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Terpenoid *N*-Heterocyclics. I

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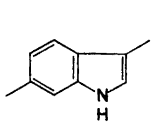
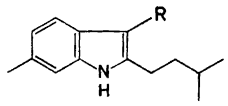
The synthesis of some indoles, indolines, and tetrahydrocarbazoles of terpenoid type is described.

For pharmacological investigations a series of nitrogen heterocyclics of terpene type were required. The simplest indole of this kind is the known 3,6-dimethylindole (I). We have prepared this compound in good yield by lithium aluminium hydride reduction of 6-methylindole-3-aldehyde. Catalytic hydrogenation of 3,6-dimethylindole furnished (±)-3,6-dimethylindoline.



I



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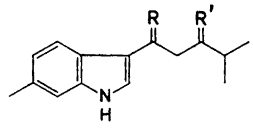
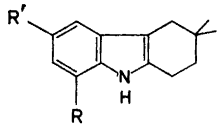
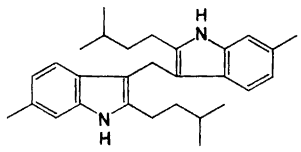


III



IV



V

The "sesquiterpene indole" II (R=CH_3) was synthesised from 2,5-dimethylaniline *via* 4-methylpentane-2,5-dimethylanilide which underwent Madelung ring closure to form 2-(3-methylbutyl)-6-methylindole (II, R=H). This indole derivative was formylated to the aldehyde II (R=CHO) which was reduced with lithium aluminium hydride to II (R=CH_3). On catalytic hydrogenation a product was obtained obviously consisting of a mixture of diastereoisomeric indolines. Since this material served our purpose no attempt was made to separate the components. The intermediate indole II (R=H),

could be reduced to the corresponding (±)-indoline either catalytically or with diborane (*cf.* Plieninger *et al.*[1] and Biswas and Jackson [2]).

Potassium borohydride reduction of II (R=CHO) gave II (R=CH_2OH). On heating (*cf.* Ref. 3) this alcohol gave V, which was also obtained from II (R=H) by condensation with formaldehyde.

For the synthesis of the isomeric "sesquiterpene indole" III (R=R′=H_2) the Grignard reagent from 6-methylindole was reacted with 4-methylpentanoyl chloride to 3-(4-methyl-1-oxopentyl)-6-methylindole, (III, R=O, R′=H_2). On reduction with lithium aluminium hydride, III (R=R′=H_2) was obtained in fair yield. Catalytic hydrogenation furnished (±)-3-(4-methylpentyl)-6-methylindoline.

The isomer of III (R=O, R′=H_2), III (R=H_2, R′=O), interesting because it has a reactive group in position 3 of the 4-methylpentyl side chain, was obtained in fair yield by reacting 6-methylindole with vinyl isopropyl ketone. Reduction with potassium borohydride gave the corresponding alcohol. Attempts to convert this compound into a tosylate or a mesylate were unsuccessful.

Fischer rearrangement of 4,4′-dimethylcyclohexanone-3-trifluoromethylphenylhydrazone gave a mixture of 5- and 7-trifluoromethyl-3,3-dimethyl-1,2,3,4-tetrahydrocarbazole (IV, R=CF_3, R′=H and R=H, R′=CF_3, respectively). The components could be separated chromatographically and their structures assigned on the basis of their IR spectra. Both were crystalline solids. The isomer IV (R=H, R′=CF_3) was dehalogenated with Raney nickel to IV (R=H, R′=CH_3). In this case, apparently, no 3,3,7-trimethyl-1,2,3,4,-4a,9a-hexahydrocarbazole was formed (*cf.* Ref. 4).

Fischer rearrangement of 4,4-dimethylcyclohexanone-3-methylphenylhydrazone furnished a mixture of 5- and 7-methyl-3,3-dimethyl-1,2,3,4-tetrahydrocarbazoles. One of the components had the same R_F value as the above 7-methyl isomer.

EXPERIMENTAL

6-Methylindole. This compound was prepared according to Marion and Oldfield.[5] Yield: 35–40 %. The more recent method given by Lorenz *et al.*[6] was found to be more laborious. Picrate, m.p. 160–161°. (Lit.[5,7,8] 161.5°, 160–161°, and 157°, respectively).

6-Methylindole-3-aldehyde. This compound was made by Vilsmeier-Haack-formylation [9] of 6-methylindole (26 g). Yield: 24 g (76 %); m.p. 191–193°. (Lit.[10] 190–192°).

3,6-Dimethylindole (I). 6-Methylindole-3-aldehyde (3.2 g) was added in three portions to a stirred suspension of $LiAlH_4$ (1.5 g) in tetrahydrofuran (250 ml). The mixture was refluxed under nitrogen for 5 h. The excess of hydride was destroyed by careful addition of water. The mixture was filtered, and the solvent was evaporated. The residue was sublimed under reduced pressure (5 mm). Yield: 2.2 g (76 %); m.p. 94–95°. (Lit.[11] 90–92°). The picrate melted at 163–164°. (Lit.[11] 163–164°).

(±)-3,6-Dimethylindoline. 3,6-Dimethylindole (4 g) was catalytically hydrogenated by the method of Smith and Utley.[12] Yield: 2.9 g (72 %); b.p. 101–103°/10 mm. Reduction by the method of Dolby and Gribble [13] gave only a low yield (<5 %). (Found: C 81.7, H 8.9, N 9.5. Calc. for $C_{10}H_{13}N$: C 81.6, H 8.9, N 9.5).

4-Methylpentane-2,5-dimethylanilide. A mixture of 2,5-dimethylaniline (243 g, 2 mole), 4-methylpentanoic acid (233 g, 2 mole) and xylene (200 ml) was refluxed for 20 h. The water formed was collected in a water separator interposed between the reaction vessel and the condenser. When still hot the reaction mixture was poured into hot (*ca.* 80°) toluene (1.5 l). On cooling crystals separated (395 g, 90 %) which were used in the follow-

ing step without further purification. For analysis a sample was recrystallized twice from ethanol; m.p. 141–142°. (Found: C 76.5; H 9.5; N 6.5. Calc. for $C_{14}H_{21}NO$: C 76.7; H 9.7; N 6.4).

2-(3-Methylbutyl)-6-methylindole (II, R=H). 5-Methylpentane-2,5-dimethylanilide (83 g) was added in five portions to a mixture of *N,N*-dimethylaniline (450 ml) and sodium amide [added as a 50 % suspension in toluene (150 ml)]. The mixture was heated 1.5 h to 190–200°, and then 0.5 h to 260° (internal temperature). Water (700 ml) was added to the cooled (70°) mixture. The crude product was extracted with ether (2×600 ml) and the combined solutions were washed with 5 % HCl, water, 5 % $NaHCO_3$, water, and then dried. The product was crystallized from light petroleum (norite), with final cooling to −25°. The crystals (76 g, 94 %), melted at 69–70°. (Found: C 83.4; H 9.4; N 7.0. Calc. for $C_{14}H_{19}N$: C 83.6; H 9.5; N 7.0). UV (C_6H_{12}): λ_{max} 223, 270, 284, 289, 295 nm (log ε 4.59, 3.91, 3.73, 3.75, 3.78).

(±)-2-(3-Methylbutyl)-6-methylindoline. Method A: Catalytic hydrogenation by the method of Smith and Utley:[12] 0.05 mole of the above indole, in a mixture of ethanol (100 ml) and 30 % fluoroboric acid (100 ml), was hydrogenated (5 h) using Adams' platinum oxide catalyst. The filtered solution was poured into 2 N NaOH (500 ml) and then extracted with ether (500 ml). The ether phase was extracted with 5 % HCl and the aqueous phase made alkaline with 5 N NaOH and then extracted with ether (2×500 ml). The product was recrystallized from pentane (cooling to −20°). Yield: 6.5 g (58 %), m.p. 38–38.5°. (Found: C 82.7; H 10.4; N 6.8. Calc. for $C_{14}H_{21}N$: C 82.7; H 10.4; N 6.9).

Method B: Reduction with diborane: 2-(3-Methylbutyl)-6-methylindole (10 g, 0.05 mole) was added with stirring to sodium borohydride (4.0 g) in monoglyme (100 ml) at 0–5°. BF_3-etherate (15 g) was added during 0.5 h at 0–5°. The mixture was then kept at room temperature for 5 h. Ethanol (10 ml) was then added followed by water (10 ml). The mixture was poured into water (400 ml) containing acetic acid (10 ml). The resulting mixture was extracted with ether (2×100 ml) and the ether phase found to contain some unchanged starting material. The aqueous phase was made alkaline with 5 N NaOH and extracted with ether. This extract was worked up as in method A. Yield: 4.2 g (37 %), m.p. 38–38.5°. UV (C_6H_{12}): λ_{max} 214, 248, 302 nm (log ε 4.29, 3.91, 3.54).

2-(3-Methylbutyl)-6-methylindole-3-aldehyde (II, R=CHO). 2-(3-Methylbutyl)-6-methylindole (0.1 mole) was formylated as described for the preparation of 6-methylindole-3-aldehyde except that the reaction mixture was not heated during the work-up. The crude product was recrystallized from benzene (11.1 g, 53 %), m.p. 175–177°. (Found: C 78.7; H 8.3; N 6.1. Calc. for $C_{15}H_{19}NO$: C 78.6; H 8.4; N 6.1).

2-(3-Methylbutyl)-3-hydroxymethyl-6-methylindole (II, R=CH_2OH). Potassium borohydride (0.5 g) was added to 2-(3-methylbutyl)-6-methylindole-3-aldehyde (1.15 g) in methanol (50 ml) at 5°. The mixture was allowed to assume room temperature and was then poured into water (200 ml). The crystals formed were recrystallized from benzene. Yield: 0.98 g (84 %); m.p. 115–130° (decomp.). (Found: C 78.1; H 9.1; N 6.1. Calc. for $C_{15}H_{21}NO$: C 77.9; H 9.2; N 6.0). IR (KBr): OH 3551(s), NH 3235(s) cm^{-1}. The diffuse melting point is due to partial decomposition. On prolonged heating (2 h, 130°) compound V is formed (*cf.* Ref. 3).

Bis-2-(3-methylbutyl)-6-methylindolyl methane (V). A mixture of water (25 ml), ethanol (50 ml), 40 % formaldehyde (2 ml) and 2-(3-methylbutyl)-6-methylindole (2 g) was heated to 65°. Water (100 ml) was added. On cooling crystals precipitated, which were recrystallized from cyclohexane/benzene (1:1). Yield: 1.6 g (77 %); m.p. 193–194°. (Found: C 84.0, H 9.2; N 6.8, M.w. 414 (MS). Calc. for $C_{29}H_{38}N_2$: C 84.0; H 9.2; N 6.8 M.w. 414).

2-(3-Methylbutyl)-3,6-dimethylindole (II, R=CH_3). 2-(3-Methylbutyl)-6-methylindole-3-aldehyde (4.5 g) was added to $LiAlH_4$ (1.0 g) in ether (250 ml) and the mixture refluxed for 2 h under nitrogen. The reaction mixture was worked up as described above for 3,6-dimethylindole. The residue was recrystallized from pentane (cooling to −25°). Yield: 2.9 g (67 %); m.p. 49–51°. (Found: C 83.7; H 9.8; N 6.5. Calc. for $C_{15}H_{21}N$: C 83.7; H 9.8; N 6.5). UV (C_6H_{12}): λ_{max} 228, 277, 285, 291, 298 nm (log ε 4.53, 3.78, 3.71, 3.62, 3.53).

2-(3-Methylbutyl)-3,6-dimethylindoline. 2-(3-Methylbutyl)-3,6-dimethylindole (0.01 mole) was hydrogenated using method A (above). The crude product was purified by distillation. Yield: 48 %, b.p. 130°/3 mm. (Found: C 83.0; H 10.6; N 6.5. Calc. for $C_{15}H_{23}N$: C 82.9; H 10.7; N 6.5). The three strongest peaks in the mass spectrum appeared at *m/e*:

217 (16 %, parent ion), 146 (100 %, loss of the methylbutyl group), 131 (67 %). UV (C_6H_{12}): λ_{max} 211, 248, 300 nm (log ε 4.33, 3.84, 3.53).

3-(4-Methyl-1-oxopentyl)-6-methylindole (III, R=O, R'=H₂). 6-Methylindole (13.1 g) in ether (100 ml) was added dropwise to a cooled (0–5°) and stirred solution of ethyl magnesium bromide from magnesium (2.4 g) and ethyl bromide (11.0 g) in ether (200 ml). The mixture was refluxed for 0.5 h and then cooled to 0–5° after which 4-methylpentanoyl chloride (13.5 g) in ether (30 ml) was added dropwise. The mixture was refluxed for 0.5 h, allowed to cool and then poured into 5 % sodium hydrogen carbonate (300 ml) and ice. The reaction mixture was worked up as usual and the oxoindole was recrystallized twice from methanol. Yield: 8.6 g (38 %); m.p. 192–193°. (Found: C 78.6; H 8.4; N 6.1. Calc. for $C_{15}H_{19}NO$: C 78.6; H 8.4; N 6.1).

3-(4-Methylpentyl)-6-methylindole (III, R=R'=H₂). 3-(4-Methyl-1-oxopentyl)-6-methylindole (2.23 g) was reduced with $LiAlH_4$ (1.0 g) as described above. The product was distilled. Yield: 1.05 g (50 %); b.p. 125°/2.5 mm, m.p. 38–39°. (Found: C 83.7; H 9.8; N 6.5. Calc. for $C_{15}H_{21}N$: C 83.7; H 9.8; N 6.5). The picrate melted at 102–103°. UV (C_6H_{12}): λ_{max} 225, 275, 283, 288, 295 nm (log ε 4.53, 3.77, 3.71, 3.67, 3.61).

(±)-3-(4-Methylpentyl)-6-methylindoline. 3-(4-Methylpentyl)-6-methylindole (0.01 mole) was hydrogenated using method A above and the reaction product distilled. Yield: 52 %, b.p. 132°/3 mm. (Found: C 82.9; H 10.7; N 6.5. Calc. for $C_{15}H_{23}N$: C 82.9; H 10.7; N 6.5). The four strongest peaks in the mass spectrum appeared at *m/e* 217 (19 %, parent ion), 144 (12 %, γ-cleavage of the alkyl chain), 132 (100 %, loss of the methylpentyl group), 117 (12 %). UV (C_6H_{12}): λ_{max} 211, 251, 300 nm (log ε 4.28, 3.77, 3.48).

3-(4-Methyl-3-oxopentyl)-6-methylindole (III), R=H₂, R'=O). 6-Methylindole (3.25 g) and vinyl isopropyl ketone [14] (5.0 g) in acetic acid (15 ml) and acetic anhydride (5 ml) was heated on a steam-bath for 45 min. The mixture was cooled and water (120 ml) was added. The solid obtained was collected and recrystallized from light petroleum. Yield: 2.1 g (45 %). Crystals, m.p. 68–71°. (Found: C 78.5; H 8.4; N 6.1. Calc. for $C_{15}H_{19}NO$: C 78.6; H 8.4; N 6.1).

3-(4-Methyl-3-hydroxypentyl)-6-methylindole. 3-(4-Methyl-3-oxopentyl)-6-methylindole (1.00 g) was dissolved in methanol (50 ml). The solution was cooled (5°) and potassium borohydride (0.5 g) was added. The mixture was allowed to assume room temperature. After 10 h water (200 ml) was added and the mixture was extracted with ether. The crude product (58–62°) was recrystallized from light petroleum/benzene (4:1). Yield: 0.72 g (70 %); m.p. 62–63°. (Found: C 77.7, H 9.1, N 6.1. Calc. for $C_{15}H_{21}NO$: C 77.9; H 9.2; N 6.1).

4,4-Dimethylcyclohexanone 3-trifluoromethylphenyl hydrazone. 3-Trifluoromethylphenylhydrazine hydrochloride [15] (15.6 g) in methanol (25 ml) was added at 25° (with slight cooling) to 4,4-dimethylcyclohexanone [16] (9.2 g) in methanol (20 ml). Crystals m.p. 134–139°. Yield: 18.3 g (90 %). (Found: N 10.0 Calc. for $C_{15}H_{19}N_2F_3$: N 9.9).

Fischer rearrangement of 4,4-dimethylcyclohexanone 3-trifluoromethylphenyl hydrazone. A mixture of the hydrazone (4.0 g), H_2SO_4 (10 ml), and acetic acid (60 ml) was heated to 85–90° for 0.5 h. The cooled solution was poured into water and the precipitate washed with water and dried. TLC-analysis of the product [silica gel G, light petroleum/benzene (4:1)] revealed the presence of two isomers A (R_F=0.44) and B (R_F=0.32). The product (2.3 g) was chromatographed on silica gel (300 g) using light petroleum/benzene (9:1). 25 ml fractions were taken. Nine of the fractions ("1–9") contained a single compound A (0.578 g) followed in fractions "19–51" by compound B (0.683 g).

Compound A was recrystallized from light petroleum (cooling to −25°), m.p. 69–70°. The infrared spectrum (KBr) showed the following peaks between 900 and 700 cm^{-1}: 883, 820, and 748 mm^{-1}. The overtone and combination tone bands at 2000–1700 cm^{-1} were studied using a Perkin-Elmer 421 instrument and with CCl_4 as solvent. The following three peaks (relative intensity in brackets) could be observed: 1874 (90), 1795 (10), and 1738 (100) cm^{-1}. From these data, characteristic of 1,2,4-substitution in aromatic systems,[17] compound A has been assigned structure IV (R=H, R'=CF_3) (7-trifluoromethyl-3,3-dimethyl-1,2,3,4-tetrahydrocarbazole). (Found: C 67.4; H 6.3; N 5.3; F 21.2. Calc. for $C_{15}H_{16}NF_3$: C 67.4; H 6.0; N 5.3; F 21.3).

Compound B was recrystallized from hexane, m.p. 115–117°. IR (CCl_4): 800, 754, 1894 (100), 1835 (70), and 1763 (40) cm^{-1}. These data are indicative of 1,2,3-substitution.[17] Thus compound B has structure IV (R=CF_3, R'=H) (5-trifluoromethyl-3,3-

dimethyl-1,2,3,4-tetrahydrocarbazole). (Found: C 67.7; H 6.2; N 5.3; F 21.0. Calc. for $C_{15}H_{16}NF_3$: C 67.4; H 6.0; N 5.3; F 21.3).

3,3,7-Trimethyl-1,2,3,4-tetrahydrocarbazole (IV, R=H, R'=CH$_3$). Raney nickel alloy (5 g) was added in five portions to a boiling mixture of dioxan (100 ml), 4 N NaOH (75 ml) and 7-trifluoromethyl-3,3-dimethyl-1,2,3,4-tetrahydrocarbazole (500 mg). After reflux (3 h) the mixture was cooled, filtered, and the filtrate poured into water (300 ml). The solid formed was extracted with ether (150 ml). The ether phase was dried and evaporated and the crude product recrystallized from light petroleum. Yield: 120 mg (30 %); m.p. 62–64°. (Found: C 84.1; H 9.2; N 6.7. Calc. for $C_{15}H_{19}N$: C 84.5; H 9.0; N 6.6). R_F=0.36. Contrary to the starting material the NMR spectrum ($CDCl_3$) showed a singlet (3H) located at τ=7.64. Apparently no 3,3,7-trimethyl-1,2,3,4,4a,9a-hexahydrocarbazole is formed. (*Cf.* Ref. 4).

Mixture of 3,3,5-trimethyl-1,2,3,4-tetrahydrocarbazole and 3,3,7-trimethyl-1,2,3,4-tetrahydrocarbazole. 3-Methylphenylhydrazine hydrochloride (14.0 g) in methanol (25 ml) was added to 4,4-dimethylcyclohexanone (9.0 g) in methanol (20 ml) and the mixture refluxed for 1 h. The solvent was removed and the residual oil was dissolved in a mixture of acetic acid (200 ml) and H_2SO_4 (40 ml) and then treated as the trifluoromethyl analogue. The two isomers formed (R_F: 0.36 and 0.32) were not separated.

Attempted cleavage of 6-methylgramine with lithium aluminium hydride. 6-Methylgramine [18] (3.0 g) was added to a stirred suspension of $LiAlH_4$ (1.0 g) in ether (150 ml). The mixture was refluxed for 10 h. Apart from traces of 3,6-dimethylindole, only 6-methylgramine was obtained upon work-up of the reaction mixture.

Gramine and 7-methylgramine [19] behaved similarly.

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