The Stereochemical Course of the Catalytic Hydrogenation of 3(2*H*)Isoquinolinones

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4-Benzylidene-1-phenyl-1,4-dihydro-3(2*H*)isoquinolinone (**2**), 4-benzyl-1-phenyl-3(2*H*)isoquinolinone (**3**) and 4-benzyl-3-ethoxy-1-phenylisoquinoline (**6**) have been hydrogenated on palladium-charcoal catalyst. The structure of the products and the ratio of the stereoisomers have been determined by nmr spectroscopy and by LIS measurements with $Eu(dpm)_3$.

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In an earlier work we reported (1) on the reaction of previously synthetized (2) 1-aryl-1,4-dihydro-3(2*H*)isoquinolinones (**1**) with aromatic aldehydes in the presence of sodium hydride or with the Avramoff reagent (3) to obtain 1-aryl-4-arylmethyl-3(2*H*)isoquinolinones. We assumed that the primary product of the reaction was the corresponding 4-benzylidene derivative (**2**), rapidly undergoing aromatization to **3** in the reaction conditions employed (Fig. 1).

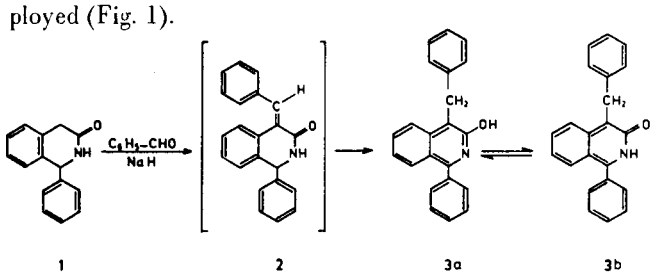

Figure 1

Following the reaction by tlc and uv spectrometry and selecting appropriate conditions, it was possible to detect and also isolate this intermediate, as a pure compound, in 30% yield. In accordance with our expectations, in alcoholic sodium ethoxide solution **2** was rapidly transformed to **3**.

An nmr spectroscopic study of the structure of **2** has shown that the benzylidene group is in the *trans* position in relation to the oxo group. The vinyl proton is then *cis* to the carbonyl, and as a result of the deshielding effect of this, its band is shifted to δ 7.68. For a *trans* vinyl proton, this band is to be expected at δ 6.7-7.0 (4).

Further evidence on the conformation of the vinyl proton has been provided by LIS measurements with $Eu(dpm)_3$. The complex is bound to the oxygen of the amide group. The LIS values of the vinyl and NH protons, Δ δ 13.6 and 13.3 ppm, respectively, determined by graphical interpolation, are in agreement with the fact that their estimated distances, r_i, from the europium atom are also nearly identical. Based on the known correlation between r_i and Δ δ in the case of a *trans* vinyl proton, its induced shift would have been substantially smaller (5,6).

Hydrogenation of the benzylidene derivative **2** is expected to result in two (one *cis* and one *trans*) 4-benzyl-1-phenyl-1,4-dihydro-3(2*H*)isoquinolinones (**4** and **5**), differing in the relative positions of the phenyl and benzyl groups. Catalytic hydrogenation of **2** in the presence of palladium-charcoal catalyst and separation of the products by column chromatography gave, indeed, two substances.

Molecular model examinations indicate that the hetero ring has a boat conformation. From the different chemical shifts of H-1, it has been established that the isomers differ in the steric positions of the phenyl group. When the proton at C-1 is equatorial, its signal is at 5.64; when it is axial, the signal shifts to 4.48 because of the diamagnetic shielding effect of the adjacent condensed phenyl ring.

The above results are supported by the LIS measurements. In accordance with the larger r_i in the case of an equatorial proton at C-1, Δ δ is 3.1, whereas for an axial proton it is 4.3 ppm.

The ratio of the two isomers in the product of catalytic hydrogenation is 65:12, *i.e.* saturation is accompanied by the formation of essentially more of the isomer containing the phenyl group in the axial position. When the 4-benzyl derivatives are prepared by direct synthesis, the nmr spectrum indicates that the two isomers are formed in practically identical amounts.

The chemical shift of the proton at C-4 is 4.01 in both isomers, showing that its steric arrangement is the same in both compounds. According to the ms spectra the more stable product is the one in which the 1-phenyl group is axial (*trans*). The intensity of M^+ in the mass spectrum is 100% for this compound, whereas for the isomer with equatorial phenyl (*cis*) it is only 6%. If the benzyl group, too, were axial, it would be necessary to reckon with the occurrence of a significant steric interaction between the two groups; this would cause destabilization, involving an appreciable steric upfield shift in the ^{13}C nmr spectrum (7). Since this was not observed, the axial position for the benzyl group can be excluded.

Similarly as described for other 3(2*H*)isoquinolinones (8), lactam-lactim tautomerism also occurs for 4-benzyl-

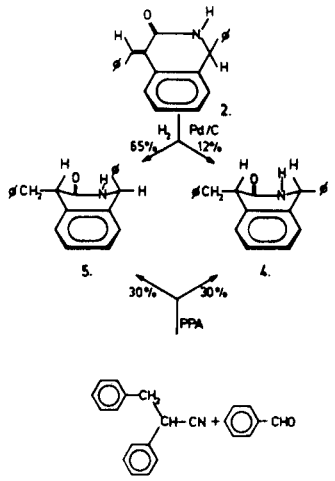

Figure 2

1-phenyl-3(2*H*)isoquinolinone (**3a** and **3b**); this is well demonstrated by the uv spectrum of an alcoholic solution of the compound: the bands at 357 and 438 nm relate to the lactim and lactam forms, respectively. In the solid phase the compound exists in the lactim form only (**3a**), as indicated by the absence of the ν (C=O) band from the infrared spectrum [ir (potassium bromide): ν 1620 (s), 3200-2500 (m)].

Alkylation of **3** by traditional methods remained unsuccessful, but using triethyloxonium tetrafluoroborate as the alkylating agent (9) the expected 4-benzyl-3-ethoxy-1-phenylisoquinoline (**6**) was obtainable in a good yield (Fig. 3).

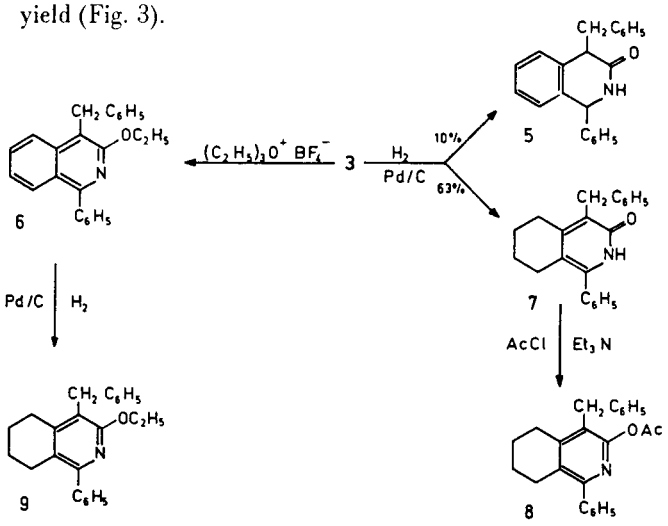

Figure 3

When 4-benzyl-1-phenyl-3(2*H*)isoquinolinone (**3**) was hydrogenated in the presence of palladium-charcoal catalyst in absolute acetic acid at room temperature, or in 96% ethanol at 60°, two products were isolated, in yields of 63 and 10%. Infrared and nmr spectra showed the main product to be 4-benzyl-1-phenyl-5,6,7,8-tetrahydro-3(2*H*)isoquinolinone (**7**) and the minor product to be *trans*-4-benzyl-1-phenyl-1,4-dihydro-3(2*H*)isoquinolinone (**5**). 4-Benzyl-1-phenyl-5,6,7,8-tetrahydro-3(2*H*)isoquinolinone exists in the lactam form not only in the solid phase (ir), but also in ethanolic solution.

The tendency to tautomerization is confirmed by the fact that acetylation led to the lactim ester **8**. This compound can be crystallized from hexane, but it undergoes spontaneous alcoholysis in ethanolic solution, this presumably being catalyzed by the basic ring nitrogen. This is confirmed by the uv spectrum of the alcoholic solution, in which the 320 nm band of the parent compound is present together with the 275 nm band characteristic of 2-alkoxypyridines (10).

The 5,6,7,8-tetrahydro derivative (**9**) was similarly formed on hydrogenation of 4-benzyl-3-ethoxy-1-phenylisoquinoline (**6**) in the presence of palladium-charocal catalyst.

To the best of our knowledge, 5,6,7,8-tetrahydro-3(2*H*)isoquinolinones have not previously been prepared by this route.

EXPERIMENTAL

Melting points were determined on a Büchi-Tottoli apparatus and are uncorrected. Infrared spectra were determined in potassium bromide pellets (Perkin-Elmer Model 457). Ultraviolet spectra were recorded in ethanolic solution; nmr spectra were determined using a JEOL PS-100 spectrometer and chemical shifts δ are given in ppm relative to internal tetramethylsilane. Mass spectra were run on a Varian MAT spectrometer at 70 ev.

4-Benzylidene-1-phenyl-1,4-dihydro-3(2*H*)isoquinolinone (**2**).

Sodium hydride (2.11 g., 0.044 mole) was added in the form of a 50% oily suspension to 400 ml. of a dry benzene solution of 8.92 g. (0.04 mole) of 1-phenyl-1,4-dihydro-3(2*H*)isoquinolinone (**1**) under nitrogen. The mixture was heated to 50°, 4.25 g. (0.04 mole) of benzaldehyde was added dropwise, and the mixture was stirred for 10 minutes at 50° and then cooled rapidly in ice-water. The organic phase was washed with 200 ml. of 10% hydrochloric acid, then with water, and dried over sodium sulfate; the solvent was then evaporated in vacuum. The residual oil was rubbed with 55 ml. of a 5:1 mixture of ether and petroleum ether; the solid material was then chromatographed on alumina. The fractions containing the product were combined and evaporated. The residual oil was treated with a 4:1 ether-petroleum ether mixture and the solid product was crystallized from acetonitrile. The pure product (3.8 g., 31%) had m.p. 192-193°; uv λ max: 314 nm (ϵ, 12,590); ir (potassium bromide): C=C 1625, C=O (amide) 1675 cm^{-1}; ^{1}H-nmr (deuteriochloroform): 5.62 (d, 1H) ($J_{CH,NH}$ = 3.0 Hz, H-1), 7.53 (d, 1H, NH), 7.68 (s, 1H, vinyl-H), 6.8-7.4 (m, 14H, 14 Ar-H).

Anal. Calcd. for $C_{22}H_{17}NO$: C, 84.85; H, 5.50; N, 4.50. Found: C, 84.63; H, 5.82; N, 4.57.

4-Benzyl-1-phenyl-1,4-dihydro-3(2*H*)isoquinolinone (**4**, **5**).

α-Benzylphenylacetonitrile (8.35 g., 0.04 mole) in 85 g. of 1:1

polyphosphoric acid (2) was stirred for 30 minutes at room temperature, and then for 1 hour at 90°. Next 4.28 g. (0.04 mole) of benzaldehyde was added over 4 hours at 120-125°, and the reaction mixture was then stirred for a further 10 hours at this temperature. After cooling, the mixture was poured into 500 ml. of ice-water and adjusted to *p*H 8 with *ca.* 120 ml. of concentrated ammonia. The resulting solid material was filtered off, washed thoroughly with water, and dried in a vacuum desiccator. The nmr spectrum indicated that this crude product contained the *cis* and *trans* isomers in a 1:1 ratio. Repeated recrystallizations from ethyl acetate gave the *cis* isomer in a yield of 20-22%. Chromatography of the crude product on alumina (chloroform) afforded both isomers in pure form in yields of 30% each.

cis-4-Benzyl-1-phenyl-1,4-dihydro-3(2*H*)isoquinolinone (**4**).

This compound had m.p. 198-199°; ^{13}C-nmr (deuteriochloroform): 59.4 C-1, 173.1 C-2, 48.5 C-4, 41.4 C (benzyl); ^{1}H-nmr (deuteriochloroform): 3.24 (q, 1H) and 3.44 (q, 1H) (J_{gem} = 12.5 Hz, CH_2-Ph), 4.01 (t, 1H) (J_{AX} = 5.0 Hz, J_{BX} = 6.5 Hz, calculated from the ABX spectra, H-4), 4.48 (s, 1H, H-1), 5.94 (s, 1H, NH), 6.37 (d, 1H), (J_o = 8 Hz, H-8), 6.7-7.25 (m, 13H, 13 Ar-H); ir (potassium bromide): NH 3180, C=O (amide) 1675 cm^{-1}; ms: m/e 313 (M^+, I = 6%).

Anal. Calcd. for $C_{22}H_{19}NO$: C, 84.31; H, 6.11; N, 4.47. Found: C, 84.84; H, 6.19; N, 4.37.

trans-4-Benzyl-1-phenyl-1,4-dihydro-3(2*H*)isoquinolinone (**5**).

This compound had m.p. 162-164°; ^{13}C-nmr (deuteriochloroform): 59.9 C-1, 172.7 C-2, 46.8 C-4, 40.2 C (benzyl); ^{1}H-nmr (deuteriochloroform): 3.30 (q, 1H) and 3.42 (q, 1H) (J_{gem} = 12.4 Hz, CH_2-Ph), 4.01 (t, 1H) (J_{AX} = 7.2 Hz, J_{BX} = 4.2 Hz, calculated from the ABX spectra, H-4), 5.64 (d, 1H) ($J_{CH,NH} \approx 1$ Hz, H-1), 6.7-7.25 (m, 15H, 14 Ar-H plus 1NH); ir (potassium bromide); NH 3190, C=O (amide) 1680 cm^{-1}; ms: m/e 313 (M^+, I = 100%).

Anal. Calcd. for $C_{22}H_{19}NO$: C, 84.31; H, 6.11; N, 4.47. Found: C, 84.25; H, 6.21; N, 4.65.

Hydrogenation of 4-Benzylidene-1-phenyl-1,4-dihydro-3(2*H*)isoquinolinone (**2**).

A solution of the 4-benzylidene derivative (**2**) (3.11 g., 0.01 mole) in 100 ml. of a 1:1 mixture of 99.5% acetic acid and ethanol was hydrogenated at room temperature and atmospheric pressure in the presence of 1 g. of 10% palladium-charcoal catalyst which had been prehydrogenated in 30 ml. of 99.5% acetic acid. The reaction mixture absorbed 270 ml. of hydrogen. The catalyst was filtered off and the solvent evaporated under vacuum. The residual oil was triturated with ether to obtain 1.7 g. of a solid, m.p. 158-160°; nmr data showed this to be a mixture of 95% *trans*-4-benzyl-1-phenyl-1,4-dihydro-3(2*H*)isoquinolinone (**5**) and 5% of the *cis* isomer (**4**).

The ethereal mother liquor was evaporated to dryness, the remaining oil triturated with 10% ammonium hydroxide and the solid substance chromatographed on neutral alumina to obtain 0.7 g. of a product; nmr data showed this to be a mixture of 61% *trans*- (**5**) and 39% *cis*-isomer (**4**). From these results the ratio of the two isomers was calculated to be about 6:1.

Hydrogenation of 4-Benzyl-1-phenyl-3(2*H*)isoquinolinone (**3**).

4-Benzyl-1-phenyl-3(2*H*)isoquinolinone (**3**) (3.11 g., 0.01 mole) was dissolved in 120 ml. of 99.5% acetic acid, and hydrogenated at room temperature and atmospheric pressure in the presence of 1 g. of 10% palladium-charcoal catalyst, which had been prehydrogenated in 30 ml. of 99.5% acetic acid. The reaction mixture absorbed *ca.* 470 ml. of hydrogen. The catalyst was filtered off, the colourless solution evaporated to dryness and the residual oil triturated with 100 ml. of cold acetone. The white solid material was filtered off, dried and crystallized from acetonitrile. The product 4-benzyl-1-phenyl-5,6,7,8-tetrahydro-3(2*H*)-isoquinolinone (**7**) (1.7 g.) had m.p. 208°; uv λ max: 328 nm (ε 11,650); ir (potassium bromide): NH 3300-2600, C=O (amide) 1635 cm^{-1}; ^{1}H-nmr (deuteriochloroform): 1.6 (m, 4H, CH_2 in positions 6 and 7), 2.47 (t, 2H) and 2.65 (t, 2H, CH_2 in positions 5 and 8), 4.81 (s, 2H, CH_2-Ph), 7.0-7.35 (m, 10H, Ar-H), 13.85 (broad, 1H, NH).

Anal. Calcd. for $C_{22}H_{21}NO$: C, 83.78; H, 6.71; N, 4.40. Found: C, 83.73; H, 6.87; N, 4.62.

The mother liquor in acetone was evaporated to dryness, the residue was triturated with concentrated ammonium hydroxide, and the solid substance was chromatographed on a neutral alumina column with chloroform elution to obtain 0.3 g. of 4-benzyl-1-phenyl-5,6,7,8-tetrahydro-3(2*H*)isoquinolinone (**7**) and 0.3 g. of *trans*-4-benzyl-1-phenyl-1,4-dihydro-3(2*H*)isoquinolinone (**5**).

3-Acetoxy-4-benzyl-1-phenyl-5,6,7,8-tetrahydroisoquinoline (**8**).

To a solution of 1.2 g. (0.0038 mole) of 4-benzyl-1-phenyl-5,6,7,8-tetrahydro-3(2*H*)isoquinolinone in 50 ml. of dry benzene there was added 1.55 g. (0.02 mole) of acetyl chloride, in the presence of 2 g. (0.02 mole) of absolute triethylamine, and the mixture was refluxed for a few minutes. It was then washed with water and with 10% aqueous sodium hydrogen carbonate solution, dried over sodium sulfate, and the benzene was evaporated. On trituration with ether, the residual oil solidified. The solid was filtered off, the ether solution evaporated to dryness and the crude product crystallized from hexane. The pure product (0.4 g., 29%) had m.p. 104°; uv λ max: 320 nm (ε 7220), 275 nm (ε 8150); ir (potassium bromide): C=O 1785 cm^{-1}; ^{1}H-nmr (deuteriochloroform): 1.65 (m, 4H, CH_2 in positions 6 and 7), 2.60 (t, 2H) and 2.68 (t, 2H, CH_2 in positions 5 and 8), 2.14 (s, 3H, CH_3CO), 6.85-7.4 (m, 10H, Ar-H).

Anal. Calcd. for $C_{24}H_{23}NO_2$: C, 80.64; H, 6.49; N, 3.92. Found: C, 80.76; H, 6.67; N, 3.95.

4-Benzyl-3-ethoxy-1-phenylisoquinoline (**6**).

4-Benzyl-1-phenyl-3(2*H*)isoquinolinone (**3**) (9.33 g., 0.03 mole) was suspended in 300 ml. of absolute dichloromethane, and a freshly prepared solution of 45.6 g. (0.24 mole) of triethyloxonium tetrafluoroborate (9) in 60 ml. of absolute dichloromethane was added dropwise, with stirring. The starting material rapidly dissolved, and the originally orange-yellow solution slowly became lemon-yellow. After 5 minutes the solution was mixed with 80 ml. of 50% potassium carbonate solution; strong frothing occurred and a colourless precipitate separated. This was filtered off and washed with dichloromethane. The combined dichloromethane solutions were evaporated under vacuum, and the residual orange oil was chromatographed on a silica gel column. The pure product (4.4 g., 43%) had m.p. 73°; ^{1}H-nmr (deuteriochloroform): 1.42 (t, 3H) and 4.57 (q, 2H) (CH_3CH_2O in position 3), 4.45 (s, 2H, CH_2-Ph), 7.0-8.0 (m, 14H, 14 Ar-H).

Anal. Calcd. for $C_{24}H_{21}NO$: C, 84.96; H, 6.24; N, 4.13. Found: C, 85.16; H, 6.32; N, 4.25.

4-Benzyl-3-ethoxy-1-phenyl-5,6,7,8-tetrahydroisoquinoline (**9**).

A solution of 1.7 g. (0.005 mole) of 4-benzyl-3-ethoxy-1-phenylisoquinoline (**6**) in 100 ml. of 99.5% acetic acid was hydrogenated at room temperature and atmospheric pressure in the presence of 0.5 g. of palladium-charcoal catalyst, prehydrogenated in 30 ml. of 99.5% acetic acid. After the adsorption of hydrogen had ceased, the catalyst was filtered off, the solvent

evaporated, and the residual oil was triturated with concentrated ammonium hydroxide. The solid was filtered off, washed thoroughly with water and dried in a vacuum desiccator. Chromatography of the crude product on a silica gel column gave 1.2 g. of a product (70%) which had m.p. 88°; ^{1}H-nmr (deuteriochloroform): 1.36 (t, 3H) and 4.46 (q, 2H) (CH_3CH_2O in position 3), 4.08 (s, 2H, CH_2-Ph), 2.75 (m, 4H, H_2-C in positions 5 and 8), 1.68 (m, 4H, H_2-C in positions 6 and 7), 7.1-7.6 (m, 10H, 10 Ar-H); uv λ max: 306 nm (ε 1535).

Anal. Calcd. for $C_{24}H_{25}NO$: C, 83.93; H, 7.34; N, 4.08. Found: C, 83.73; H, 7.54; N, 4.39.

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