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The Synthesis of Some 3-Indolylvinylene Ketones*

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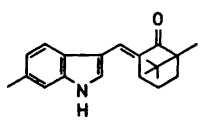
Condensation of 2-hydroxymethylenecamphor and 4-methyl-3-oxo-1-pentenol-1 with 6-methylindole produced 3-[11-(2-oxo-3-methylenebornyl)]-6-methylindole (*1*) and 3-(3-oxo-4-methylpentylidene)-6-methylindole (*2b*), respectively. Bis-(6-methyl-3-indolyl)methane (*5*, $R_1=CH_3$) was a by-product in both condensations. Compounds of type *2* could also be prepared by condensation of 3-formylindoles with methyl ketones. Addition of 1-alkyn-3-ones to indoles was found to be a less suitable route to these compounds.

In continuation of our study of terpenoid indoles,[1–3] 3-[11-(2-oxo-3-methylenebornyl)]-6-methylindole (*1*) and the related compound (*2b*) have now been prepared. Condensation (in acetic acid at 95° for 0.5 h) of 2-hydroxymethylenecamphor and 4-methyl-3-oxo-1-pentenol-1, with 6-methylindole gave *1* and *2b*, respectively. Chromatographic purification of the products was necessary. Bis-(6-methyl-3-indolyl)-methane was obtained as a by-product (4 % for *1* and 18 % for *2b*) in both condensations. To account for this, the mechanism shown in Scheme A was initially suggested. Further experiments showed, however, that this mechanism can, if at all, only be partly operative, as the cleavage of, *e.g.*, 2-hydroxymethylenecamphor is too slow under the given conditions (*cf.* Ref. 4).



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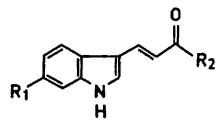

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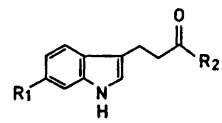
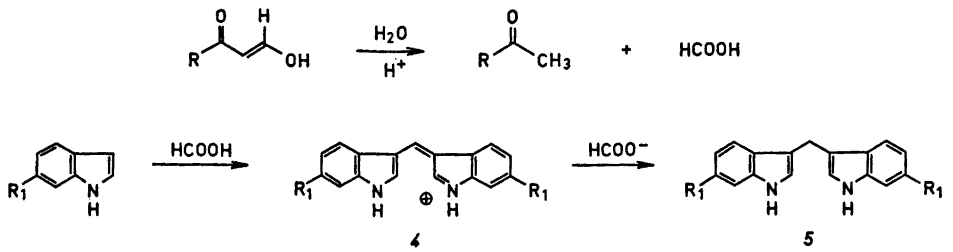


3

a $R_1=H$ $R_2=CH_3$
b $R_1=CH_3$ $R_2=CH(CH_3)_2$
c $R_1=H$ $R_2=CH(CH_3)_2$
d $R_1=CH_3$ $R_2=CH_3$

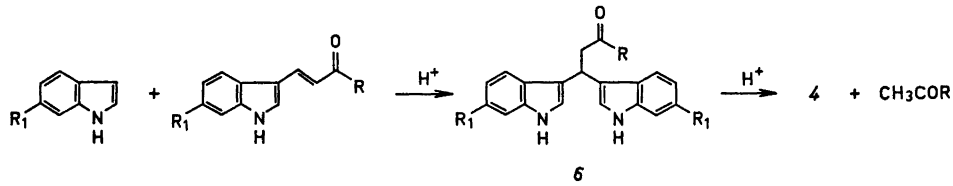
a $R_1=H$ $R_2=CH_3$
b $R_1=CH_3$ $R_2=CH(CH_3)_2$

* Part III in the series "Terpenoid *N*-Heterocyclics"; for part II see Ref. 3.



Scheme A.

The indolenine salt (*4*) required in the Leuckart reduction step, which should be rapid enough for the relevant conditions (*cf.* Ref. 5), may, however, be formed *via* the cleavage reaction shown in Scheme B.

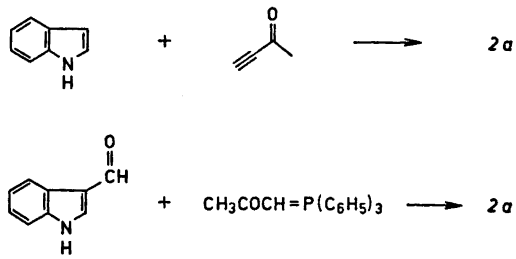


Scheme B.

An attempted synthesis of *6* ($R_1 = H$, $R = CH_3$) from indole and *2a* resulted, probably *via* addition of indole to *4*, in tris-(3-indolyl)methane. Under mild Leuckart conditions (2h/140°) tris-(3-indolyl)methane furnished *5* ($R_1 = H$) and indole, showing the reversibility of this addition (*cf.* Ref. 6).

Compound *2b* could be prepared more satisfactorily by condensation of 6-methyl-3-formylindole with methyl isopropyl ketone. But this necessitated the use of strong alkali and long reaction times (3 days) in order to obtain acceptable yields (50 %). Compound *2a*, but not compound *1* could be similarly prepared.

Scheme C summarizes two other routes to compounds of type *2* using *2a* as a model.



Scheme C.

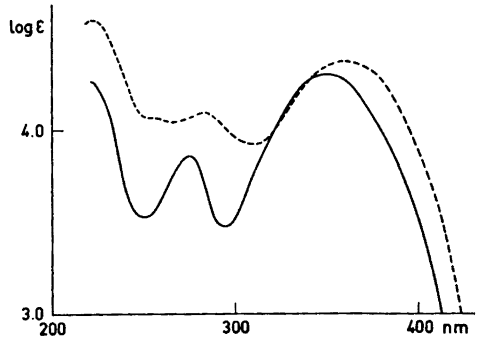


Fig. 1. UV-spectra of *1* (– – –) and *2c* (———) in ethanol.

The addition of 1-butyn-3-one to indole gave *2a* in low yield accompanied by formation of dark by-products. Chromatographic purification was necessary. The yield in the Wittig reaction was also unsatisfactory (20 %, *cf.* Ref. 7).

Catalytic hydrogenation of *2b* gave the known [2] compound *3b*. Compound *3a* could be similarly prepared.

The structure of *1* was proven by its composition and by spectroscopic methods. The IR spectrum, which showed a strong band at 3360 cm^{-1} (NH) eliminated the indolenine tautomer of *1* as a possible structure.

The UV spectrum (Fig. 1) agreed reasonably well with those of *2a* and *2c*, suggesting that *1* has the same configuration as these compounds, for which *trans*-configurations are likely in view of their mode of formation. This assignation is further supported [8] by the high values ($J = 16$ Hz) of the NMR coupling constants of the olefinic protons in *2a* and *2c*.

EXPERIMENTAL

3-[11-(2-Oxo-3-methylenebornyl)]-6-methylindole (*1*). *Method A*. A solution of 6-methylindole (13.1 g, 0.1 mol) and 2-hydroxymethylene-(+)camphor [4] (18.0 g 0.1 mol) in acetic acid (150 ml) was heated (95°) for 20 min. After cooling the mixture was slowly poured, while stirring, into water (800 ml). The solid formed was dried and then chromatographed on silica gel, CH_2Cl_2/MeOH (98 : 2) being used as eluent. The fractions containing *1* were evaporated and the residue recrystallized from carbon tetrachloride/hexane (1/2) with final cooling to −15°. Yield: 12.4 g (42 %); m.p. 161 – 162°. (Found: C 81.5; H 7.9; N 5.0. Calc. for $C_{20}H_{23}NO$: C 81.9; H 7.9; N 4.8.) $[\alpha]D = +523°$ (*c* 11.4, $CHCl_3$).

Method B. *N*-Methylaniline (11.3 g) in benzene (70 ml) was added to ethylmagnesium bromide (from Mg, 2.6 g, and ethyl bromide, 13.3 g, in ether, 80 ml) with cooling and stirring. After 1 h at 25°, (+)-camphor (15.2 g) in benzene (35 ml) was added. After further 2 h at 25° 6-methyl-3-formylindole (14.5 g) was gradually added. The mixture was refluxed for 4 h, cooled and water (100 ml) added. The organic phase was dried and evaporated and the residue extracted with pentane, and then with hot carbon tetrachloride. Evaporation of the last-mentioned extract gave crude *1*, which was recrystallized as described in method A. Yield: 8.9 g (30 %); m.p. and mixed m.p. 161 – 162°.

3-(3-Oxo-4-methylpentylidene)indole (2c). An aqueous solution of KOH (100 ml, 6 M) was added dropwise at 10° to a well-stirred mixture of 3-formylindole (14.5 g, 0.1 mol),

ethanol (120 ml) and methyl isopropyl ketone (22 ml). The clear solution obtained was heated to 70° for 0.5 h, allowed to stand for 3 days at 25°, and then poured into a mixture of water (400 ml) and light petroleum (100 ml). The yellow solid obtained, on pH-adjustment to 7 – 9, was collected, dried and crystallized from methylcyclohexane. Yield: 8.7 g (41 %); m.p. 131 – 132°. (Found: C 78.7; H 7.1; N 6.7. Calc. for $C_{14}H_{15}NO$: C 78.8; H 7.1; N 6.6.) NMR($CDCl_3$): $\tau = 8.75$ (d, 6, CH_3); $\tau = 7.01$ (heptet, 1, CH); $\tau = 3.15$ and $\tau = 2.05$ (2d, 2, HC=CH), $J = 16$ Hz.

3-(3-Oxo-4-methylpentylidene)-6-methylindole (2b). *Method A.* 6-Methylindole (0.1 mol) and 4-methyl-3-oxo-1-pentenol-1 (prepared *in situ* from its sodium salt) was condensed as described for compound *1*. Yield: 5.0 g (22 %), m.p. 113 – 114°. (Found: C 79.0; H 7.6; N 6.2. Calc. for $C_{15}H_{17}NO$: C 79.3; H 7.5; N 6.2.) NMR ($CDCl_3$): $\tau = 8.80$ (d, 6, CH_3); $\tau = 7.62$ (s, 3, 6-CH_3); $\tau = 3.17$ and $\tau = 2.04$ (2d, 2, HC=CH), $J = 16$ Hz.

Method B. 6-Methyl-3-formylindole (0.1 mol) and methyl isopropyl ketone was condensed as described above for compound *2c*. Yield: (46 %), m.p. 113 – 114°.

Method C. 6-Methylindole (13.1 g, 0.1 mol) and 4-methyl-1-pentyn-3-one [9] (9.6 g, 0.1 mol) in methanol (50 ml) were refluxed for 4 h. The solvent was driven off, the dark residue chromatographed on silica gel with CH_2Cl_2/MeOH (95: 5) as eluent. The fractions containing the desired product were evaporated, and the residue crystallized from methylcyclohexane gave pure *2b*. Yield: (30 %), m.p. 113 – 114°.

The products obtained by all the methods were identical.

3-(3-Oxobutylidene)indole (2a). *Method A.* An aqueous solution of KOH (100 ml, 2 M) was added dropwise at 10° to a well-stirred mixture of 3-formylindole (14.5 g, 0.1 mol), methanol (100 ml) and acetone (22 ml, 0.3 mol). The clear solution obtained was kept for 3 days at 20° and then poured into water (400 ml) and the pH-value adjusted to 7 – 9. The yellow solid obtained was collected, dried and crystallised from toluene (with final cooling to – 30°). Yield: 9.6 g (52 %); m.p. 142 – 143°. (Found: C 77.6; H 6.2; N 7.4. Calc. for $C_{12}H_{11}NO$: C 77.8; H 6.0; N 7.6.) NMR ($CDCl_3$): $\tau = 7.62$ (s, 3, CH_3); $\tau = 3.20$ and $\tau = 2.14$ (2d, 2, HC=CH), $J = 16$ Hz.

Method B. Indole (11.7 g, 0.1 mol) and 1-butyn-3-one (6.8 g, 0.1 mol) in methanol (40 ml) were refluxed for 4 h. The solvent was driven off and the dark residue chromatographed on silica gel with methylene chloride/methanol (95 : 5) as eluent. The fractions containing the desired product were evaporated; and the residue recrystallized from toluene gave pure *2a*. Yield: 5.5 g (30 %), m.p. 142 – 143°.

Method C. 3-Formylindole (14.5 g, 0.1 mol) in *N,N*-dimethylformamide (100 ml) was added dropwise to 2-oxopropylidenetriphenylphosphorane (0.1 mol, prepared from 2-oxopropyltriphenylphosphonium chloride 35.5 g, 0.1 mol, and sodium hydride 2.4 g, 0.1 mol) in *N,N*-dimethylformamide (150 ml) while striring at 70°. After further 2 h at this temperature, the mixture was cooled and poured into water (600 ml). The solid formed was dried and chromatographed on silica gel with CH_2Cl_2/MeOH (95 : 5) as eluent. Yield: 3.7 g (20 %), m.p. 142 – 143°.

The products obtained by all three methods were identical, with a sample [10] kindly provided by Dr. Z. Procházka. His product was obtained by an aldol condensation of 3-formylindole and acetone. (No experimental details were given.)

3-(4-Methyl-3-oxopentyl)-6-methylindole (3b). Compound *2b* (1 g) in ethanol (50 ml) was catalytically hydrogenated over 5 % Pd/C using standard conditions. The crude product was recrystallized from light petroleum (40 – 60°). Yield: (90 %), m.p. 68 – 71° (lit.[2] 68 – 71°).

3-(3-Oxobutyl)indole. Compound (*2a*) was hydrogenated as described for *3b*. The crude product was recrystallized from methanol. Yield: (52 %), m.p. 93 – 94° (lit.[11] 93 – 94°).

Bis-(6-methyl-3-indolyl)methane. Aqueous formaldehyde (38 %, 0.4 ml) was condensed with 6-methylindole (0.01 mol) using the method given by Thesing.[12] Yield: 0.86 g (63 %, m.p. 142 – 144°. (Found: C 83.0; H 6.7; N 10.0. Calc. for $C_{19}H_{18}N_2$: C 83.2; H 6.6; N 10.2.)

Bis-(6-methyl-*3*-indolyl)methane was also produced by working up suitable fractions obtained by the condensation of 6-methylindole with 2-hydroxymethylenecamphor and 4-methyl-3-oxo-1-pentanol-1. The yields were 4 and 18 %, respectively.

Bis-(6-methyl-3-indolyl)methane is sensitive to light, air and acids (*cf.* Ref. 13).

Reductive cleavage of tris-(3-indolyl)methane. A mixture of tris-(3-indolyl)methane [14] (3.6 g, 0.01 mol), formic acid (13.8 g, 0.03 mol) and triethylamine (20.2 g, 0.02 mol) was heated (140°) for 4 h. After cooling, water (100 ml) was added. The semi-solid mass obtained was dried and then chromatographed on silica gel, using CH_2Cl_2 as eluent.

The following compounds were isolated; indole ($R_F = 0.80$; Yield: 60 %), bis-(3-indolyl)-methane ($R_F = 0.59$; Yield: 50 %), tris-(3-indolyl)methane ($R_F = 0.28$; Yield: 30 %).

Reaction of 3-(3-oxobutylidene)indole (2a) *with indole.* 3-(3-Oxobutylidene)indole (1.85 g, 0.01 mol) and indole (2.34 g, 0.02 mol) in acetic acid (15 ml) were heated (90°) with light protection for 10 min. After cooling (10°) the crystals of tris-(3-indolyl)methane were collected and dried. Yield: 2.6 g (72 %), m.p. 244 – 246° (lit.[14] 244 – 246°).

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