The Reactions of Pindolol, Mepindolol, Carazolol, and Related Model Compounds with Triethyl Orthoformate: Pathways and Products of a New Colour Reaction

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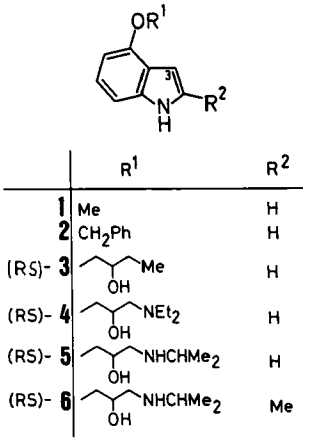
The acid-catalysed electrophilic tandem substitutions of pindolol, mepindolol, and carazolol and some related model compounds with triethyl ortho formate give rise to new derivatives from the trishetaryl methane series. In some cases also further functionalised heterocycles were isolated. The structural aspects of the new trishetarylmethanes were discussed as C_3-symmetric molecular propellers, respectively. The importance of the described reaction as colour reaction was mentioned.

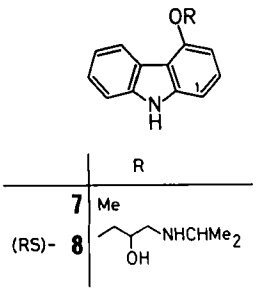
Zur Reaktion von Pindolol, Mepindolol, Carazolol und verwandten Modellverbindungen mit Orthoameisensäuretriethylester: Reaktionswege und Produkte einer neuen Farbreaktion

Bei der säurekatalysierten electrophilen Tandem-Substitution von Pindolol, Mepindolol und Carazolol sowie bei einigen verwandten Modellverbindungen werden mit Orthoameisensäuretriethylester neue Trishetarylmethane erhalten. In einigen Fällen entstehen auch weitere funktionalisierte Heterocyclen. Die strukturellen Aspekte der neuen Trishetarylmethane als C_3-symmetrische molekulare Propeller werden diskutiert, auf die Bedeutung der vorgestellten Reaktionen als Farbreaktion wird hingewiesen.

Analytically exploitable colour reactions continue to play a major role in the drug analysis[1-3]. A new and topical scope of application for colour reactions is presented, for example, in the DAB 9 and the second edition of the European Pharmacoepia[4]. In order to attain a sufficient substrate specificity for a colour reaction, knowledge of the chemical processes as well as of the structures of the coloured products is indispensible. This is especially valid in those cases involving spectrophotometrical assessment of coloured reaction solutions.

In continuation of our investigations[1,2] on the elucidation of colour reactions for drug analysis, we now report on further results of a new colour reaction developed in our laboratory[5] for electron-rich, heteroaromatic drugs, namely the reaction system "heteroarene derivatives/triethyl orthoformate". Our preparative work with orthoesters or dialkoxycarbenium ions, respectively, as electrophiles[6] stimulated us to undertake a wideranging colour screening with orthoesters. We have found thereby that electron-rich aromatic[5] and heteroaromatic drugs in particular produce very sensitive and selective colour reactions both in drop test and in test-tube tests when treated with triethyl orthoformate as an a^1-reagent [via $HC(OEt)^2$] under acid catalysis. The detection limits of these reactions are close to those of the *van Urk* reaction[2]. From the range of racemic heteroaromatic drugs available, we have selected pindolol (**5**), mepindolol (**6**), and carazolol (**8**) as well as the structurally related model compounds **1-4** and **7** for our investigations. Here also, the concept of "model substance versus drug" established by us for comparative analysis of products and reaction pathways has again proved itself fully.





Reaction Pathways and Structures of the Products

On the basis of our results with **1-8**, which will be discussed below, the major reaction pathway of the transformations of **1-8** with triethyl orthoformate can be clearly defined (Scheme 1) as a tandem electrophilic heteroaromatic substitution together with an oxidation step. In the first step, a regioselective electrophilic substitution gives rise to **I** which is in equilibrium with the heteroaromatic aldehyde **II**. A subsequent electrophilic reaction of **I** or **II** with **1-8** leads, in turn, to the cyanine **III**. These components, which are already coloured, in many cases possess a sufficient electrophilic potential (kinetic reactivity) and can ultimately attain C_3 symmetry after a further s_EAr reaction with the starting compound. The new tris(heteroaryl)methane leucobases **IV** are finally - especially in the presence of oxidising agents [$FeCl_3$, $Pb(OAc)_4$] - dehydrogenated to form the trinuclear cyanines **V**. Compounds **III** and **V** represent the coloured components of this colour reaction.

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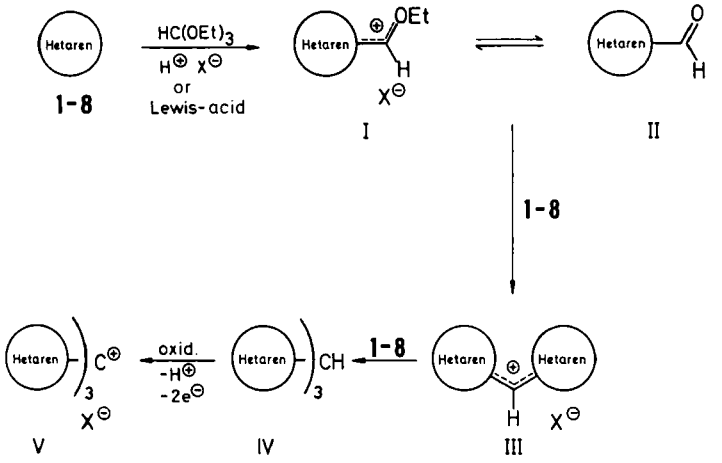


Scheme 1

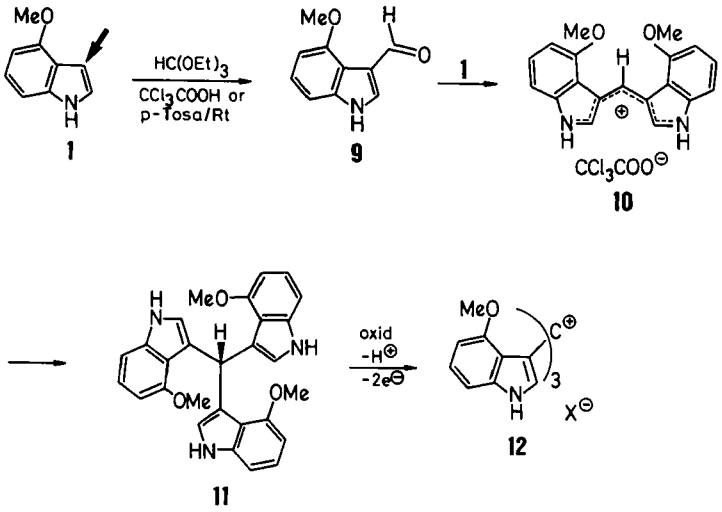
Mechanistic confirmation of Scheme 1 was obtained in all cases by the preparative isolation and structural analytical characterisation of the leucobases **IV** and, in some cases, also of their "precursors". In these individual cases, however, the reaction conditions and the acid catalysts had to be varied in order to achieve preparatively useful results.

For the unequivocal elucidation of the mechanism of the reactions of triethyl orthoformate with **5, 6,** and **8,** we initially investigated the structurally more simple model substances **1-4** and **7**. In the reactions with the simple "pindolol/mepindolol" model substance **1** and with **7**[7], we were also able to isolate several of the reaction products shown in Scheme 1 in preparative amounts as a consequence of stability factors. In the other cases, however, we were only able to isolate the C_3-symmetrical tris(heteroaryl)methane leucobases **IV**. Since compounds **IV** practically represent nearly the end of the colour reaction sequence, they are decisive compounds for the rational elucidation of the reaction mechanisms.

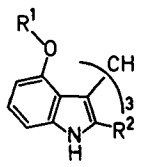
In the electrophilic tandem reaction of 4-methoxyindole (**1**) (Scheme 2), the indole-3-carbaldehyde **9**, the novel, bis-benzo-annellated pentamethine cyanine **10a** (as the trichloroacetate; **10b** = tetrafluoroborate), and the C_3-symmetrical tris(indolyl)methane **11** could be isolated in preparatively useful amounts by variations of the reaction conditions. Like all leucobases of the indole series[8], compound **11** is very sensitive to oxidation and, for example, can be dehydrogenated by $FeCl_3$/HCl to the heteroanalogous triphenylmethane dye **12**. However, as a consequence of its ready decomposition, **12** could not yet be purified sufficiently for an unambiguous structural analysis.

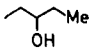
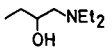
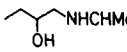
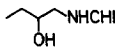
Even in the cases of successive increases in size of the side chain in the 4-alkoxyindole, the reaction sequence analogous to that observed with **1** took place. In the reactions of triethyl orthoformate with the synthetic model substances **2-4** and, finally, with the drugs **5** and **6**, we also obtained the novel, molecular three-bladed propellers[8,9] **13-17**. The yields were sensitively controlled by the spatial requirements of the alkoxy groups and this is in good agreement with considerations of *Büchi-Dreiding* molecular models. In the reaction of compound **6**, the yieldlowering effect of the indole 2-methyl group was additionally apparent.

In analogy to our initial investigations on the molecular structures and dynamics of molecular propellers of the indole series[10], compounds **11, 13-17** should also take up C_3 or C_3-skeletal propeller conformations in solution (and most probably also in single crystals[10]). Our own force field calculations (see Figure 1) as well as differential $^1H,^1H$-NOE



Scheme 2



	R^1	R^2	Yield [%]
13	CH_2Ph	H	71
14		H	53
15		H	22
16		H	31
17		Me	9

measurements are unequivocally in accord with the existence of the propeller conformations for the minimum energy states of **11** and **13-17**. In Figure 1 the computer-simulated skeletal models of **11** (**P**- and **M**-helix) and **16** (exemplarily **M**-helix with **RRS** side-chain configuration) are shown as examples.

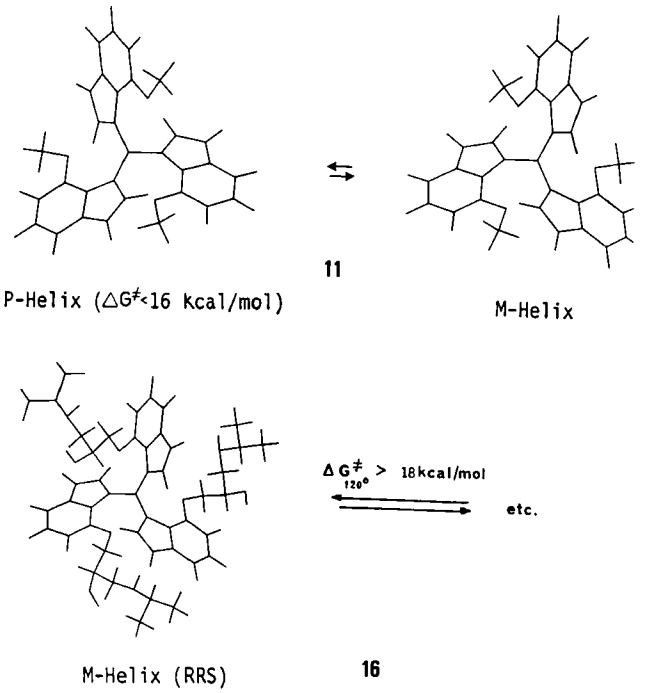


Fig. 1: Skeletal molecular models of **11** and **16** (computer simulation, energy minimisation according to force field calculations, molecular modeling software ALCHEMY II, "Tripos Associates"). The torsional angle of the three "indolyl blades" to the reference plane[8,9] amounts to 45°. Viewed in the direction of the axis of the helix.

The 400 MHz ^{1}H-NMR spectra of compounds **11** and **13** (at 20°C) reflect the expected C_3 symmetry with rapid exchange. The energy barrier to C_3 propeller stereoisomerisation should amount to less than 16 kcal/mol (see Figure 1 for the example of compound **11**). In contrast, the ^{1}H-NMR spectra of compounds **14, 15, 16,** and **17** at a measurement temp. of 20°C are complicated (signal broadening, signal overlapping). Reduction of the measurement temp. did not bring about a change in the signal pattern; hence, the temp. range of the slow exchange (slow propeller stereoisomerisation) must be around 20°C. Recordings of the ^{1}H-NMR spectra of **14-16** at higher temp. showed that the average coalescence temp. was at about 120°C in all cases except for compound **17** where it was clearly above 120°C.

The average energy barrier to the propeller stereoisomerization $\Delta G^{\neq}$ for compounds **14-17** should thus be markedly more than 18 kcal/mol[11]. The general complexity of the ^{1}H-NMR spectra (see Figure 2 for the spectra of compound **16**) is caused by the combination of two chirality elements (central and axial chirality).

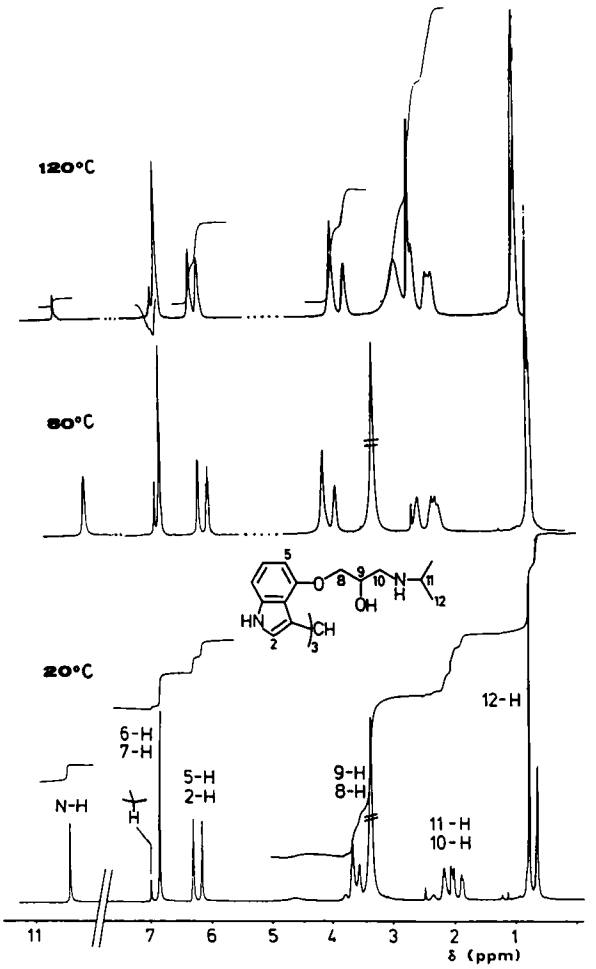
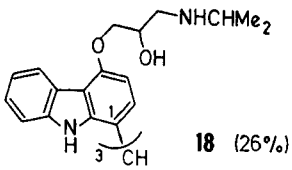


Fig. 2: 400 MHz ^{1}H-NMR spectra of **16** at 20, 80, and 120°C in D_6-DMSO (At 20°C there exists a formal mixture of stereoisomers which result from the combination of the chirality elements of axial and central chirality. In addition, the purely conformational limitations of movement of the "side-chains" which also ultimately influence the barrier to purely propeller stereoisomerization must be taken into consideration).

The electronically donor-activated carbazoles **7** and **8** react regiospecifically at C-1 with triethyl orthoformate. In

the case of **7**, as shown above for the reaction of **1**, several "intermediates" (Scheme 1) can also be isolated; this has already been described[7]. For stability reasons, "only" the leucobase **18** can be isolated in the case of the electrophilic substitution reaction with (**R/S**)-carazolol (**8**). No dynamic effects could be observed in the ^{1}H-NMR spectrum of **18** measured at 20°C and this is reflected in the C_3-skeletal symmetry of the propeller conformations which undergo rapid interconversion (fast exchange on the NMR time scale). The markedly lower energy barrier to propeller stereoisomerisation ($\Delta G^{\neq} < 16$ kcal/mol) in comparison to those of compounds **14-17** can be predicted unambiguously from considerations of *Büchi-Dreiding* molecular models.



18 (26%)

The present experimental results confirm in all of the cases examined a clean and specific mechanistic pathway for this new orthoester colour reaction. The applications of this colour reaction in the qualitative and quantitative analyses of selected drug series will be reported in a separate publication concerned solely with the analytical aspects.

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Experimental Part

Melting points: Büchi SMP-20 capillary m.p. apparatus, uncorrected. - CHN-microanalysis: Carlo Erba Strumentazione model 1106 apparatus. - ^{1}H-NMR spectra: Bruker WM 400 (400 MHz) (δ scale, tetramethylsilane as internal standard). - EI-mass spectra: Varian MAT 7. - FD-mass spectra: Varian MAT 711. - FAB-mass spectra: Finnigan MAT 312. - UV/VIS spectra: Varian Carry 210. - IR spectra: Beckman IR 4220. - Column chromatography: 80 x 3 cm column of Merck silica gel 60 (0.063 - 0.2 mm). - Centrifugal thin layer chromatography (CLC): Harrison Research model 7924 T apparatus, Merck silica gel 60 PF_{254}, layer thickness 2 mm. - Flash chromatography (FC): column capacity 200 ml, Merck silica gel 60 (0.040-0.063 mm). - Medium pressure liquid chromatography (MPLC): Büchi 681 apparatus, LiChroprep® Si 60, Merck, 25-40 µm.

4-Methoxy-3-carbaldehyde (**9**)

A) *Preparation using triethyl orthoformate*

4-Methoxyindole (**1**; 74 mg, 0.5 mmol) was mixed with triethyl orthoformate (148 mg, 1 mmol) and 7.5 ml of 5% trichloroacetic acid (2.3 mmol of acid) in anhydrous CH_2Cl_2 was added. The mixture became red immediately. After 20 min the mixture was neutralised with dilute aqueous NH_3 and extracted with three 20 ml portions of CH_2Cl_2. The org. phase was dried with $CaCl_2$, concentrated, the resultant crude product was taken up in a small volume of ethyl acetate, and separated by CLC [petrol ether (40-60°C)/ethyl acetate, 1/1] to give pale yellow crystals which were recrystallised from methanol. Yield 31 mg (36%); the yield could be increased considerably be increasing the ortho ester and acid concentrations.

B) Vislmeier-Haack formylation[12]

4-Methoxyindole (**1**; 147 mg, 1 mmol) was dissolved in dimethylformamide, the solution was cooled, and PCl_3 (0.11 ml, 1.18 mmol) was added dropwise. The mixture was warmed to 40°C. After a total reaction time of 1 h, 5 ml of ice/water were added whereupon the formed precipitate dissolved. As soon as the solution became clear it was made basic by 5% aqueous NaOH and warmed again for a short time on a water bath. The precipitate formed on basification was separated and washed several times with water. The product was almost pure according to TLC and was recrystallised from methanol. Yield 142 mg (82%). - M.p. 156°C (MeOH); Lit.[12] m.p. 162-163°C. - EI-MS (70 eV): m/z (%) = 175 ($M^{+\cdot}$, 100), 174 (19), 160 (34), 159 (17), 157 (12), 146 (38), 144 (43), 104 (89). - IR (KBr): ν (cm^{-1}) = 3250 (m, br., NH), 3110 (w), 3010 (w), 2970 (w), 2930 (w), 2890 (w), 2840 (w), 1720 (w), 1650 (s), 1585 (m), 1510 (s), 1460 (m), 1450 (m), 1430 (m), 1390 (s), 1360 (s), 1325 (s), 1305 (m), 1270 (m), 1240 (s), 1190 (w), 1175 (w), 1125 (w), 1090 (s), 1055 (w), 970 (m), 850 (w), 790 (m), 745 (m), 700 (w). - ^{1}H-NMR (400 MHz, D_6-DMSO): δ (ppm) = 3.94 (s, 3H, OCH_3), 6.74 (br. d, ^3J = 7 Hz, 1H, H-5), 7.09-7.18 (m, 2H, H-6, H-7), 8.05 (s, 1H, H-2), 10.33 (s, 1H, CHO), 12.22 (s, 1H, NH). - $C_{10}H_9NO_2$ (175.2) Calcd. C 68.6 H 5.18 N 8.0 Found C 68.3 H 5.28 N 7.9.

Bis(4-methoxyindol-3-yl)methylium Trichloroacetate (**10a**)

4-Methoxyindole (**1**; 74 mg, 0.5 mmol) and triethyl orthoformate (148 mg, 1 mmol) were dissolved together in 5 ml anhydrous CH_2Cl_2. On addition of trichloroacetic acid (50 mg, 0.31 mmol) the solution turned intense violet. Within the following 15 min the reaction mixture was swirled several times. After 1 h, the precipitate was filtered off and washed several times with CH_2Cl_2. The remaining red-violet, metallic-shining needles were pure according to TLC analysis. Yield 81 mg (51%). - m.p. 240-250°C (decomp., discolouration above about 130°C). - EI-MS (70 eV): m/z (%) = 306 (13), 147 (100), 132 (73). - IR (KBr): ν (cm^{-1}) = 3300-2700 (m, br.), 1730 (s, br.), 1600 (m), 1560 (s), 1500 (m), 1450 (m), 1390 (s), 1355 (w), 1330 (s), 1305 (w), 1270 (s), 1245 (m), 1165 (m), 1140 (s), 1090 (w), 1070 (s), 970 (m), 840 (m), 780 (m), 730 (m). - UV/VIS (0.5% H_2SO_4 in methanol): λ max (nm) (log ε) = 560 (4.47). - $C_{21}H_{17}Cl_3N_2O_4$ (631.1) Calcd. C 43.8 H 2.87 N 4.4 Cl 33.7 Found C 44.0 H 2.79 N 4.3 Cl 33.7.

Bis(4-methoxyindol-3-yl)methylium Tetrafluoroborate (**10b**)

4-Methoxyindole (**1**; 147 mg, 1 mmol was dissolved together with triethyl orthoformate (74 mg, 0.5 mmol) in 4 ml of anhydrous CH_2Cl_2 and HBF_4 diethyl etherate (0.5 mmol, 0.7 ml of 54% HBF_4 in diethyl ether) was added dropwise. The mixture was swirled several times at room temp. and a dark precipitate formed. After 10 min, the precipitate was filtered off; it consists of practically pure product according to TLC and was recrystallised from methanol to furnish fine, dark green, highly matted needles. Yield 148 mg (76%). - M.p. 220-223°C (decomp., methanol). - EI-MS (70 eV): m/z (%) = 306 (3), 148 (30), 147 (100), 132 (4), 104 (87). - FD-MS: m/z (%) = 305 (M_+ - BF_4, 100), 304 (16). - IR (KBr): ν (cm^{-1}) = 3400-2600 (m, br.), 1600 (m), 1565 (s), 1505 (m), 1450 (m), 1400 (s), 1360 (w), 1335 (s), 1305 (w), 1275 (s), 1170 (m), 1150 (m), 1070 (s, br.), 970 (m), 790 (m), 780 (m), 730 (m). - ^{1}H-NMR (400 MHZ, CD_3OD): δ (ppm) = 4.15 (s, 6H, OCH_3), 7.06 (d, ^3J = 8.1 Hz, 2H, H-5 or H-7), 7.25 (d, ^3J = 8 Hz, 2H, H-7 or H-5), 7.42 (t, ^3J = 8 Hz, 2H, H-6), 8.98 (s, 2H, H-2), 10.13 (s, 1H, methine H). - UV/VIS (0.5% H_2SO_4 in methanol): λ max (nm) (log ε) = 560 (4.41). - $C_{19}H_{17}N_2O_2 \cdot BF_4$ (392.2) Calcd. C 58.2 H 4.37 N 7.1 Found C 57.3 H 4.41 N 6.9.

3,3',3"-Methylidynetris(4-methoxyindole) (**11**)

4-Methoxyindole (**1**; 147 mg, 1 mmol) together with p-toluenesulphonic acid monohydrate (19 mg, 0.1 mmol) and triethyl orthoformate (296 mg, 2

mmol) were dissolved in 2.2 ml methanol. The mixture got violet rapidly and after 20 min a light-coloured precipitate began to form. After 6 h, this precipitate was washed several times with methanol to furnish a light violet-coloured amorphous powder. Yield 87 mg (58%). - M.p. 325°C (decomp.). - EI-MS (70 eV): m/z (%) = 451 ($M^{+\cdot}$, 100), 450 (11), 436 (4), 420 (9), 305 (7), 304 (19), 303 (9), 290 (7), 289 (14), 273 (11), 225 (8), 160 (4). - IR (KBr): ν (cm^{-1}) = 3400 (s, NH), 3070 (w), 2990 (w), 2920 (w), 2830 (w), 1610 (m), 1580 (s), 1500 (s), 1460 (m), 1450 (m), 1430 (m), 1420 (w), 1360 (s), 1330 (m), 1300 (w), 1285 (w), 1260 (s), 1225 (w), 1185 (w), 1160 (w), 1120 (m), 1075 (s), 1050 (w), 1030 (m), 980 (w), 840 (w), 815 (w), 770 (s), 740 (s), 690 (w). - ^{1}H-NMR (400 MHz, D_6-DMSO): δ (ppm) = 3.59 (s, 9H, OCH_3), 6.32 (mc, 3H, H-5), 6.44 (d, ^3J = 1.2 Hz, 3H, H-2), 6.85-6.90 (m, 6H, H-6, H-7), 7.28 (s 1H, methine H), 10.48 (d, ^3J = 1 Hz, 3H, NH). - $C_{28}H_{25}N_3O$ (451.5) Calcd. C 74.5 H 5.58 N 9.3 Found C 74.4 H 5.59 N 8.9.

(R/S)-1-(4-Indolyloxy)-2-butanol (**3**)

4-Hydroxyindole (399 mg, 3 mmol) and NaOH (125 mg, 3.1 mmol) were dissolved in 15 ml water, then (*R/S*)-1,2-epoxybutane (648 mg, 9 mmol) was added dropwise. The mixture was stirred at room temp. for 12 h, the pH of the mixture was then adjusted to 8 by aqueous NH_4Cl solution, and the mixture was finally extracted with four 50 ml portions of CH_2Cl_2/isopropanol (4/1). The combined org. phases were dried with $CaCl_2$, concentrated under vacuum, and the viscous crude product was purified by FC (chloroform/methanol, 95/5). The substance could not be crystallised from various solvents but separated as a pale greencoloured, viscous oil after removal of residual solvents under vacuum. Yield 357 mg (58%). - EI-MS (70 eV). m/z (%): 205 ($M^{+\cdot}$, 21), 134 (11), 133 (100), 132 (11), 105 (13), 104 (14), 77 (6). - IR (KBr): ν (cm^{-1}) = 3600-3100 (s, br., OH, NH), 2910 (s, br.), 1610 (w), 1585 (s), 1500 (m), 1440 (m), 1410 (w), 1355 (s), 1285 (m), 1240 (s), 1130 (m), 1055 (m), 1030 (w), 995 (w), 970 (w), 920 (w), 900 (w), 740 (s). - ^{1}H-NMR (400 MHz, D_6-DMSO): δ (ppm) = 0.94 (t, ^3J = 7.4 Hz, 3H, CH_3), 1.40-1.50 and 1.60-1.68 (2m, 2H, CH_2CH_3), 3.74-3.81 (m, 1H, CHOH), 3.88-3.97 (m, 2H, OCH_2CHOH), 4.83 (d, ^3J = 5.2 Hz, 1H, OH), 6.42-6.46 (m, 2H, H-3, H-5), 6.93-6.99 (m, 2H, H-6, H-7), 7.19 (t, ^3J = 2.6 Hz, 1H, H-2), 11.03 (s, 1H, NH). - $C_{12}H_{15}NO_2$ (205.3) Calcd. C 70.2 H 7.37 N 6.8 Found C 69.9 H 7.13 N 7.0.

(R/S)-1-(4-Indolyloxy)-3-diethylamino-2-propanol (**4**)

Procedure modified according to Ref.[13]

4-Hydroxyindole (532 mg, 4 mmol) and NaOH (160 mg, 4 mmol) were dissolved in 5 ml water and then treated with (*R/S*)-epichlorhydrin (500 mg, 5.4 mmol). The mixture was stirred at room temp. for 14 h, then neutralised and extracted with diethyl ether. The ether phase was dried, evaporated, and the residue was heated under reflux with 5 ml of diethylamine for 8 h. Excess amine was removed under reduced pressure, the residue was dissolved in a small volume of $CHCl_3$, and separated by CLC (eluents: 1. $CHCl_3$, 2. $CHCl_3$/methanol, 90/10, 3. $CHCl_3$/methanol, 90/10 under a NH_3 atmosphere). The product separated as a light brown, viscous oil. Yield 714 mg (68%). - EI-MS (70 eV): m/z (%) = 262 ($M^{+\cdot}$, 2), 158 (2), 133 (12), 132 (19), 104 (19), 104 (23), 86 (100). - IR (KBr): ν (cm^{-1}) = 3600-3100 (s, br., NH, OH), 2930 (s), 2830 (s), 1620 (w), 1590 (s), 1505 (m), 1450 (m), 1370 (s), 1290 (m), 1250 (s), 1175 (w), 1060 (s), 905 (w), 750 (s). - ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 1.05 (t, ^3J = 7.2 Hz, 3H, CH_3), 2.51-2.72 (m, 6H, $CH_2N(CH_2)_2$), 3.0-4.0 (br. s, 1H, OH), 4.07-4.13 and 4.16-4.20 (2m, 3H, OCH_2CHOH), 6.52 (d, ^3J = 7.5 Hz, 1H, H-5), 6.65 (mc, 1H, H-3), 7.00 (d, ^3J = 8.2 Hz, 1H, H-7), 7.06-7.10 (m, 2H, H-2, H-6), 8.29 (br. s, 1H, NH). - $C_{15}H_{22}N_2O_2$ (262.4) Calcd. C 68.7 H 8.45 N 10.7 Found C 68.3 H 8.28 N 10.9.

3,3',3"-Tris(4-benzyloxyindolyl)methane (**13**)

The procedure described above for product **11** was followed starting from 4-benzyloxyindole (**2**; 200 mg, 0.9 mmol). The product was obtained as an amorphous powder with a violet-coloured surface. Yield 145 mg (71%). - M.p. 245°C. - EI-MS (70 eV) m/z (%) = 679 ($M^{+\cdot}$, 9), 588 (5), 457 (3), 456 (6), 406 (12), 366 (6), 365 (10), 223 (31), 132 (34), 104 (17), 91 (100). - IR (KBr): ν (cm^{-1}) = 3420 (s, NH), 3050 (w), 2900 (w), 1615 (m), 1585 (m), 1545 (w), 1500 (s), 1455 (m), 1420 (w), 1380 (w), 1360 (s), 1325 (m), 1260 (s), 1240 (m), 1220 (s), 1120 (w), 1070 (s), 1055 (m), 1030 (m), 775 (m), 750 (m), 735 (s), 700 (m). - ^{1}H-NMR (400 MHz, D_6-DMSO): δ (ppm) = 4.81 (s, 6H, CH_2), 6.26 (s, 3H, H-2), 6.34 (d, ^3J = 7.7 Hz, H-5), 6.82 (m, 21 H, H-6, H-7 and CH_2-C_6H_5), 7.24 (s, 1H, methine H), 10.54 (s, 3H, NH). - $C_{46}H_{37}N_3O_3$ (679.82) Calcd. C 81.3 H 5.49 N 6.2 Found C 81.5 H 5.48 N 5.9

3,3',3"-Tris[4-(2-hydoxy-n-butoxy)-indolyl]methane (**14**)

The procedure described for **11** was followed starting from 4-(2-hydroxy-n-butoxy)-indole (**3**; 158 mg, 0.77 mmol). The product was obtained as an amorphous powder with a light violet-coloured surface. Yield 86 mg (53%). - M.p. 291°C (decomp.). - EI-MS (70 eV): m/z (%) = 625 ($M^{+\cdot}$, 100), 552 (11), 422 (11), 421 (16), 420 (32), 348 (15), 289 (12), 276 (23), 275 (34), 205 (20), 146 (28), 133 (87), 104 (19). - IR (KBr): ν (cm^{-1}) = 3510 (m), 3420 (m), 3300 (s), 2960 (m), 2920 (m), 2870 (m), 1610 (w), 1580 (m), 1540 (w), 1500 (w), 1460 (m), 1435 (m), 1360 (s), 1325 (m), 1255 (s), 1230 (m), 1120 (m), 1085 (s), 1055 (m), 1030 (m), 925 (w), 775 (m), 735 (s). - ^{1}H-NMR (400 MHz, D_6-DMSO): δ (ppm) = 0.28-0.38 and 0.50-0.57 (2m, 9H, CH_3), 0.76-0.79, 0.91-1.03, and 1.3-1.48 (3m, 6H, CH_2CH_3), 2.6-3.68 (several m, 9H, OCH_2CHOH), 6.02-6.07 (m, 3H, H-2), 6.23-6.26 (m, 3H, H-5), 6.59, 6.66, and 6.73 (3s, 1H, methine H), 6.86 (m, 6H, H-6, H-7), 10.32-10.37 (m, 3H, NH); OH could not be localised. - $C_{37}H_{43}N_3O_6$ (625.8) Calcd. C 71.1 H 6.93 N 6.7 Found C 70.9 H 6.84 N 6.5.

3,3',3"-Tris[4-(2-hydroxy-3-isopropylamino-n-propyloxy)-indolyl]methane (**16**)

(*R/S*)-Pindolol (**5**; 496 mg, 2 mmol) was dissolved in a mixture of 20 ml CH_2Cl_2, 1.75 ml glacial acetic acid, triethyl orthoformate (592 mg, 4 mmol), and trichloroacetic acid (390 mg, 2.4 mmol). The colour of the reaction mixture slowly changed to red-violet; after about 30 min a pale precepitate started to form. After 12 h at room temp., the precipitate was removed by suction filtration, and washed with a small amount of cold CH_2Cl_2. The product mixture was separated by MPLC (eluents: 1. ethyl acetate/methanol, 70/30; 2. ethyl acetate/methanol/diethylamine, 70/30/2) to furnish colourless, amorphous crystals. Yield 156 mg (31%). - M.p. 184°C (MeOH). - HR-MS: m/z = 754.9780 (calcd. for $C_{43}H_{58}N_6O_6$: 754.9783). - FD-MS: m/z (%) = 755 ($M^{+\cdot}$, 100), 754 (14), 625 (10). - IR (KBr): ν (cm^{-1}) = 3600-3100 (s, br., OH, NH), 2970 (s), 2930 (m), 2870 (w), 1615 (w), 1585 (m), 1540 (w), 1505 (m), 1435 (m), 1385 (w), 1360 (s), 1330 (w), 1260 (s), 1230 (m), 1175 (w), 1120 (m), 1090 (s), 1030 (s), 985 (w), 775 (m), 735 (s). - ^{1}H-NMR (400 MHz, 20°C, D_6-DMSO): δ (ppm) = 0.65-0.67 (2m, 18H, $CH(CH_3)_3$), 1.87-2.2 (4m, 9H, CH_2NCH), 3.56-3.82 (m, 9H, OCH_2CHOH), 4.3-4.8 (br. s, 3H, OH), 6.15 (br. s, 3H, H-5 or H-2), 6.30 (mc, 3H, H-2 or H-5), 6.86 (br. d, 6H, H-6, H-7), 7.00 (s, 1H, methine H), 10.43 (br. s, 3H, indole NH); aliphatic NH: very broad and not localised.

3,3',3"-Tris[4-(2-hydoxy-3-diethylamino-n-propyloxy)-indolyl]methane (**15**)

(*R/S*)-indole **4** (714 mg, 2.72 mmol) together with triethyl orthoformate (809 mg, 5.47 mmol) and trichloroacetic acid (527 mg, 3.23 mmol) were dissolved in 2.35 ml glacial acetic acid and 27 ml CH_2Cl_2. The mixture

was stirred at room temp. for 5 h, then made alkaline by dilute NH_3 and extracted twice with 30 ml portions of CH_2Cl_2/isopropanol (4/1). The org. phase was concentrated, the residue taken up in a small volume of methanol and purified by CLC (eluents: 1. chloroform under NH_3, 2. chloroform/methanol, 97/3, under NH_3). Pale brown amorphous crystals were obtained from the main fraction. Yield 155 mg (22%). - M.p. 130°C. - $C_{46}H_{64}N_6O_6$ (797.1). - FD-MS: m/z (%) = 797 ($M^{+\cdot}$, 100). - IR (KBr): ν (cm^{-1}) = 3600-3100 (several bands, br., OH, NH), 2960 (s), 2920 (m), 2860 (w), 2810 (w), 1610 (w), 1585 (m), 1540 (w), 1500 (s), 1435 (m), 1360 (s), 1325 (w), 1255 (s), 1165 (w), 1120 (m), 1080 (s), 1030 (w), 770 (m), 730 (s). - ^{1}H-NMR (400 MHz, 20°C, D_6-DMSO): δ (ppm) = 0.57-0.68 (m, 18H, CH_3), 1.72-2.11 (m, 18H, $CH_2N(CH_2)_2$), 3.39-3.84 (m, 9H, OCH_2CHOH), 4.3 (br. s, 3H, OH), 6.09-6.14 (m, 3H, H-5 or H-2), 6.24-6.29 (m, 3H, H-2 or H-5), 6.83-6.86 (m, 6H, H-6, H-7), 6.99, 7.06, and 7.16 (3s, 1H, methine H), 10.36-10.45 (m, 3H, indole NH); aliphatic NH, broad and not localised.

3,3',3"-Tris[2-methyl-4-(2-hydroxy-3-isopropylamino-n-propyloxy)-indolyl]methane (**17**)

(*R/S*-Mepindol sulphate (sulphate of compound **6**; 311 mg, 1 mmol) together with triethyl orthoformate (592 mg, 4 mmol) and *p*-toluenesulphonic acid monohydrate (38 mg, 0.2 mmol) were dissolved in 2.2 ml methanol. The mixture rapidly turned red-violet and was stirred at 50°C for 8 h. The mixture was then made alkaline by dilute NH_3, extracted once with 25 ml CH_2Cl_2 and twice with 25 ml portions of CH_2Cl_2/isopropanol (4/1). The org. extracts were combined, dried with Na_2SO_4, concentrated, and the residue was taken up in a small volume of methanol. Product separation was achieved by CLC [eluents: 1. $CHCl_3$ under NH_3 (separation of starting material); 2. $CHCl_3$/methanol, 96/4 under NH_3]. On concentration of the product fractions, **17** precipitated as a solid which was dissolved in methanol and reprecipitated by addition of ethyl acetate to furnish pale pink-coloured amorphous crystals. Yield 23 mg (9%). - M.p. 237-244°C (decomp.). - $C_{46}H_{64}N_6O_6$ (797.1). - FD-MS: m/z (%) = 797 ($M^{+\cdot}$, 100), 796 (28). - IR (KBr): ν (cm^{-1}) = 3600-3100 (several braod bands, OH, NH), 2960 (m), 2920 (w), 2860 (w), 1615 (w), 1585 (w), 1550 (w), 1500 (m), 1440 (s), 1380 (w), 1360 (m), 1245 (s), 1170 (m), 1120 (s), 1100 (s), 990 (w), 765 (w), 730 (w). - ^{1}H-NMR (400 MHz, D_6-DMSO): δ (ppm) = 0.70-0.84 (2m, 18H, $CH(CH_3)_2$), 1.41-1.48 (m, 9H, indole C-2 - CH_3), 1.68-2.5 (m, 9H CH_2NCH), 3.34-3.69 (m, 9H, OCH_2CHOH), 6.24-6.27 (m, 3H, H-5), 6.73-6.80 (m, 6H, H-6, H-7), 7.47-7.52 (m, 1H, methine H), 10.18-10.22 (m, 3H, indole NH); aliphatic NH; very broad and not localised).

1,1',1"-Tris[4-(2-hydroxy-3-isopropylamino-n-propyloxy)-carbazolyl]-methane (**18**)

(*R/S*)-Carazolol (**8**; 400 mg, 1.34 mmol) together with triethyl orthoformate (400 mg, 2.7 mmol) and trichloroacetic acid (1 g, 6.14 mmol) were dissolved in 20 ml CH_2Cl_2. The mixture became green-blue. After 2 h, the mixture was shaken with a mixture of NH_3 and ice/water and extracted with three 30 ml portions of CH_2Cl_2/isopropanol (1/4). The org. phase was dried and concentrated in a rotary evaporator. The residue was taken up in a small volume of methanol/$CHCl_3$ (1/1) and separated by CLC (eluent: $CHCl_3$/methanol, 92/8, under NH_3). The solid residue obtained from the main product fractions was dissolved in a small amount of CH_2Cl_2 and the product **18** separated on addition of petrol ether (40-60°C) as an almost white amorphous precipitate. Yield 105 mg (26%). M.p.: conversion into a highly viscous red mass above about 125°C which became less viscous on further heating. - FAB-MS: m/z (%) = 905 ($M^{+\cdot}$, 77), 327 (100). - IR (KBr): ν (cm^{-1}) = 3600-3100 (br., OH, NH), 2970 (m), 2930 (w), 2870 (w), 1600 (s), 1510 (m), 1450 (s), 1390 (w), 1355 (m), 1285 (m), 1270 (s), 1220 (w), 1175 (w), 1105 (s), 1015 (w), 790 (w), 750 (m). - ^{1}H-NMR (400 MHz, 20°C, D_6-DMSO): δ (ppm) = 0.98 (mc, 18H, $CH(CH_3)_2$), 2.72, 2.87 (2mc, 9H, CH_2NCH), 4.05 (mc, 9H, OCH_2CHOH), 5.09 (br. s, 3H, OH), 6.48 (s, 6H, H-2, H-3), 6,71 (s, 1H, methine H), 7.10 (t, ^3J = 7.5 Hz, 3H, H-6 or H-7), 7.27 (t, ^3J = 7.6 Hz, 3H, H-7 or H-6), 7.41 (d, ^3J = 8 HZ, 3H, H-8), 8.23 (d, ^3J = 7.7 Hz, 3H, H-5), 10.80 (s, 3H, carbazole NH); aliphatic NH broad and not localised. - $C_{55}H_{64}N_6O_6$ (905.2) Calcd. C 73.0 H 7.13 N 9.3 Found C 73.0 H 6.78 N 9.2.

References

1 U. Pindur, Pharm. Acta Helv. *61*, 326 (1986).

2 U. Pindur, Jahrbuch Pharmalabor 1987, E. Ebel, ed., VCH Verlagsgesellschaft Weinheim, 1987. - U. Pindur and H. Witzel, Dtsch. Apoth. Ztg. *128*, 2127 (1988).

3 S. Ebel, Handbuch der Arzneimittel-Analytik, 1st Edn., Verlag Chemie, Weinheim, New York, 1977 - B. Kakač and Z.J. Vejdělek, Handbuch der photometrischen Analyse organischer Verbindungen, Vol. 1, Vol. 2, and supplementary volumes, Verlag Chemie, Weinheim, 1974-1983.

4 K. Hartke and E. Mutschler, DAB 9 Kommentar, Vols. 1-3, Wissenschaftliche Verlagsgesellschaft, Stuttgart 1987, 1988.

5 U. Pindur and H. Witzel, Pharm. Acta Helv. *63*, 164 (1988).

6 U. Pindur, J. Müller, C. Flo, and H. Witzel, Chem. Soc. Rev. *16*, 75 (1987) and ref. cited there. - J. Müller, Thesis, University of Würzburg 1986. C. Flo, Thesis, University of Mainz 1989.

7 H. Witzel and U. Pindur, J. Heterocyclic Chem. *25*, 907 (1988).

8 U. Pindur and E. Akgün, Pharm. Unserer Zeit *12*, 135 (1983).

9 For the dynamic stereochemistry of molecular propellers, see: K.P. Meurer and F. Vögtle, Top. Curr. Chem. *127*, 1 (1985). - K. Mislow, Acc. Chem. Res. *9*, 26 (1976). - K. Mislow, D. Gust, P. Finochiaro, and R.J. Boettcher, Top. Curr. Chem. *47*, 2 (1974).

10 For the first single crystals X-ray structural analysis of a molecular C_3 three-bladed propeller in the indole series, see: W. Massa, J. Müller, and U. Pindur, Z. Naturforsch. *41b*, 762 (1986).

11 H. Günther, NMR-Spektroskopie, Georg Thieme Verlag, Stuttgart 1983.

12 M. Somei, F. Yamada, M. Kunimoto, and C. Kaneka, Heterocycles *22*, 797 (1984).

13 F. Seeman, E. Wiscott, P. Niklaus, F. Troxler, Helv. Chim. Acta *54*, 2411 (1971).

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