TERPENIC METHYL KETONES DERIVED FROM LIMONENE, (+)-3-CARENE, AND α-PINENE IN FISCHER'S INDOLE SYNTHESIS.

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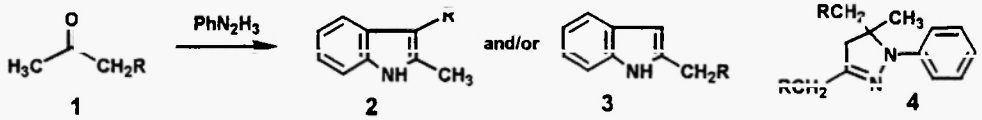
Abstract: Methyl ketones derived from monoterpene hydrocarbons limonene, α-pinene, and (+)-3-carene are converted into a new terpendoles in Fischer's indole synthesis. Regioselectivity of indole formation depend on the structural features of starting ketones but not on the reaction conditions.

Introduction.

Recently a new type of an effective acyl-CoA cholesterol acyltransferase (ACAT) inhibitors termed terpendoles has been reported (1,2) and the structure-activity relationships within the indole-terpenoids has been investigated (3,4). All this terpendoles consist of indole and diterpene moieties. No information was found about similar biological activity of terpendoles consisting of monoterpenoid frame. We supposed to obtain a new indoloterpenoids from monoterpenic ω-keto nitriles by Fischer's method. The ω-keto nitriles, derived from mono- and bicyclic terpenes (5), are convenient and versatile precursors for syntheses of a number of nitrogen heterocycles such as quinoxalines (6), pyrazoles (7,8), pyrazolinoles (8), and isoxazolinoles (7). Previous attempts to apply Fischer's method for the synthesis of indoles from monoterpene ketones failed (9,10,11), for example, phenylhydrazone of camphor gave indole-type compound only as minor product, the product belonging to another structural type because of rearrangement of the carbon skeleton (9). In our work we used another type of starting carbonyl compounds – monoterpenoid methyl ketones **7**, **9**, **11** and aliphatic analogue **5** (***Scheme***). Variation of the Fischer's reaction conditions for methyl ketones **1** is known to lead to different indole-type products **2** and **3** due to different α-positions of the carbonyl (CH_3- or CH_2-position) involved in the reaction. Sometimes abnormal reaction resulted in N-arylpyrazoline **4** was observed (12,13) [for the discussion of the mechanism of the N-arylpyrazoline formation including coupling of a pair of molecules of a hydrazone [see ref. (13)].

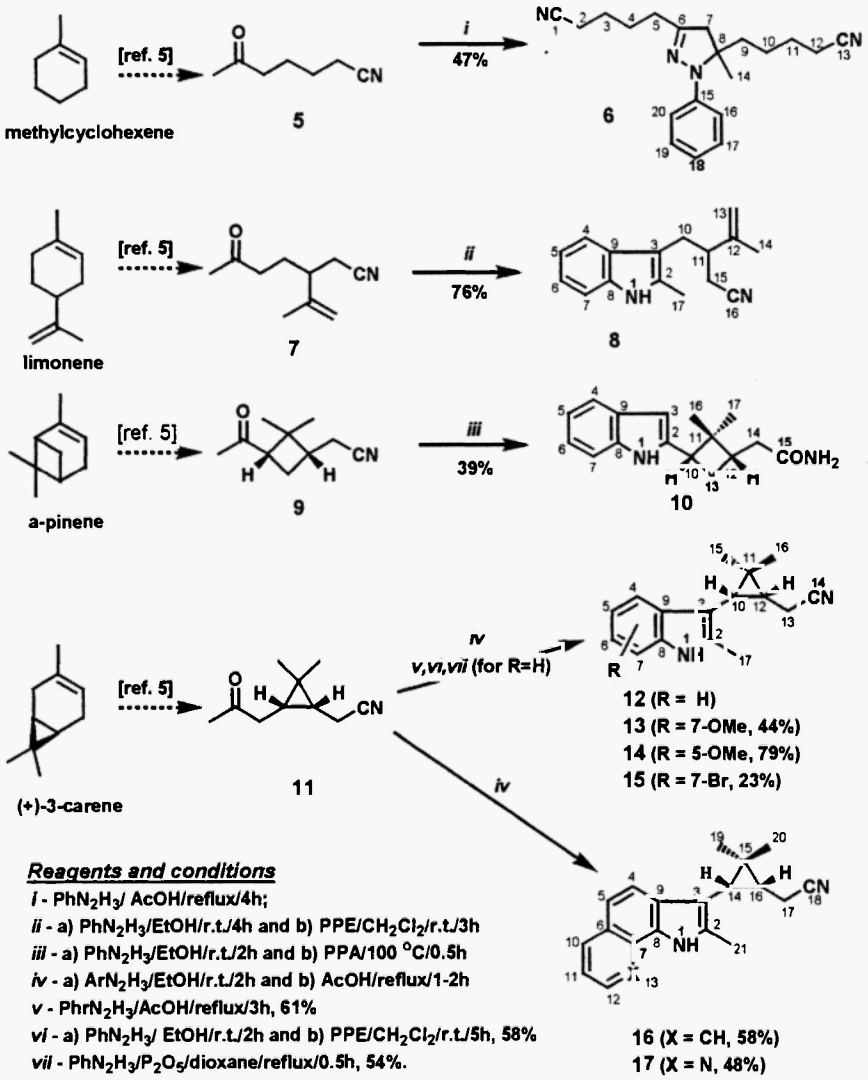


1 2 3 4

Results and discussion.

We have carried out all transformations under the conditions, that are most often used for Fischer's indole synthesis (14): refluxing of a ketone with an arylhydrazine in acetic acid, heating of the resulting arylhydrazone (a) in acetic or polyphosphoric (PPA) acids, (b) with anhydrous zinc chloride in absolute ethanol, (c) in the presence of polyphosphoric acid ester (PPE). We found that in case of compounds **5**, **7**, **9**, **11** regioselectivity of the indoles formation did not depend on the reaction conditions, but has been predetermined by structure of the methyl ketones. The reaction conditions effected just on the ability of the starting ketones to participate in the heterocyclization.

Scheme.



Reaction of 6-oxoheptanenitrile phenylhydrazone **5** in acetic acid gives rise the formation of *N*-phenylpyrazoline **6** in contrast to the reaction of 5-oxohexanenitrile N-phenyl-N-methylhydrazone in 10% aq.

H_2SO_4 or PPA resulted in indole type products (15).No pyrazoline type products is detected in case of the other methyl ketones **7**, **9** and **11**. Thus. in the presence of PPE phenylhydrazone of ketone **7** is converted to indole **8** in 76% yield, although the product obtained is rather unstable at room temperature. Reaction of phenylhydrazone of ketone **7** in acetic or polyphosphoric acids as well as with anhydrous $ZnCl_2$ in absolute ethanol results in simple hydrolysis and recovering of the starting compound **7**, no formation of indole **8** being detected [compare with (16)]. Reaction of phenylhydrazone of ketone **9** both in acetic acid and PPE also results in starting ketone. However. when a solution of the hydrazone in PPA is heated at 100°C for 30 min, formation of indole **10** occurs, the cyano group is transforming to amide because of partial hydrolysis (17). As compared to the molecules **5**, **7** and **11**, ketone **9** has no methylene group next to the carbonyl, so the indolization involves the methyl group.

The best results in Fischer's reaction can be obtained for indolization of arylhydrazones of ketone **11**: indole **12** is formed in good yields in acetic acid and with PPE in CH_2Cl_2, or with P_2O_5 in dry dioxane. Refluxing of an aryl hydrazone of ketone **11** in acetic acid seems to be the best conditions for indolization of *o*-methoxy-, *p*-methoxy-, and *o*-bromo- phenylhydrazones as well as α-naphtyl- and 8-quinolylhydrazones. *p*-Methoxy derivative is transformed to the corresponding indole **14** faster and provides higher yield of the indole as compared to the other substituted arylhydrazones, that is in agreement with the relative reactivity of substituted arylhydrazones of cyclohexanone in Fischer's indole synthesis (18).

Conclusion.

A number of new indoloterpenoids derived from *seco*-monoterpenic ω-keto nitriles have been synthesized. Structures of the new products have been established by IR, UV, NMR ^1H- and ^{13}C-spectroscopy and mass-spectrometry.

Experimental.

Melting points were determined using a *Kofler* hot-stage. IR spectra were recorded on a *Specord M-80* spectrophotometer. ^1H and ^{13}C NMR spectra were recorded for 5-10% solutions on a *Bruker 'AC 200* spectrometer (200.13 MHz for ^1H and 50.32 MHz for ^{13}C). Chemical shifts were calculated relative to the solvent signals used as the internal standards: $CDCl_3$, CD_3OD, C_6D_6 and $(CD_3)_2CO$. Optical rotations were measured on a *Polamat A* polarimeter. MS spectra were recorded on a *Finnigan MAT 8200* mass spectrometer using electron impact ionization technique (70 ev). Elemental analyses were performed using a *Hewlett Packard 185* and *Carlo Erba 1106* analyzers. All reagents and solvents were of commercial quality. Preparative chromatography was performed on a silica gel column (100-200 mesh) and the solvents were distilled prior to use as eluent.

Method A. General procedure for the synthesis of indoles from a ketone and an arylhydrazine in acetic acid:

Phenylhydrazine (3.3 mmol) was added to a solution of a ketone (3.0 mmol) in glacial acetic acid (5 mL) and the mixture was refluxed for 3-4h. The reaction mixture was poured into water (10 mL), 25% aq. NH_3 was added to pH~8, and the organic products were extracted with ethyl acetate (3×10 mL). The combined extracts were washed with water (15 mL), brine (15 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure to give the crude product which was then purified by column chromatography (SiO_2, C_6H_6-EtOAc).

*Method B. General procedure for the synthesis of indoles from arylhydrazones of ketone **11** in acetic acid:*

Arylhydrazine hydrochloride (3.30 mmol) and Na_2CO_3 powder (0.16 g, 1.51 mmol) were added to a solution of ketone **11** (0.50 g, 3.03 mmol) in EtOH (5 mL), and the mixture was stirred for 2h at room temperature. The precipitate was filtered off and the filtrate was evaporated under reduced pressure. The residue was dissolved in glacial acetic acid (10 ml) and heated at reflux for 3-4h. The reaction mixture was poured into water (20 mL), 25% aq. NH_3 was added to pH~8, and the organic products were extracted with t-butyl methyl ether (3×10 mL). The combined organic extracts were washed with water (15 mL), brine (15 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure to give the crude product as brown oil which was then purified by column chromatography (SiO_2, petroleum ether-EtOAc).

Method C. Procedure for the synthesis of indoles from an phenylhydrazones in polyphosphoric acid:

Phenylhydrazine (3.3 mmol) was added to a solution of ketone (3.0 mmol) in EtOH (5 mL) and the mixture was stirred for 2h at room temperature. After removing of the solvent under reduced pressure the resulted phenylhydrazone was recrystallized from aq. EtOH.

The phenylhydrazone (3.3 mmol) was added to a vigorous stirred PPA (10.0 g) (19) and the mixture kept at 100°C for 30 min. The reaction mixture was poured into water (20 mL), 25% aq. NH_3 was added to pH~8, and the organic products were extracted with t-butyl methyl ether (3×10 mL). The combined organic extracts were washed with water (15 mL), brine (15 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure to give the crude product which was then purified by column chromatography (SiO_2, pentane-EtOAc).

Method D. Procedure for the synthesis of indoles from arylhydrazones in polyphosphoric acid ester:

Arylhydrazine (1.1 mmol) was added to a solution of a ketone (1.0 mmol) in EtOH (5 mL), the mixture was stirred for 2-4h at room temperature and the solvent was removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (5 mL) followed by the addition of PPE (1.0 g) (20). The reaction mixture was stirred for 2-3h at room temperature. The solvent was distilled off and the residue was poured into water (10 mL) followed by addition of 25% aq. NH_3 (to pH~8), and the organic products were extracted with t-butyl methyl ether (3×10 mL). The combined organic extracts were washed with water (15 mL), brine (15 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure to give the crude product which was then purified by column chromatography (SiO_2, petroleum ether-EtOAc).

*Method E. Synthesis of indole **12** from phenylhydrazone of ketone **11** in dioxane with phosphorus pentaoxide.*

A solution of ketone **11** (0.50 g, 3.03 mmol) and phenylhydrazine (3.30 mmol) in dry dioxane (10 mL) was stirred for 30 min at room temperature. Phosphorus pentaoxide (2.0 g) was added to the resulting mixture and the reaction mixture was refluxed for 30 min. The precipitate was filtered off and the filtrate was evaporated under reduced pressure to leave the residue which was dissolved in glacial acetic acid (10 mL) and the solution was heated at reflux for 3-4h. The reaction mixture was poured into water (20 mL), 25% aq. NH_3 was added to pH~8, and the organic products were extracted with t-butyl methyl ether (3×10 mL). The combined organic extracts were washed with water (15 mL), brine (15 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure to give the crude product as a solid which was crystallized from aq. EtOH to give indole **12** (0.39 g, 54%).

(±)-1-phenyl-3,5-di-(4-cyanobutyl)-5-methyl-2-pyrazoline **6** (prepared by *Method A*)*:* Yellowish oil. IR (ν_{max}/cm^{-1}, neat): 2240 (C≡N), 1710 (C=N), 1580, 1485, 745 and 690(C-H_{arom}); MS (m/z, %): 322 (M^+, 12), 241 (18), 240 (97), 181 (14), 180 (13), 172 (24), 171 (14), 149 (19), 83 (17), 82 (18), 78 (50), 77 (32), 57(21), 55 (27), 43 (100); ^{1}H NMR (200.13 MHz, C_6D_6-CCl_4): 1.21 (3H, s, Me-14), 1.25-1.40 (4H, m), 1.40-1.66 (6H, m) and 1.94 (2H, m) (H-3, H-4, H-5, H-9, H-10 and H-11), 2.08 (2H, t, J 6.6) and 2.20 (2H, t, J 6.6) (H-2 and H-12), 2.40 and 2.66 (2H, d, J 8.5, H-7, AB-system), 6.74 (1H, tt, J 6.65, 1.8, H-18), 7.05 (2H, m, H-16 and H-20), 7.09 (2H, m, H-17 and H-19). ^{13}C NMR (50.32 MHz, C_6D_6-CCl_4): 118.68 and 118.83 s (C-1 and C-13), 17.00 and 17.03 t (C-2 and C-12), 23.73, 25.18, 25.50 and 25.84 t (C-3, C-4, C-10 and C-11), 29.54 (t, C-5), 145.58 (s, C-6), 49.39 (t, C-7), 67.94 (s, C-8), 38.84 (t, C-9), 25.66 (q, C-14), 149.19 (s, C-15), 116.78 (d, C-16), 128.93 (d, C-17), 120.44 (d, C-18), 128.93 (d, C-19), 116.78 (d, C-20). Found: C 74.21, H 7.97, N, 17.51; calc. for $C_{20}H_{26}N_4$ C 74.50, H 8.13, N 17.38.

(±)-2-methyl-3-(2-cyanomethyl-3-methyl)but-1-en-3-yl)-1H-indole **8** (prepared by *Method D*)*:* Yellowish oil. UV (λ_{max}/nm, in EtOH): 227 (ε 33000), 283 (ε 7000), 292 (ε 6200); IR (ν_{max}/cm^{-1}, 1% in CCl_4): 3470 (N-H), 2240 (C≡N), 1455 (C=C_{arom}), 1135 and 895; MS (m/z, %): 239 (2), 238 (M^+, 13), 158 (6), 145 (11), 144 (100), 143 (8), 128 (2), 115 (3), 77 (3); ^{1}H NMR (200.13 MHz, $CDCl_3$): 1.71 (3H, s, Me-14), 1.81—1.85 (3H, m, H-10 and H-11), 2.33 (2H, m, H-15), 2.39 (3H, s, Me-17), 4.88 (1H, d, J 2.0, H-13a), 4.94 (1H, d, J2.0, H-13b), 6.78—7.20 (4H, m, H-4, H-5, H-6 and H-7), 8.28 (1H, s, NH); ^{13}C NMR (50.32 MHz, $CDCl_3$): 143.77 and 143.89 s (C-2 and C-8), 110.25 (s, C-3), 119.40 (d, C-4), 128.88 (d, C-5), 128.88 (d, C-6), 112.74 (d, C-7), 128.63 (s, C-9), 28.47 (t, C-10), 42.54 (d, C-11), 145.63 (s, C-12), 113.76 (t, C-13), 18.76 (q, C-14), 21.82 (t, C-15), 118.00 (s, C-16), 14.47 (q, C-17). Found: C 80.37, H 7.38, N 11.92; calc. for $C_{16}H_{18}N_2$ C 80.63, H 7.61, N 11.75.

(±)-[cis-3-(1H-indol-2-yl)-2,2-dimethylcyclobutyl]acetamide **10** (prepared by *Method C*): Yellowish oil. UV (λ_{max}/nm, in EtOH): 224 (ε 31000), 283 (ε 8400), 290 (ε 7200); IR (ν_{max}/cm^{-1}, 1% in $CHCl_3$): 3530 and 3410 ($CONH_2$), 3475 (NH), 1675 (C=O), 1450 (C=C_{arom}); MS (m/z, %): 256 (M^+, 5), 144 (14), 143 (100), 97 (14), 85 (28), 83 (16), 82 (49), 55 (11), 47 (10), 43 (13), 32 (22), 28 (99); ^{1}H NMR (200.13 MHz, $(CD_3)_2CO$): 0.74 (3H, s, Me-16), 1.23 (3H, s, Me-17), 2.02—2.14 (1H, m, H-13a), 2.26 (1H, dd, J 7.5, 7.5, H-13b), 2.29—2.34 (2H, m, H-15a and H-15b), 2.45—2.53 (1H, m, H-12), 3.23 (1H, dd, J 10.0, 7.5, H-10), 6.17 (1H, m, H-3), 6.36 and 6.88 (2H, br.s, $CONH_2$), 6.92 (1H, ddd, J 7.0, 7.0, 1.5, H-5)*. 6.98 (1H, ddd, J 7.0, 7.0, 1.5,

H-6)*, 7.28 (1H, dm, J 7.0, H-4), 7.44 (1H, dm, J 7.0, H-7), 10.0 (1H, br.s, NH); ^{13}C NMR (50.32 MHz, $(CD_3)_2CO$): 137.51 and 140.63 s (C-2 and C-8), 99.84 (d, C-3), 119.55, 120.12 and 121.03 d (C-4, C-5 and C-6), 111.39 (d, C-7), 129.68 (s, C-9), 42.75 (d, C-10), 43.73 (s, C-11), 39.94 (d, C-12), 27.96 (t, C-13), 37.33 (t, C-14), 174.93 (s, C-15), 18.18 (q, C-16), 30.31 (q, C-17). Found: C 75.20, H 7.82, N 11.03; calc. for $C_{16}H_{20}N_2O_1$ C 74.97, H 7.86, N 10.93.

(+)-10R,12R-2-methyl-3-[2,2-dimethyl-3-(cyanomethyl)cyclopropyl]-1H-indole **12** (prepared by *Methods A,D,E*): White crystals with m.p. 143-145°C (aq. EtOH); $[\alpha]^{21}_{578}$ +145 (c 3.19, $CHCl_3$); UV (λ_{max}/nm; in EtOH): 227 (ε 32500), 284 (ε 7800), 290 (ε 7100); IR (ν_{max}/cm^{-1}, in KBr): 3350 $(N\text{-}H)_{indole}$, 2250 (C≡N), 1455 $(C{=}C)_{arom}$, 750 and 735 $(C\text{-}H)_{arom}$; MS (m/z, %): 238 (M^+, 18), 199 (19), 198 (100), 183 (15), 182 (21), 168 (20), 167 (14), 154 (8), 144 (9), 130 (7), 115 (8), 77 (7), 41 (9); ^{1}H NMR (200.13 MHz, $CDCl_3$): 1.13 (3H, s, Me-15), 1.33 (1H, ddd, J 9.0, 8.4 and 5.7, H-12), 1.39 (3H, s, Me-16), 1.80 (1H, dq, J 8.4 and 1.0, H-10), 1.93 (1H, dd, J 17.5 and 9.0, H-13a), 2.36 (3H, d, J 1.0, Me-17), 2.62 (1H, dd, J 17.5 and 5.7, H-13b), 7.03 (1H, ddd, J 9.0, 7.3 and 1.7, H-5), 7.08 (1H, ddd, J 8.3, 7.3 and 1.7, H-6), 7.19 (1H, dd, J 9.0 and 1.7, H-4), 7.40 (1H, dd, J 8.3 and 1.7, H-7), 7.86 (1H, s, NH); ^{13}C NMR (50.32 MHz, $CDCl_3$): 134.01 and 135.51 s (C-2 and C-8), 106.75 (s, C-3), 118.78, 119.34 and 121.24 d (C-4, C-5 and C-6), 110.17 (d, C-7), 129.13 (s, C-9), 22.75 (d, C-10), 18.68 (s, C-11), 22.45 (d, C-12), 15.00 (t, C-13), 119.84 (s, C-14), 16.57 (q, C-15), 28.45 (q, C-16), 13.00 (q, C-17). Found: C 80.80, H 7.86, N 11.77; calc. for $C_{16}H_{18}N_2$ C 80.63, H 7.61, N 11.75.

(+)-10R,12R-2-methyl-3-[2,2-dimethyl-3-(cyanomethyl)cyclopropyl]-7-methoxy-1H-indole **13** (prepared by *Method B*): White crystals with m.p. 128-130°C (EtOAc-hexane). $[\alpha]^{24}_{578}$ +133 (c 3.78, $CHCl_3$); UV (λ_{max}/nm; in EtOH): 226 (ε 38200), 274 (ε 6400), 290 (ε 4100); IR (ν_{max}/cm^{-1}, in KBr): 3390, 3350 $(N\text{-}H)_{indole}$, 2245 (C≡N), 1460 $(C{=}C)_{arom}$, 1255, 1090, 780 and 730 $(C\text{-}H)_{arom}$; MS (m/z, %): 268 (M^+, 20), 229 (15), 228 (100), 213 (11), 212 (9), 198 (17), 197 (8), 196 (6), 183 (4), 182 (13), 107 (5); ^{1}H NMR (200.13 MHz, $(CD_3)_2CO$): 1.10 (3H, s, Me-15), 1.31 (1H, ddd, J 9.2, 8.8 and 5.8, H-12), 1.35 (3H, s, Me-16), 1.74 (1H, dq, J 8.8 and 1.2, H-10), 1.99 (1H, dd, J 17.5 and 9.2, H-13a), 2.40 (3H, d, J 1.2, Me-17), 2.75 (1H, dd, J 17.5 and 5.8, H-13b), 3.88 (3H, s, OMe-18), 6.56 (1H, d, J 8.0, H-4), 6.88 (1H, dd, J 8.0 and 8.0, H-5), 7.05 (1H, d, J 8.0, H-6), 9.91 (1H, s, NH); ^{13}C NMR (50.32 MHz, $(CD_3)_2CO$): 131.69 and 135.33 s (C-2 and C-8), 107.38 (s, C-3), 112.73 (d, C-4), 119.94 (d, C-5), 102.00 (d, C-6), 146.66 (s, C-7), 126.89 (s, C-9), 23.79 (d, C-10), 19.14 (s, C-11), 23.69 (d, C-12), 15.27 (t, C-13), 120.93 (s, C-14), 16.90 (q, C-15), 28.70 (q, C-16), 13.01 (q, C-17), 55.52 (q, C-18). Found: C 76.41, H 7.56, N 10.50; calc. for $C_{17}H_{20}N_2O$ C 76.09, H 7.51, N 10.44.

(+)-10R,12R-2-methyl-3-[2,2-dimethyl-3-(cyanomethyl)cyclopropyl]-5-methoxy-1H-indole **14** (prepared by *Method B*): White crystals with m.p. 160-162°C (EtOAc-hexane); $[\alpha]^{24}_{578}$ +124 (c 4.36, $CHCl_3$); UV (λ_{max}/nm; in EtOH): 226 (ε 27000), 285 (ε 8300), 294 ε 7600); IR (ν_{max}/cm^{-1}, in KBr): 3390, 3360 $(N\text{-}H)_{indole}$, 2240 (C≡N), 1475 $(C{=}C)_{arom}$, 1215, 1145, 845 and 795 $(C\text{-}H)_{arom}$; MS (m/z, %): 268 (M^+, 21), 229 (17), 228 (100), 213 (8), 212 (7), 198 (12), 197 (5), 182 (7); ^{1}H NMR (200.13 MHz, $(CD_3)_2CO$): 1.10 (3H, s, Me-15), 1.34 ддд (1H, ddd, J 8.7, 8.6 and 6.0, H-12), 1.36 (3H, s, Me-16), 1.76 (1H, dq, J 8.6 and 1.1, H-10), 2.06 дд (1H, dd, J 17.5 and 8.7, H-13a), 2.36 (3H, d, J 1.1, Me-17), 2.72 (1H, dd, J 17.5, 6.0, H-13b), 3.82 (3H, s, Me-18), 6.67 дд (1H, dd, J 8.7 and 3.0, H-6), 6.96 д (1H, d, J 3.0, H-4), 7.14 (1H, d, J 8.7, H-7), 9.76 (1H, s, NH); ^{13}C NMR (50.32 MHz, $(CD_3)_2CO$): 132.01 and 136.44 s (C-2 and C-8), 106.74 (s, C-3), 101.82 (d, C-4), 154.75

(s, C-5), 111.23 and 111.76 d (C-6 and C-7), 130.69 (s, C-9), 23.69 (d, C-10), 19.07 (s, C-11), 23.61 (d, C-12), 15.18 (t, C-13), 121.13 (s, C-14), 16.92 (q, C-15), 28.71(q, C-16), 13.18 (q, C-17), 55.91 (q, C-18). Found: C 76.29, H 7.75, N 10.37, calc. for $C_{17}H_{20}N_2O$ C 76.09, H 7.51, N 10.44.

(+)-10R,12R-2-methyl-3-[2,2-dimethyl-3-(cyanomethyl)cyclopropyl]-7-bromo-1H-indole **15** (prepared by *Method B*): White crystals with m.p. 110-114°C (EtOAc-hexane); $[\alpha]^{24}_{578}$ +136 (c 4.16, $CHCl_3$); UV (λ_{max}/nm; in EtOH): 228 (ε 39200), 286 (ε 9200), 294 (ε 7800); IR (ν_{max}/cm^{-1}, in KBr): 3320 $(N\text{-}H)_{indole}$, 2240 (C≡N), 1475 $(C{=}C)_{arom}$, 755 and 730 $(C\text{-}H)_{arom}$; MS (m/z, %): 318 (M^++2, 19), 316 (M^+, 18), 279 (14), 278 (96), 277 (16), 276 (98), 197 (14), 183 (15), 182 (100), 181 (15), 167 (15), 84 (14); ^{1}H NMR (200.13 MHz, $(CD_3)_2CO$): 1.10 (3H, s, Me-15), 1.36 (3H, s, Me-16), 1.36 (1H, ddd, J 9.5, 8.8 and 5.8, H-12), 1.77 (1H, dq, J 8.8 and 0.8, H-10), 2.02 (1H, dd, J 17.5 and 9.5, H-13a), 2.42 (3H, d, J 0.8, Me-17), 2.76 (1H, dd, J 17.5 and 5.8, H-13b), 6.90 (1H, dd, J 8.0 and 8.0, H-5), 7.19 (1H, d, J 8.0, H-4), 7.45 (1H, d, J 8.0, H-6), 10.10 (1H, s, NH); ^{13}C NMR (50.32 MHz, $(CD_3)_2CO$): 135.05 and 137.43 s (C-2 and C-8), 104.37 (s, C-3), 119.06, 120.81 and 123.87 d (C-4, C-5 and C-6), 108.50 (s, C-7), 131.97 (s, C-9), 23.72 (d, C-10), 19.21 (s, C-11), 23.56 (d, C-12), 15.26 (t, C-13), 120.81 (s, C-14), 16.91 (q, C-15), 28.60 (q, C-16), 13.05(q, C-17). Found: C 60.56, H 5.65, N 8.86, Br 25.10; calc. for $C_{16}H_{17}BrN_2$ C 60.58, H 5.40, N 8.83, Br 25.19.

(+)-10R,12R-2-methyl-3-[2,2-dimethyl-3-(cyanomethyl)cyclopropyl]-benzo[6,7]-1H-indole **16** (prepared by *Method B*): White crystals with m.p. 167-169°C (EtOAc-hexane); $[\alpha]^{24}_{578}$ +135 (c 4.08, $CHCl_3$); UV (λ_{max}/nm; in EtOH): 218 (ε 30500), 269 (ε 55000), 294 (ε 10000), 333 (ε 1600), 350 (ε 800); IR (ν_{max}/cm^{-1}, in KBr): 3350 $(N\text{-}H)_{indole}$, 2250 (C≡N), 805 and 750 $(C\text{-}H)_{arom}$; MS (m/z, %): 288 (M^+, 25), 249 (21), 248 (100), 233 (38), 232 (16), 218 (17), 217 (12), 117 (7), 109 (6); ^{1}H NMR (200.13 MHz, $(CD_3)_2CO$): 1.13 (3H, s, Me-19), 1.39 (1H, ddd, J 9.2, 8.8 and 6.0, H-16), 1.40 (3H, s, Me-20), 1.87 (8.8 and 1.2, H-14), 2.05 (1H, dd, J 17.8 and 9.2, H-17a), 2.47 (3H, d, J 1.2, Me-21), 2.81 (1H, dd, J 17.8 and 6.0, H-17b), 7.33 (1H, ddd, J 8.5, 7.0 and 2.0; H-7), 7.43 (1H, d, J 8.8, H-4), 7.46 (1H, ddd, J 9.0, 7.0 and 2.0; H-8), 7.61 (1H, d, J 8.8, H-5), 7.87 (1H, dd, J 9.0 and 2.0; H-21), 8.22 (1H, dd, J 8.5 and 2.0; H-18), 10.85 (1H, s, NH); ^{13}C NMR (50.32 MHz, $(CD_3)_2CO$): 131.42, 133.95 and 131.27 s (C-2, C-8 and C-9), 108.69 (s, C-3), 120.22, 120.50, 120.97, 124.00, 126.03 and 129.43 d (C-4, C-5, C-10, C-11, C-12 and C-13), 123.20 and 126.03 s (C-6 and C-7), 23.82 (d, C-16), 19.48 (s, C-15), 24.01 (d, C-14), 15.42 (t, C-17), 121.66 (s, C-18), 16.92 (q, C-19), 28.72 (q, C-20), 13.05 (q, C-21). Found: C 83.49, H 7.10, N 9.74; calc. for $C_{20}H_{20}N_2$ C 83.30, H 6.99, N 9.71.

(+)-10R,12R-2-methyl-3-[2,2-dimethyl-3-(cyanomethyl)cyclopropyl]-pyndino[3,2]-1H-indole **17** (prepared by *Method B*): Yellowish viscous oil, hydrochloride with m.p. 187-189°C (CH_3CN); $[\alpha]^{24}_{578}$ +77 (c 3.99, $CHCl_3$); UV (λ_{max}/nm; in EtOH): 221 (ε 35600), 276 (ε 46100), 354 (ε 4130); IR (ν_{max}/cm^{-1}, in KBr): 2700-2300 (R^3NH^+), 2245 (C≡N), 1645, 1365, 820 and 765$(C\text{-}H)_{arom}$; MS (m/z, %): 289 (M^+, 16), 250 (19), 249 (100), 234 (22), 233 (16), 219 (14), 45 (19), 36 (22), 31 (32), 28 (19); ^{1}H NMR (200.13 MHz, CD_3OD): 1.08 (3H, s, Me-19), 1.44 (3H, s, Me-20), 1.47 (1H, ddd, J 9.5, 8.5 and 6.0, C-16), 1.86 (1H, dq, J 8.5 and 1.0, C-14), 2.01 (1H, dd, J 18.0 and 9.5, H-17a), 2.58 (3H, d, J 1.0, Me-21), 2.76 (1H, dd, J 18.0 and 6.0, H-17b), 7.62 (1H, dd, J 8.0 and 5.8; H-11), 7.69 (1H, d, J 8.8, H-4), 7.91 (1H, d, J 8.8, H-5), 8.89 (1H, dd, J 5.8 and 1.0; H-10), 9.00 (1H, dd, J 8.0 and 1.0; H-12); ^{13}C NMR (50.32 MHz, CD_3OD): 112.10 (s, C-3), 121.20, 122.55, 127.40,

127.94 and 134.99 s (C-2, C-6, C-8, C-9 and C-18), 142.04 (s, C-7), 119.16, 120.28 and 125.03 d (C-4, C-5 and C-11), 140.85 and 147.50 d (C-10 and C-12), 24.11 (d, C-14), 19.86 (s, C-15), 23.22 (d. C-16), 15.41 (t, C-17), 16.91 (q, C-19), 28.52 (q, C-20), 13.45 (q, C-21). Found: C 70.26, H 6.35, N 12.81, Cl 10.70; calc. for $C_{19}H_{20}ClN_3$ C 70.04, H 6.19, N 12.90, Cl 10.88.

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