A MECHANISTIC DEVIATION IN THE BISCHLER INDOLE SYNTHESIS

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Abstract: When α-bromo-2,4,5-trimethoxybutyrophenone reacted with *p*-toluidine, the unexpected 3,5-dimethyl-2-(2,4,5-trimethoxybenzyl)indole was obtained. This mechanistic deviation was also observed with α-bromo-2,4,5-trimethoxyvalerophenone and α-bromo-2,4,5-trimethoxycaprophenone; however, when α-bromo-2,4,5-trimethoxypropiophenone was used, 3,5-dimethyl-2-(2,4,5-trimethoxyphenyl)indole was formed, instead of a benzyl indole.

Introduction

The communications related to the Bischler indole synthesis have been reviewed several times (1-5). Since the reaction of an α-haloketone with excess of an aryl amine can afford indole derivatives in which the substituents at C-2 and C-3 can be interchanged, it was considered of interest to carry on the reaction with substrates different to those used previously, in order to ascertain the structures of the obtained compounds.

Results and Discussion

Since the substances used formerly as starting compounds in the Bischler indole synthesis are either phenacyl halides or α-halo-propiophenones, with two or three carbon atoms in the side chain, it hinted us to assay α-haloketones with longer side chains. Thus, we chose to effect the reaction between α-bromo-2,4,5-trimethoxybutyrophenone, **1**, and *p*-toluidine. The theoretically expected products are the isomeric indole derivatives **2** and **3**.

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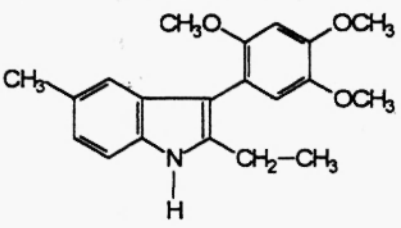

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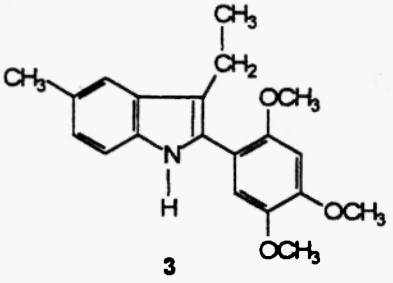

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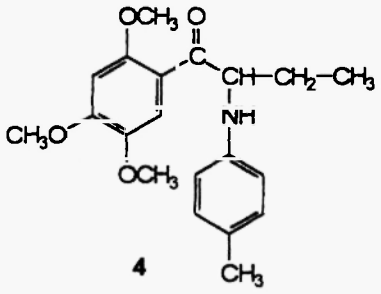
Compound **2** would result via the easily formed α-arylaminoketone **4**, and the α-(*p*-toluidino)anil derivative **5**:



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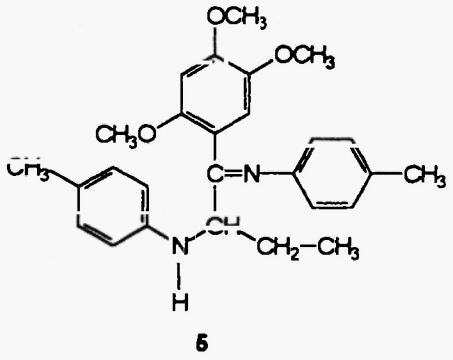

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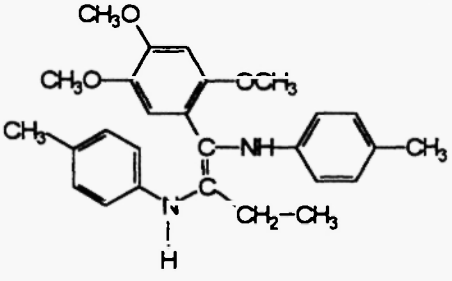
On the other hand, compound **3** results from a double isomerization of **5** via the enediamine **6** and the new α-(*p*-toluidino)anil **7**:



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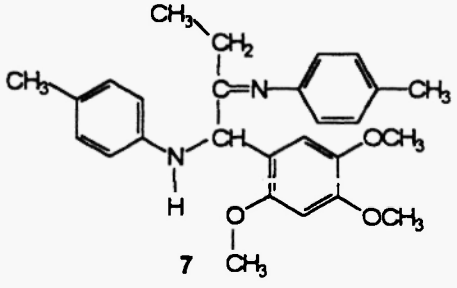

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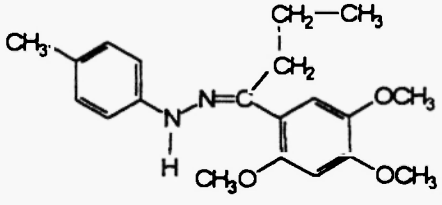
In order to identify unambiguously one of the isomers, **2** or **3**, the last one was prepared by the Fischer method from the *p*-tolylhydrazone of 2,4,5-trimethoxybutyrophenone, **8**, and boron trifluoride. Cf. (6). The ^{1}H-NMR data of **3** ($CDCl_3$, 300 MHz) are indicated in the formula.



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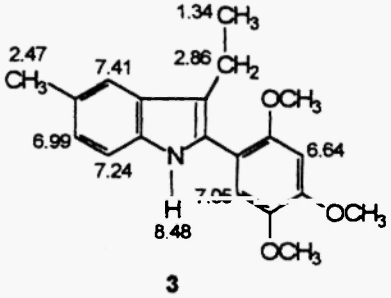

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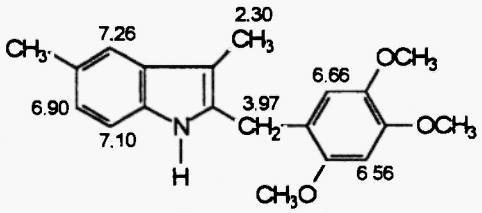
However, the reaction of α-bromo-2,4,5-trimethoxybutyrophenone with *p*-toluidine yielded a compound with no ethyl group, thus discarding structures **2** and **3**. The resulting indole was identified as 3,5-dimethyl-2-(2,4,5-trimethoxybenzyl)indole, **9**. In addition to the ^{1}H-NMR data obtained in $CDCl_3$ solution (in the formula), a determination of the spectrum in trifluoroacetic acid shows a doublet at 1.78 ppm (CH_3 β to nitrogen) and a quartet at 4.33 ppm (H-3), both with J = 8 Hz, due to the formation of the 3-H indolium salt (7), **10**, thus proving that the methyl group is at C-3. Besides, the CH_2 singlet appears now at 4.36 ppm due to the electron withdrawal effect of the protonated imino group.



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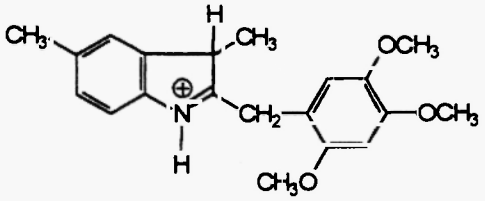

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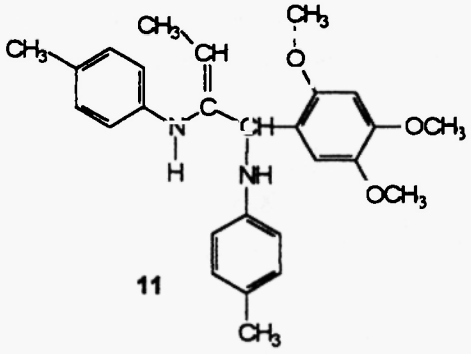
The formation of the benzyl indole **9** can be explained by a further isomerization of intermediate **7** to the enamine **11**, which on



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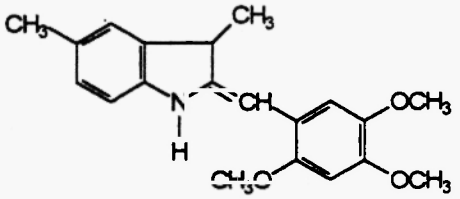

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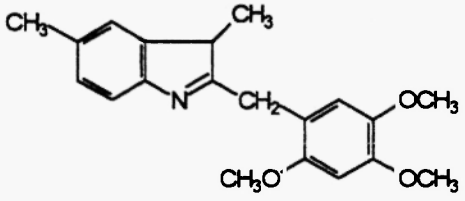
elimination of a *p*-toluidine molecule from the sp^3 carbon atom and subsequent cyclization yields the trimethoxybenzylidene indoline **12**, which rearranges to the indole derivative **9**, probably via the indolenine **13**.



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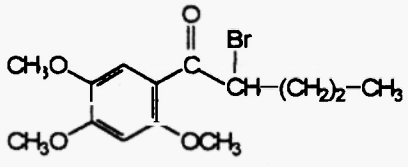
Next, we look if the higher homologous bromo ketones **14** and **15** react in a similar manner with *p*-toluidine. In fact both haloketones,



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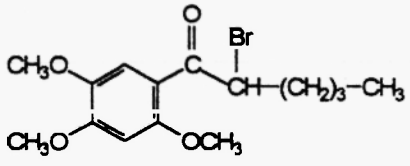

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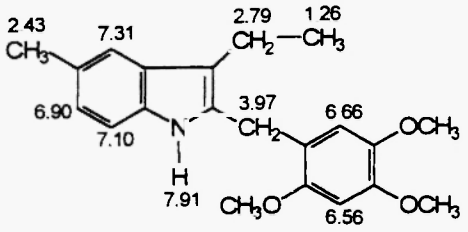
the valerophenone **14** and the caprophenone **15**, yielded benzylindole derivatives, whose structures are **16** and **17**.



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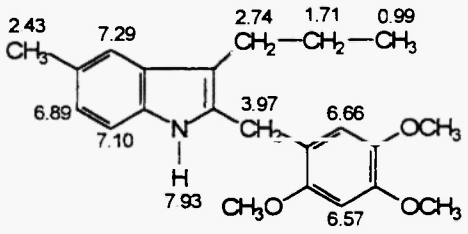

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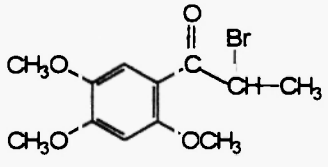
On the other hand, α-bromo-2,4,5-trimethoxypropiophenone, **18**, the lower homologue of the bromobutyrophenone **1**, gave rise to 3,5-dimethyl-2-(2,4,5-trimethoxyphenyl)indole, **19**. This compound is formed after two isomerizations, instead of the three proposed



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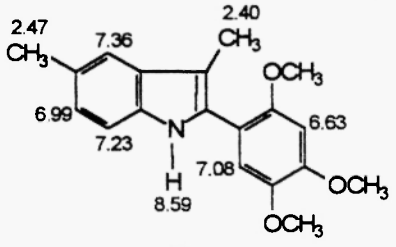

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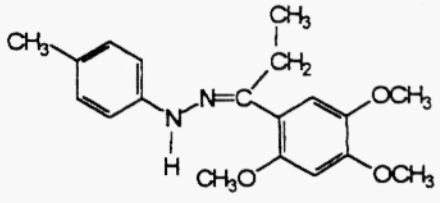
ones in the case of the benzyl indoles described (**9**, **16** and **17**). The propounded intermediate **11** for the formation of the benzyl indoles possess a trisubstituted double bond, but when α-bromo-2,4,5-trimethoxypropiophenone is employed, an intermediate of type **11** would possess a less stable disubstituted double bond and this was not formed. Thus the 2-arylindole **19** is obtained from an intermediate like **7**, with a methyl instead of the ethyl group. The identity of indole **19** was confirmed when the same compound was obtained from 2,4,5-trimethoxypropiophenone *p*-tolylhidrazone, **20**, and boron trifluoride etherate.



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The results obtained are in agreement with the proposed mechanistic pathways and an explanation has been given of why the observed deviations occur or not.

Experimental

The IR spectra were recorded in a Perkin-Elmer FTIR-1600 spectrophotometer, using KBr wafers. The ^{1}H-NMR spectra were obtained in a Varian Inova 300 spectrometer, in $CDCl_3$ solution and TMS as internal standard. The EI-MS data were acquired using a JEOL JMS-SX 102 A double-focusing instrument with electron energy 70 eV.

Only significant data are provided. The methoxyl signals have been obviated.

The required *alkyl-2,4,5-trimethoxyphenyl ketones* were prepared from 1,2,4-trimethoxybenzene (5 g), 4.2 centimoles of the proper aliphatic acid and 36 g of polyphosphoric acid. Cf. (8). The reaction mixture was heated 4 h at 45-50°C with stirring and in anhydrous conditions. After cooling, the heavy oil was poured very slowly, with efficient scratching, in water (250 ml). The solid was filtered, washed thoroughly with water and crystallized from MeOH or aqueous MeOH.

2,4,5-Trimethoxybutyrophenone. M.p. 76-77.5°C (MeOH-H_2O). IR (KBr) 1640 cm^{-1}. ^{1}H-NMR (δ) 1.71, sextet (β-CH_2); 6.57, s (H-3); and 7.48 ppm, s (H-6). M.W. calc. for $C_{13}H_{18}O_4$, 238. MS (ei): M$^+$ 238, 20 %; m/z 195, 100 % (ArCO+).

2,4,5-Trimethoxyvalerophenone. M.p. 62-63°C (MeOH-H_2O). IR (KBr) 1658 cm^{-1}. ^{1}H-NMR (δ) 0.92, t (CH_3); 1.5, m (2 CH_2) and 2.93 ppm, t (CO-CH_2). M.W. calc. for $C_{14}H_{20}O_4$, 252. MS (ei): M$^+$ 252, 12 %; m/z 195, 100% (Ar-CO+).

2,4,5-Trimethoxycaprophenone. M.p. 82-84°C (MeOH). Caproic anhydride was used. Reaction time: 7 h. IR (KBr) 1660 cm^{-1}. ^{1}H-NMR (δ) 1.34, m (2 CH_2); 1.65, m (CH_2); and 2.91 ppm, t (α-CH_2). M.W. calc. for $C_{15}H_{22}O_4$, 266. MS (ei): M$^+$ 266, 44 %; m/z 195, 100 % (Ar-CO+).

2,4,5-Trimethoxypropiophenone. M.p. 107-108°C (MeOH). IR (KBr) 1658 cm^{-1}. ^{1}H-NMR (δ) 1.14, t (CH_3); 2.94, q (CH_2); 6.48, s (H-3); and 7.41 ppm, s (H-6). M.W. calc. for $C_{12}H_{16}O_4$, 224. MS (ei): M$^+$ 224, 27 %; m/z 195, 100 % (Ar-CO+).

α-Bromoketones. To a solution of 2 centimoles of the alkyl-2,4,5-trimethoxyphenylketone in AcOH (10 ml) bromine was added (1 ml, 2 centimoles). The first drops were added at 35-40°C and the rest at 25°C during 40 min. The reaction mixture was poured in ice water. The separated dark green oil was taken in ether, washed with 5 % $Na_2S_2O_3$, 5 % $NaHCO_3$ and NaCl solution. The solution dried and concentrated yielded a solid which was crystallized as indicated below.

α-Bromo-2,4,5-trimethoxybutyrophenone, **1**. M.p. 65-65.5°C (MeOH-H_2O). IR (KBr) 1640 cm^{-1}. ^{1}H-NMR (δ) 5.38, d, J = 7 Hz and 5.45 ppm, d, J = 7 Hz (CH-Br). M.W. calc. for $C_{13}H_{17}O_4Br$, 317. MS (ei): $M_1^{\cdot+}$ 316, 72 %; $M_2^{\cdot+}$ 318, 72 % ; m/z 195, 100 % (Ar-CO+).

α-Bromo-2,4,5-trimethoxyvalerophenone, **14**. M.p. 67-68°C (MeOH-H_2O). IR (KBr) 1658 cm^{-1}. ^{1}H-NMR (δ) 5.46, d, J = 7 Hz and 5.53 ppm, d, J = 7 Hz (CH-Br). M.W. calc. for $C_{14}H_{19}O_4Br$, 331. MS (ci): M_1H^+ 331, 50%; M_2H^+ 333, 48 % ; m/z 195, 100 % (Ar-CO+).

α-Bromo-2,4,5-trimethoxycaprophenone, **15**. M.p. 55-56°C (ether-hexane). IR (KBr) 1655 cm^{-1}. ^{1}H-NMR (δ) 5.45, d, J = 7 Hz and 5.52 ppm, d, J = 7 Hz (CH-Br). M.W. calc. for $C_{15}H_{21}O_4Br$, 345. MS (ei): $M_1^{\cdot+}$ 344, 20 %; $M_2^{\cdot+}$ 346, 19.5 % ; m/z 195, 100 % (Ar-CO+).

α-Bromo-2,4,5-trimethoxypropiophenone, **18**. M.p. 72-73°C (ether). IR (KBr) 1658 cm^{-1}. ^{1}H-NMR (δ) 1.83, d, J = 7 Hz (CH_3) and 5.60 ppm, q, J = 7 Hz (CH-Br). M.W. calc. for $C_{12}H_{15}O_4Br$, 303. MS (ei): $M_1^{\cdot+}$ 302, 88 %; $M_2^{\cdot+}$ 304, 74 % ; m/z 195, 100 % (Ar-CO+).

2,4,5-Trimethoxybutyrophenone p-tolylhydrazone, **8**. M.p. 79-81°C (EtOH). IR (KBr) 3320 cm^{-1} (NH). M.W. calc. for $C_{20}H_{26}O_3N_2$, 342. MS (ei): $M^{\cdot+}$ 342, %; m/z 105, 100% (C_7H_7N+); m/z 236, 27% (C_3H_7(Ar)CN+).

3-Ethyl-5-methyl-2-(2,4,5-trimethoxyphenyl)indole, **3**. A solution of the above *p*-tolylhydrazone (1 g) in AcOH (2.5 ml) and $BF_3{\cdot}Et_2O$ (0.375 ml) was refluxed for 20 minutes and filtered while hot. The indole crystallized on cooling. One crystallization from MeOH-H_2O gave golden leaflets, m.p. 133-134°C. IR (KBr) 3368 and 3353 cm^{-1}(NH). ^{1}H-NMR (δ) 1.34, t, J = 7.8 Hz and 2.86 ppm, q, J = 7.8 Hz (C_2H_5 at C-3); 2.47 ppm, s (CH_3 at C-5). M.W. calc. for $C_{20}H_{23}O_3N$, 325. MS (ei): $M^{\cdot+}$ 325, 100 %;

Substituted benzylindoles. The required α-bromo-2,4,5-trimethoxyphenyl ketone (3 mmoles) and *p*-toluidine (21 mmoles) were refluxed gently in N_2 atmosphere for 1 h. Upon cooling, ether was added (25 ml) and the *p*-toluidine hydrobromide filtered. The filtrate was washed with 2 % HCl, with 5 % $NaHCO_3$ and with NaCl solution, then dried and concentrated (Rotavapor) and crystallized from ether-hexane.

3,5-Dimethyl-2-(2,4,5-trimethoxybenzyl)indole, 9. M.p. 129-131°C. IR (KBr) 3394 cm^{-1} (NH). ^{1}H-NMR (δ) 2.30, s (CH_3 at C-3); 2.43, s (CH_3 at C-5); and 3.97 ppm, s (benzylic CH_2). M.W. calc. for $C_{20}H_{23}O_3N$, 325. MS (ei): $M^{\cdot+}$ 325, 100 %;

3-Ethyl-5-methyl-2-(2,4,5-trimethoxybenzyl)indole, **16**. M.p. 124-126°C. IR (KBr) 3374 cm^{-1} (NH). ^{1}H-NMR (δ) 1.26, t, J = 7.5 Hz and 2.78, q, J = 7.5 Hz (C_2H_5 at C-3); 2.43, s (CH_3 at C-5) and 3.97 ppm, s (benzylic CH_2). M.W. calc. for $C_{21}H_{25}O_3N$, 339. MS (ei): $M^{\cdot+}$ 339, 100 %;

5-Methyl-3-propyl-2-(2,4,5-trimethoxybenzyl)indole, **17**. M.p. 134-136°C. IR (KBr) 3397 cm^{-1} (NH). ^{1}H-NMR (δ) 0.99, t, J = 7.2 Hz (CH_3); 1.71, sextet, J = 7.2 Hz (CH_2); 2.75ppm, t, J = 7.2 Hz (CH_2); 2.43, s (CH_3 at C-5); and 3.97 ppm, s (benzylic CH_2). M.W. calc. for $C_{22}H_{27}O_3N$, 353. MS (ei): $M^{\cdot+}$ 353, 100 %;

2,4,5-Trimethoxypropiophenone p-tolylhydrazone, **20**. M.p. 96-98°C (EtOH). IR (KBr) 3320 cm^{-1} (NH). M.W. calc. for $C_{19}H_{24}O_3N_2$, 328. MS (ei): $M^{\cdot+}$ 328, 100 %; m/z 222, 44 % ($M^{\cdot+}$ – HN–C_6H_4–CH_3).

3,5-Dimethyl-2-(2,4,5-trimethoxyphenyl)indole, **19**. Was prepared from compound **20** in similar manner as indole **3**. M.p. 128-129°C (MeOH). IR (KBr) 3442 cm^{-1} (NH). ^{1}H-NMR (δ) 2.40, s (CH_3) and 2.47 ppm, s (CH_3). M.W. calc. for $C_{19}H_{21}O_3N$, 311. MS (ei): $M^{\cdot+}$ 311, 100 %; m/z 296, 30 % ($M^{\cdot+}$ – 15).

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