7.63; Cl 9.58; N 3.79.

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