The Fischer Indolisation of (±)-3-Methylcyclopentanone Phenylhydrazone

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Fischer indolisation of (±)-3-methylcyclopentanone phenylhydrazone under three different conditions affords in each case a mixture of (±)-1-and 2-methyl-1,2,3,4-tetrahydrocyclopent[*b*]indoles **4b** and **4a**, respectively. These mixtures were quantitatively analysed using proton nuclear magnetic resonance spectroscopy and their recrystallisation led to the isolation of compound **4a**. The structure of this was distinguished from the isomeric structure **4b** by its oxidation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone to afford compound **4c**, the ultraviolet spectrum of which was characteristic of a 3- and not a 2- acylindole chromophore and was almost superimposable upon that of the model compound **4d**.

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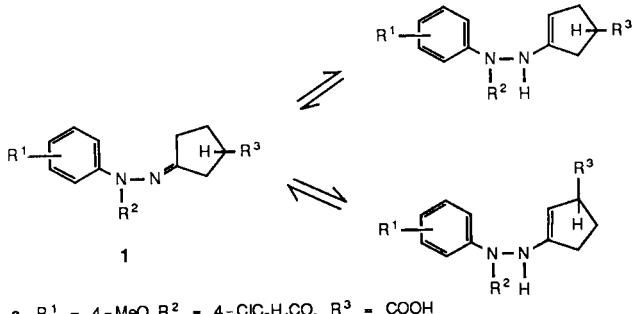
The Fischer indolisation of unsymmetrically substituted (other than 2-substituted) cycloalkanone arylhydrazones can possibly afford two isomeric indolic products [1] which, starting from (±)-3-substituted cyclopentanone arylhydrazones would be the corresponding (±)-1- and 2-substituted 1,2,3,4-tetrahydrocyclopent[*b*]indoles. Of these latter reactions that have so far been studied, both possible products were claimed [2] to be formed starting from 3-carboxycyclopentanone N_{α}-(4-chlorobenzoyl)-4-methoxyphenylhydrazone **1a** and in others only the isolation of the corresponding 2-carboxy-1,2,3,4-tetrahydrocyclopent[*b*]indoles were reported [3,4]. However, yields of these sole products were far from excellent and it is likely that the 1-substituted isomers were also formed, although unspecified methods to detect them were unsuccessful [3]. Mechanistically, both isomeric products should be produced from the indolisation of 3-substituted cyclopentanone arylhydrazones **1** since there is no reason why, irrespective of the nature of R^3, the hydrazone **1** -enehydrazine (**2** or **3**) tautomerism, the initial stage in the indolisation mechanism [5] and the one that ultimately determines which isomeric product is produced, should produce exclusively either **2** or **3**.

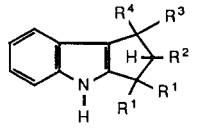


1

a, R^1 = 4-MeO, R^2 = 4-ClC_6H_4CO, R^3 = COOH
b, R^1 = R^2 = H, R^3 = Me

3

The Fischer indolisation of (±)-3-methylcyclopentanone phenylhydrazone **1b** has now been effected using either dilute aqueous sulfuric acid or glacial acetic acid as catalysts and under non-catalytic conditions in boiling ethan-1,2-diol under reflux [6]. Proton nuclear magnetic resonance spectroscopic analysis of the resulting three non-basic total reaction products indicated in each the presence of both possible products, **4a** and **4b**, by the two doublets centred at δ 1.24 and 1.34 (J = 6.3 and 6.7 Hz, respectively) which were ultimately assignable to the respective $CHCH_3$ groups as shown below. Furthermore, integration of these doublets showed that the ratios of compounds **4a:4b** in these total products were 1.66, 2.66 and *ca.* 1.0, respectively.



4

a, R^1 = R^3 = R^4 = H, R^2 = Me
b, R^1-R^3 = H, R^4 = Me
c, R^1 = H, R^2 = Me, R^3 + R^4 = O
d, R^1 = R^2 = H, R^3 + R^4 = O
e, R^1-R^4 = H,
f, R^1 + R^1 = O, R^2 = R^3 = H, R^4 = Me

Attempts to separate the two isomeric components from these mixtures using thin layer or column chromatography were unsuccessful and although a 90% separation was achieved using an analytical high pressure liquid chromatography column of ODS hypersil with a mobile phase of methanol-water (2:3), a separation could not be effected using a preparative column. Very surprisingly, however, crystallisation of the mixtures from methanol readily afforded in the pure state one of the two indolic products, that with the methyl doublet δ 1.24 in its proton nuclear magnetic resonance spectrum.

Attempts to distinguish between structures **4a** and **4b** for this product using proton nuclear magnetic resonance spectroscopy were unsuccessful, the spectrum being extremely complex because of the non-equivalence of the hydrogen nucleii in each of the methylene groups, and because of the uncertainty in assignment of the relative chemical shifts of the aliphatic hydrogen nucleii. However, the structure of the product was readily established as **4a** by its oxidation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, a reagent which selectively oxidises a methylene group at the 3-position of an indole nucleus [7,8], into compound **4c**, the structure of which was readily confirmed by the very close similarity of its infrared and especially its ultraviolet spectra with those of compound **4d** which was synthesised by the similar oxidation [8] of 1,2,3,4-tetrahydrocyclopent[*b*]indole **4e** [9]. It has been found that oxidation of the 2-methyl group into a 2-formyl group is a competing reaction in the oxidation of 2,3-dimethylindole by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone into 3-formyl-2-methylindole and it is therefore possible that oxidation of a methylene group at an indolic 2-position could occur when the preferred site adjacent to the indolic 3-position is blocked, as, for example, in structure **4b**. However, structure **4f** is readily eliminated as the possible structure of the present oxidation product by consideration of its ultraviolet spectroscopic properties which are not only almost identical to those of compound **4d** but are characteristic of a 3-acylindole chromophore whose ultraviolet spectrum is significantly different from that of a 2-acylindole chromophore [8,10,11].

Clearly, oxidation with 2,3-dichloro-5,6-dicyno-1,4-benzoquinone offers a facile and generally applicable method of structurally distinguishing between the two isomeric products resulting from the Fischer indolisation of the arylhydrazones of 3-substituted cycloalkanones and their acyclic analogues.

EXPERIMENTAL

Melting points were determined on a Kofler hot-stage and are uncorrected. Infrared spectra were recorded as mulls in liquid paraffin on a Pye Unicam SPE-100 spectrophotometer, ultraviolet spectra were measured in 96% ethanol on a Unicam SP1750 spectrophotometer and proton nuclear magnetic resonance spectra were recorded in deuteriochloroform with tetramethylsilane as the internal standard using, unless otherwise stated, a Bruker WP80 pulsed FT spectrometer. Mass spectra were recorded on a Kratos MS-25 instrument connected to a DS-55 data system. Column chromatography was effected with neutral Brockmann alumina (BDH) and thin layer chromatography was carried out using Polygram Alox N/UV_{254} plates (0.2 mm) supplied by Camlab, Cambridge, England. Organic extracts were dried with sodium carbonate and evaporated under reduced pressure on a Buchi evaporator. Ether refers to diethyl ether.

Fischer Indolisation of (±)-3-Methylcyclopentanone Phenylhydrazone **1b**.

Method 1.

To 4.0 g of (±)-3-methylcyclopentanone was added 5.7 g of phenylhydrazine. An exothermic reaction ensued. After warming a few minutes on a steam-bath, the resulting hydrazone was dissolved, with warming, in a solution of 4 ml of concentrated sulfuric acid in 90 ml of water and the resulting solution was boiled under reflux, with stirring, for 1 hour. After cooling, the red-colored oily suspension which had separated from the orange-colored aqueous medium was extracted into 2 x 50 ml of ether, the combined ethereal solutions were washed sequentially with 2 x 25 ml of 10% hydrochloric acid and 2 x 25 ml of water and the resulting yellow ethereal solution was dried and the solvent evaporated to afford 3.9 g (55%) of a mixture of (±)-1- and 2-methyl-1,2,3,4-tetrahydrocyclopent[*b*]-indoles **4b** and **4a**, respectively, as a red-brown oil which, upon standing at room temperature, soon crystallised.

Method 2.

To a stirred solution of 9.8 g of (±)-3-methylcyclopentanone in 36 ml of glacial acetic acid which was boiling under reflux was added dropwise during 1 hour 10.8 g of phenylhydrazine. After the stirring and boiling under reflux had been continued for a further 2 hours, the orange-colored solution was cooled to room temperature, 50 ml of water was added and the resulting liberated oil was extracted into 2 x 30 ml of ether. Subsequent "work-up" following the procedure outlined in Method 1 yielded a non-basic dark-brown oil which, after passage through an alumina column using ether as eluting solvent gave 6.3 g (37%) of a mixture of (±)-1- and 2-methyl-1,2,3,4-tetrahydrocyclopent[*b*]indoles **4b** and **4a**, respectively, as a tan-colored semicrystalline residue.

Method 3.

A mixture of 10.8 g of phenylhydrazine with 9.8 g of (±)-3-methylcyclopentanone in 60 ml of toluene was boiled under reflux with the azeotropic removal of water (Dean-Stark head) for 3 hours. The solvent was then removed to leave the hydrazone as an orange oil which soon completely crystallised upon standing at room temperature. This solid was dissolved, upon warming, in 80 ml of ethan-1,2-diol and the deep-yellow solution was gently boiled under reflux for 5 hours, after which time the evolution of ammonia, which had initially been copious, had ceased. After cooling the reaction mixture to room temperature, 100 ml of water was added and the liberated oil was extracted into 2 x 40 ml of ether. The combined ethereal extracts were "worked up" following the procedure described in Method 1 to afford 12.4 g (72%) of a mixture of (±)-1- and 2-methyl-1,2,3,4-tetrahydrocyclopent[*b*]indoles **4b** and **4a**, respectively, as a red-brown semicrystalline solid.

The infrared spectra of the above three mixtures were very similar and, in particular, they all exhibited strong absorption at ν max 3400 ± 10 and weak absorption 3490 ± 10 cm^{-1} (indolic NH) with no other absorption > 1630 cm^{-1} other than that of CH stretching. Likewise, the three mixtures exhibited closely similar proton nuclear magnetic resonance spectra with δ 8.00-6.65 (5H, m, aromatic H, NH), 3.55-1.85 (5H, m, 2 x CH_2, CH), 1.24 and 1.34 (3H, d's, J = 6.3 and 6.7 Hz, respectively, $CHCH_3$). Crystallisation of any of the mixtures from methanol yielded approximately 50% of the available (±)-2-methyl-1,2,3,4-tetrahydrocyclopent[*b*]indole **4a** as pale-tan plates, mp 83-85° (with sweating from 73°) which after passage through a column of neutral alumina in petroleum (bp 30-40°)-ether (1:1) followed by recrystallisation from petroleum (bp 60-80°) were obtained as white plates, mp 86-88° (with sublimation from 77°); ir: ν max 3400 ± 10 (strong), 3490 ± 10 (weak) cm^{-1} [*cf.* 1,2,3,4-tetrahydrocyclopent[*b*]indole **4e** [9], 3390 ± 10 (strong), 3475 ± 10 (weak)] (NH); uv: λ max 279,229, λ infl 287, λ min 248 nm (log ϵ 3.75, 4.39, 3.67, 3.19, respectively) [*cf.* 1,2,3,4-tetrahydrocyclopent[*b*]indole **4e** [9], λ max 279.5, 230, λ infl 288, λ min 249 (log ϵ 3.83, 4.45, 3.74, 3.26, respectively)]; ^{1}H-nmr: δ (recorded on a Varian XL-300 spectrophotometer) 1.24 (3H, d, J = 6.3 Hz, CH_3CH), 2.36-2.56 (2H, m, CH_2), 2.94-3.16 (3H, m, CH_2 + CH), 7.08-7.21 (2H, m), 7.21-7.34 (1H, m), 7.42-7.52 (1H, m) (4 x aromatic H), 7.72 (1H, br, s, NH); ms: m/e 171 (M^+, 78), 156 (100).

Anal. Calcd. for $C_{12}H_{13}N$: C, 84.2; H, 7.6; N, 8.2. Found: C, 84.4; H, 7.65; N, 8.0.

2,3-Dichloro-5,6-dicyano-1,4-benzoquinonone Oxidation of (±)-2-Methyl-1,2,3,4-tetrahydrocyclopent[*b*]indole **4a**.

An ice-cooled solution of 271 mg of (±)-2-methyl-1,2,3,4-tetrahydrocyclopent[*b*]indole **4a** in a mixture of 15.5 ml of tetrahydrofuran and 1.5 ml of water was deoxygenated by passage of a stream of nitrogen through it for 10 minutes and was then maintained under an atmosphere of nitrogen whilst a solution of 877 mg of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone dissolved in 6 ml of tetrahydrofuran was added dropwise over a period of 10 minutes. During the initial phases of the addition, transient dark blue-black colored areas were observed in the reaction mixture which then faded to afford a yellow solution, but at the completion of the addition, the solution was a dark red-brown color. Stirring was then continued for a further hour, the reaction mixture being allowed to warm to room temperature during this period. Evaporation of the solvent then left a red-brown solid residue which was extracted with 2 x 10 ml of ethyl acetate. Evaporation of the ethyl acetate afforded a red-brown solid which was triturated with ether and the total ethereal solution and residual solid subjected to column chromatography. Initial elution with 300 ml of ether to remove any unchanged starting material (none was obtained) was followed by elution with 600 ml of ethyl acetate which afforded, after removal of the solvent, (±)-2-methyl-1,2,3,4-tetrahydrocyclopent[*b*]indol-1-one **4c** as a pale-yellow solid which after trituration with ether yielded 91 mg (31%) of white prisms, mp 188-189°. Recrystallisation from chloroform gave white plates, mp 188-189°; ir: ν max 3140 ± 10, 1655 ± 5 cm^{-1} (NH and C=O, respectively); uv: λ max 290, 282, 260, 237, 214, λ min 286, 278, 244, 224 nm (log ε 3.94, 3.92, 4.29, 4.23, 4.48, 3.90, 3.89, 4.07, 3.89, respectively); ^{1}H-nmr: δ 1.36 (3H, d, J = 7.2 Hz, C*H*$_3$CH), 2.55-3.51 (3H, m, CH_2 + CH), 7.17-7.42 (3H, m), 7.86-8.00 (1H, m) (4 x aromatic H), 8.93 (1H, br, s, NH); ms: m/e 185 (M^+, 93), 170 (100).

Anal. Calcd. for $C_{12}H_{11}NO$: C, 77.8; H, 5.95; N, 7.55. Found: C, 77.6; H, 5.95; N, 7.4.

1,2,3,4-Tetrahydrocyclopent[*b*]indol-1-one **4d**.

Using the procedure described above for the oxidation of compound **4a** to compound **4c**, 157 mg of 1,2,3,4-tetrahydrocyclopent[*b*]indole **4e** [9] was reacted with 504 mg of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone to produce 91 mg (53%) of 1,2,3,4-tetrahydrocyclopent[*b*]indol-1-one **4d** as pale-tan prisms, mp 247-248° [lit [8] mp 252-253° (from ethanol)]; ir: ν max 3180 ± 10, 1650 ± 5 [lit [8] (Nujol), 3200 and 1655 cm^{-1}] (NH and C=O, respectively); uv: λ max 290, 280, 259, 237, 214 [lit [8] (ethanol), 290, 283, 260, 237]; λ min 285, 278, 244, 224 nm (log ε 3.95, 3.93, 4.31, 4.25, 4.45, 3.92, 3.91, 4.09, 3.95, respectively.

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