Reactions of 1-Isopropyl-3-methyl- and 2,3-Dimethylindoles with Triethyl Orthoformate: New Trisindolylmethanes

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Indoles **1** and **2** react with triethyl orthoformate under proton-catalyzed conditions to form trisindolylmethanes. The regioisomer distribution of the products is controlled by steric and electronic factors.

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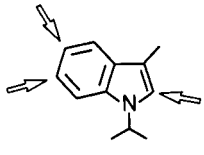
Indoles react with ethyl orthoformate (a^1-synthon) under proton-catalyzed conditions to form trisindolylmethanes [1]. We have previously discussed the course of the reaction and formation of the products [1,2] for the example of the reactions with 2-unsubstituted and 3-substituted methylindoles. In the present paper, we report on analogous reactions with the less nucleophilic and, in one case, sterically hindered indoles **1** and **2** and describe the synthesis of new trisindolylmethanes.

1-Isopropyl-3-methylindole (**1**) is relatively unreactive and is only converted to the regioisomeric trisindolylmethanes **4-6** after heating under reflux with triethyl orthoformate for 60 hours. After column chromatographic separation of the crude product, two fractions are obtained initially, each in 1.9% yield. In their mass spectra, each fraction exhibits a trisindolylmethane molecular ion peak at m/e = 529 (100% relative intensity). The methanes **4**, **5**, and **6** can be isolated, however with loss in yield, after several preparative tlc separations. A complete, mutual purification of the regioisomers cannot be achieved in spite of repeated tlc. It can be seen from the 400 MHz pmr spectra in all three cases that a mutual contamination of about 1-5% is present. However, reliable structural assignments for the new trisindolylmethanes **4-6** can be made on the basis of the 400 MHz pmr spectra.



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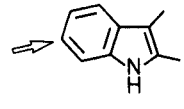
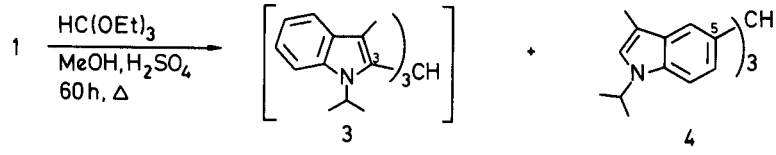
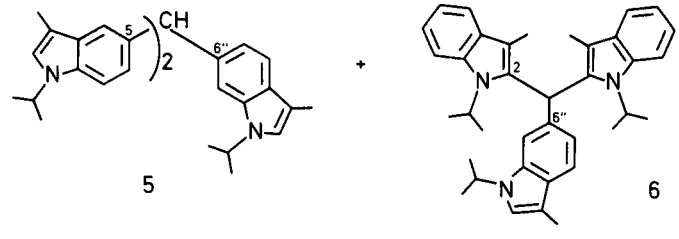


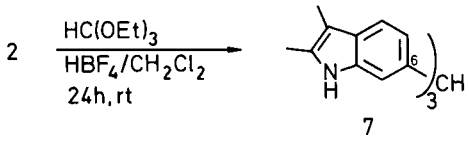
2

Information confirming the regiochemistry was obtained from the positions of the resonances of H-4 and H-2 of the indole skeletons in **4-6** as well as the characteristic coupling patterns of the indole protons [3] (see experimental section). The regioisomer **3** in which linking occurs exclusively at the 2-position is not formed for steric reasons.

2,3-Dimethylindole (**2**) reacts with triethyl orthoformate in dichloromethane in the presence of tetrafluoroboric acid much more rapidly and with high regioselectivity to form the 6,6',6''-trisindolylmethane **7**. The regiochemistry at position 6 of the indole skeleton in the product is completely in accord with that of the product of the reaction of **2** with aromatic aldehydes [3].







7

From the above results and our previous observations, the following conclusions on the regiochemistry of the trisindolylmethane formation may be drawn. 3-Unsubstituted indoles react to produce the 3-isomeric compounds [1], 3-methyl- and 1,3-dimethylindoles react to form exclusively the 2-isomeric trisindolylmethanes [2]. When the steric requirements of the 1,3-substitution are increased (as, for example, in **1**), a substitution also takes place on the benzene nucleus of the indole skeleton. 2,3-Dialkylindoles react exclusively and regioselectively at the benzene nucleus (6-position).

EXPERIMENTAL

Melting points were determined using a Büchi 510 apparatus, and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 177 spectrophotometer. Proton magnetic resonance spectra were measured at 400 MHz on a Bruker WM 400 spectrometer. Chemical shift values are reported in δ units (parts per million) relative to tetramethylsilane as an internal standard. Mass spectra were obtained from an LKB Producter 2091 instrument (electron impact, 70 eV). Elemental analyses were performed on a Carlo Erba Strumentazione Model 1106 apparatus. Silica gel 60 (Merck) was used for column chromatography and for thin layer chromatography.

Reaction of 1-Isopropyl-3-methylindole (**1**) with Triethyl Orthoformate.

The indole **1** (6.0 g, 34.6 mmoles) was dissolved with 1.71 g (11.5 mmoles) of triethyl orthoformate in 30 ml of methanol and treated with 5 drops of concentrated sulfuric acid. The mixture was heated under reflux for 60 hours while further portions of 1.71 g of the ortho ester was added every 12 hours. The reaction mixture was then cooled to 0°, made alkaline with aqueous ammonia solution, and extracted with *n*-hexane. The organic extract was evaporated to dryness and the residue subjected to column chromatographic separation (eluent: *n*-hexane:dichloromethane, 5:1). The two fractions obtained were purified further by preparative tlc (solvent system: *n*-pentane:benzene, 2:1; four-fold development). The three fractions thus obtained were desorbed from the silica gel with dichloromethane and the products slowly precipitated from the dichloromethane solutions by dropwise addition of methanol.

Tris[1-isopropyl-3-methylindol-5-yl]methane (**4**).

This compound was obtained in 0.75% (46 mg) as colorless crystals; ir (potassium bromide): 3080, 3030, 3010, 2985, 2930, 2870, 1480, 1450, 1400, 1380, 1360, 1305, 1280, 1230, 1200, 1170, 1140, 1125, 1075, 795, 790, 770, 755, 730, 720 cm^{-1}; pmr (deuteriochloroform): δ 1.46 (d, ^3J = 6.5 Hz, 18H, isopropyl-CH_3), 2.23 (d, ^4J = 1 Hz, 9H, H_3C-C3), 4.57 (sept, ^3J = 6.5 Hz, 3H, isopropyl-CH), 5.94 (s, 1H, methine-H), 6.93 (d, ^4J = 1 Hz, 3H, H-C2), 7.08 (dd, $^3J_{6,7}$ = 8.5 Hz, $^4J_{4,6}$ = 1.5 Hz, 3H, H-C6), 7.18 (d, $^3J_{6,7}$ = 8.5 Hz, 3H, H-C7), 7.40 (d, $^4J_{4,6}$ = 1.5 Hz, 3H, H-C4); ms: m/e = 529 (M^+, 100%).

Anal. Calcd. for $C_{37}H_{43}N_3$ (529.77): C, 83.89; H, 8.18; N, 7.93. Found: C, 83.71; H, 7.99; N, 7.89 (*circa* 1% contamination by the other regioisomers).

Bis[1-isopropyl-3-methylindol-5-yl][1-isopropyl-3-methylindol-6-yl]methane (**5**).

This compound was obtained in <0.1% yield (5 mg) as colorless crystals; ir (potassium bromide): 3020, 2980, 2870, 1610, 1550, 1475, 1450, 1380, 1360, 1300, 1290, 1230, 1200, 1140, 790, 775, 755, 740, 735, 725 cm^{-1}; pmr (deuteriochloroform): signals of the 5-linked unit, δ 1.46 (d, ^3J = 6.75 Hz, 12H, isopropyl-CH_3), 2.22 (d, ^4J = 1 Hz, 6H, H_3C-C3), 4.57 (sept, ^3J = 6.75 Hz, 2H, isopropyl-CH), 6.93 (d, ^4J = 1 Hz, 2H, H-C2), 7.07 (dd, $^3J_{6,7}$ = 8.5 Hz, $^4J_{4,6}$ = 1.5 Hz, 2H, H-C6), 7.19 (d, $^3J_{6,7}$ = 8.5 Hz, 2H, H-C7), 7.40 (d, $^4J_{4,6}$ = 1.5 Hz, 2H, H-C4); signals of the 6-linked unit, δ 1.40 (d, ^3J = 6.75 Hz, 6H, isopropyl-CH_3), 2.32 (d, ^4J = 1 Hz, 3H, H_3C-C3), 4.48 (sept, ^3J = 6.75 Hz, 1H, isopropyl-CH), 6.92 (d, ^4J = 1 Hz, 1H, H-C2), 6.99 (dd, $^3J_{4,5}$ = 8.5 Hz, $^4J_{5,7}$ = 1.5 Hz, 1H, H-C5), 7.19 (s, 1H, H-C7), 7.42 (d, $^3J_{4,5}$ = 8.5 Hz, 1H, H-C4); 5.94 (s, 1H, methine-H); ms: m/e = 529 (M^+, 100%).

[Bis(1-isopropyl-3-methylindol-2-yl)][1-isopropyl-3-methylindol-6-yl]methane (**6**).

This compound was obtained in a yield of 0.65% (39.5 mg) as colorless crystals; ir (potassium bromide): 3090, 3050, 3030, 2970, 2935, 2880, 1480, 1465, 1455, 1410, 1385, 1365, 1340, 1325, 1300, 1235, 1220, 1180, 1135, 1105, 1020, 775, 730 cm^{-1}; pmr (deuteriochloroform [5]): signals of the 2-linked unit, δ 1.26, 1.32, 1.44, 1.46 (4d, broadened, ^3J = 6.75 Hz, isopropyl-CH_3), 1.54, 1.70 (2s, broadened, 6H, H_3C-C3), 4.60 (m, 3H, isopropyl-CH), 7.05 (t, broad, ^3J = 7.5 Hz, 2H, H-C5), 7.13 (dt, ^3J = 7.5 Hz, ^4J = 1.3 Hz, 2H, H-C6), 7.22 (d, ^3J = 8.5 Hz, 1H, H-C7), 7.50 (d, ^3J = 8.5 Hz, 2H, H-C4); signals of the 6-linked unit, δ 1.50 (d, ^3J = 6.75 Hz, 6H, isopropyl-CH_3), 2.21 (d, ^3J = 1 Hz, 3H, H_3C-C3), 6.99 (d, ^4J = 1 Hz, H-C2), 7.0 (d, 1H), 7.31 (s, 1H), 7.51 (d, overlapped, 1H, indole-H), 6.10 (s, 1H, methine-H); ms: m/e = 529 (M^+, 100%).

Reaction of 2,3-Dimethylindole (**2**) with Triethyl Orthoformate.

Tris[2,3-dimethylindol-6-yl]methane (**7**).

To a solution of 6.0 g (41.3 mmoles) of the indole **2** in 60 ml of dichloromethane was added dropwise over a period of 30 minutes a solution of 3.1 g (20.9 mmoles) of triethyl orthoformate and 3.3 g (20.4 mmoles) of tetrafluoroboric acid (as a 54% solution of tetrafluoroboric acid in diethyl ether) in 20 ml of dichloromethane. After a reaction time of 24 hours at room temperature, the mixture was cooled to 0° and made alkaline with aqueous ammonia solution. The dichloromethane phase was separated, dried, and treated with some methanol. After about 24 hours at 0°, slow crystallization of **7** occurred, yield 1.64 g (18%), colorless crystals, mp 290°; ir (potassium bromide): 3400 (NH), 3030, 2930, 2870, 1630, 1470, 1420, 1350, 1335, 1245, 1160, 800, 785, 710 cm^{-1}; pmr (hexadeuterioacetone): δ 2.15 (s, 9H, CH_3), 2.29 (s, 3H, CH_3), 5.79 (s, 1H, methine-H), 6.86 (dd, $^3J_{4,5}$ = 8 Hz, $^4J_{5,7}$ = 1.5 Hz, 3H, H-C5), 6.88 (s, 3H, H-C7), 7.25 (d, $^3J_{4,5}$ = 8 Hz, 3H, H-C4), 9.50 (s, 3H, NH); ms: m/e = 445 (M^+, 100%).

Anal. Calcd. for $C_{31}H_{31}N_3$ (445.62): C, 83.56; H, 7.01; N, 9.43. Found: C, 83.45; H, 7.16; N, 9.30.

REFERENCES AND NOTES

[1] E. Akgün and U. Pindur, *J. Heterocyclic Chem.*, **20**, 1303 (1983).

[2] J. Müller and U. Pindur, *Arch. Pharm. (Weinheim)*, **317**, 555 (1984); J. Müller, Thesis, University of Würzburg (Germany), 1986.

[3] E. Schiffl and U. Pindur, *J. Heterocyclic Chem.*, **23**, 651 (1986).

[4] U. Pindur and E. Schiffl, *Monatsh. Chem.*, in press.

[5] Compound **6** exists as rotamers on the nmr time scale. Additionally the isopropyl *methyl* protons of the 2-linked units are diastereotopic, because this group is localized in the outer sphere of the symmetric plane of the whole molecule.