Hydrogenation of Substituted 1-Arylisoquinolin-3(2H)-ones to 5,6,7,8-Tetrahydro- and 1,4-Dihydroisoquinolin-3(2H)-ones

László Hazai and Gyula Deák*

Institute of Experimental Medicine, Hungarian Academy of Sciences,
H-1450 Budapest, P. O. Box 67, Hungary

Gábor Tóth

NMR Laboratory, Technical Analytical Research Group,
Hungarian Academy of Sciences and Technical University,
H-1111 Budapest, Gellért tér 4, Hungary

József Tamás

Central Research Institute of Chemistry, Hungarian Academy of Sciences,
H-1525 Budapest, P. O. Box 17, Hungary
Received October 17, 1988

Catalytic hydrogenation of variously substituted 1-arylisoquinolin-3(2H)-ones **1** gave, depending on the substituents, 5,6,7,8-tetrahydroisoquinolin-3(2H)-ones (**2**) and/or the corresponding 1,4-dihydro derivatives **3**. Saturation of the compounds fused with benzene ring furnished as the main products the 9,10-dihydro- (**4** and **5**) and 5,6-dihydroisoquinolin-3(2H)-ones (**6**) in the case of benzo[f] and benzo[h] anellation, respectively, in addition to the 1,4-dihydro compounds detected or isolated as by-products.
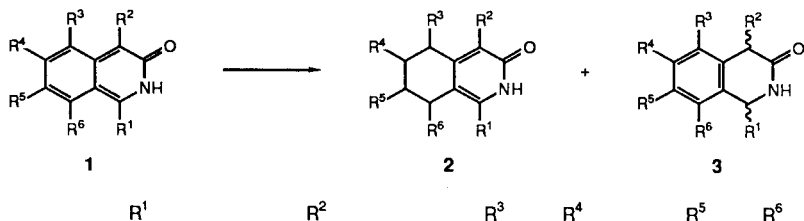
In a previous communication [1] we reported on the hydrogenation of 1,4-disubstituted isoquinolin-3(2H)-ones (3-isoquinolinols) prepared in our laboratory. In the course of a study of the hydrogenation of compounds of type **1** (R^1 = Ph; R^2 = Me, i-Pr, Ph; R^3 = R^4 = R^5 = R^6 = H) it was found that the main products were - except for the case of R^2 = i-Pr - the 5,6,7,8-tetrahydro derivatives **2**; as by-products the 1,4-dihydro compounds **3** were isolated whose steric structures were also established.

In the present work the hydrogenation experiments have been extended to isoquinolin-3(2H)-one derivatives **1** containing different substituents (Scheme 1).

Of the methoxy-substituted compounds, first the hydrogenation of 6,7-dimethoxy-4-benzyl-1-phenylisoquinolin-3(2H)-one (**1a**) [2] was investigated. It was found that even at elevated pressures and temperatures only the unchanged starting material could be recovered from the reaction mixture; neither the 5,6,7,8-tetrahydro- **2a**, nor the 1,4-dihydroisoquinolinone **3a** could be detected among the products.

In order to examine the effect of the presence of methoxy groups, 4-veratryl-1-phenylisoquinolin-3(2H)-one (**1b**) was also prepared using the method described by us earlier [2,3]. This compound could be hydrogenated under the

Scheme 1

|	R^1	R^2	R^3	R^4	R^5	R^6
a	C_6H_5	$CH_2C_6H_5$	H	OCH_3	OCH_3	H
b	C_6H_5	$CH_2C_6H_3(OCH_3)_2$-3,4	H	H	H	H
c	C_6H_5	H	CH_3	H	H	H
d	C_5H_4N-4	$CH_2C_5H_4N$-4	H	H	H	H
e	C_6H_5	H	-CH=CH-CH=CH-		H	H
f	C_6H_5	$CH_2C_6H_5$	-CH=CH-CH=CH-		H	H
g	C_6H_5	$CH_2C_6H_5$	H	H	-CH=CH-CH=CH-	

given conditions, *i.e.* in acetic acid solution, in the presence of palladium-on-charcoal catalyst, at atmospheric pressure and ambient temperature, to give the 5,6,7,8-tetrahydro derivative **2b** and the 1,4-dihydro compound **3b** in 53% and 19% yield, respectively.

The hydrogenation of compounds containing no substituent at position 4 was also studied; the compound available for this examination was the 5-methyl derivative **1c**. In this experiment the main product was the 1,4-dihydroisoquinolinone **3c** that was in all respects identical with the compound synthesized earlier [4] from *o*-methylbenzyl cyanide and benzaldehyde by cyclization in polyphosphoric acid. Workup of the reaction mixture gave the 1-phenyl-5-methyl-5,6,7,8-tetrahydroisoquinolin-3(2*H*)-one (**2c**) in 20% yield.

Hydrogenation of the 1,4-(*N*-heterocyclic), *i.e.* pyridine-ring-containing compound, 4-(4-picolinyl)-1-(4-pyridyl)-isoquinolin-3(2*H*)-one (**1d**) gave a number of unidentifiable decomposition products also; only the 1,4-dihydro compound **3d** could be isolated in the pure state from the reaction mixture.
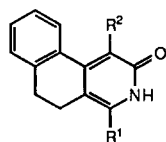
4 R¹ = C₆H₅, R² = H
5 R¹ = C₆H₅, R² = CH₂C₆H₅
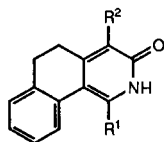
6 R¹ = C₆H₅, R² = CH₂C₆H₅

In the hydrogenation of isoquinolin-3(2*H*)-ones fused with benzene ring, such as 1-phenylbenzo[*f*]isoquinolin-3(2*H*)-one (**1e**), the main product was the 9,10-dihydro derivative **4** accompanied by a smaller amount of the 1,4-dihydro compound **3e**; the latter had been prepared by us earlier by a definitive synthesis from 1-naphthylacetonitrile and benzaldehyde in polyphosphoric acid [5]. Reduction of the 4-benzyl-substituted compound **1f** gave a similar result; the 9,10-dihydro derivative **5** was isolated as a pure substance, but the by-product 1,4-dihydro compound **3f** could not be obtained as a homogeneous product, hence its structure and yield were established by nmr spectroscopy. In the case of the benzo[*h*] derivative **1g** the main product 5,6-dihydroisoquinolinone **6** was isolated in a good yield, but the minor product **3g** could only be detected and its structure identified owing to separation problems similar to the case of **3f**.

On the basis of the above experiments it can be stated that the hydrogenation of the benzo derivatives **1e,f,g** takes place - as expected on the analogy of previous experience - at the 9,10-position, **4, 5**, in the benzo[*f*] compounds, and at the 5,6-position, **6**, in the benzo[*h*]isoquinolinones. The formation of derivatives hydrogenated in the aromatic ring was not detected. Although no data for the

energies of mesomerism are available from the literature, we assume that the energy loss of the mesomerism due to the cessation of the azaphenanthrene-lactam structure in **1e, f**, and **g** which exist mainly in the quinoidal form [2,6] is the circumstance which allows the formation of the main products **4, 5**, and **6** and allows the formation of the by-products **3e, f**, and **g**. In the first case an aromatic benzene ring beside the pyridone ring is produced and in the second instance a naphthalene structure is produced. Thus under the given reaction conditions the saturation of the aromatic ring would not have been expected.

EXPERIMENTAL

Melting points were determined on a Büchi-Tottoli apparatus and are uncorrected. The ir spectra were taken with a Perkin-Elmer 457 spectrometer. The ¹H nmr spectra were recorded on a JEOL FX-100 instrument. Mass spectra were obtained with an AEI MS-902 spectrometer (70 eV, direct insertion, 165°).

4-Veratryl-1-phenylisoquinolin-3(2*H*)-one (**1b**).

1-Phenyl-1,4-dihydroisoquinolin-3(2*H*)-one (**3**, R¹ = Ph, R² = R³ = R⁴ = R⁵ = R⁶ = H) (4.46 g, 20 mmoles) [7] was dissolved at 60°, under a stream of nitrogen, in dry toluene (300 ml). Sodium hydride (1.2 g, 22 mmoles; 50% dispersion in mineral oil) was added and the mixture was stirred for 30 minutes. A solution of 3,4-dimethoxybenzaldehyde (3.32 g, 20 mmoles) in toluene (15 ml) was then added dropwise. The mixture was stirred 15 hours at 100°. After cooling, it was poured into water (400 ml), allowed to stand overnight, and the precipitated product was filtered off and dried to give 5.2 g (70%) of **1b**, mp 182° (from benzene); ir (potassium bromide): ν C=N 1620, ν OH 3540 cm⁻¹.

Anal. Calcd. for $C_{24}H_{21}NO_3$: 77.61; H, 5.70; N, 3.77. Found: C, 77.74; H, 5.78; N, 3.93.

Hydrogenation of 4-Veratryl-1-phenylisoquinolin-3(2*H*)-one (**1b**).

Compound **1b** (18.7 g, 50 mmoles) was hydrogenated in 95% acetic acid (200 ml) in the presence of 10% palladium-on-charcoal (Engelhardt) catalyst (2 g) until the absorption of hydrogen ceased. The catalyst was removed by filtration, the filtrate was evaporated to dryness and the residue dissolved in acetone. Storage of the solution in a freezer resulted in the separation of the greater part (8 g) of the 5,6,7,8-tetrahydro derivative **2b**, which was filtered off and dried. The acetonic filtrate was evaporated to dryness and the residual oil rubbed with dilute (1:1) ammonium hydroxide. The resulting solid was chromatographed on a column of aluminum oxide, using chloroform as eluent. In this way an additional amount (2 g) of **2b** and the 1,4-dihydro derivative **3b** (3.49 g) were isolated. The data for the products are the following:

4-Veratryl-1-phenyl-5,6,7,8-tetrahydroisoquinolin-3(2*H*)-one (**2b**).

This compound was obtained in a yield of 53% (10 g), mp 197-199° (from butanol); ir (potassium bromide): ν C=O 1625 cm⁻¹; ¹H nmr (deuteriochloroform): δ CH₂(CH₂)₂CH₂ 2.44 t (2), 1.4-1.9 m (4), 2.70 t (2), MeO 3.80 s (3), 3.83 s (3), ArCH₂ 3.86 s (2), ArH 6.73 m (2), 6.90 s (1), Ph-1 7.39 m (5); ¹³C nmr: δ CH₂ 22.3, 22.5, 26.4, 27.5, 30.9, MeO (2x) 55.9, veratryl CH 111.1, 112.4, 120.3, Ph-1 C_{ortho}, C_{meta} 129.1, 128.4, C_{para} 129.0, C_{ipso} 140.8, C(=O) 163.0, C-1 150.0 quaternary carbons 114.3, 127.2, 133.1, 134.2, 147.2, 148.8.

Anal. Calcd. for $C_{24}H_{25}NO_3$: C, 76.77; H, 6.71; N, 3.73. Found: C, 76.64; H, 6.75; N, 4.00.

4-Veratryl-1-phenyl-1,4-dihydroisoquinolin-3(2H)-one (3b).

This compound was obtained in a yield of 19% (3.49 g), mp 135-137°; ir (potassium bromide): ν C=O 1660 cm⁻¹; ¹H nmr (deuteriochloroform): δ CH₂CH 3.22 m (2), (ABX-type), 3.89 t (1), MeO 3.54 s (3), 3.83 s (3), H-1 5.59 m (1), ArH 6.33 d (1) (J ∼ 2 Hz), 6.44 dd (∼8.5 Hz, 2 Hz), 6.6-6.8 m (3), 6.9-7.4 m (7).

Anal. Calcd. for $C_{24}H_{23}NO_3$: C, 77.19; H, 6.21; N, 3.75. Found: C, 77.51; H, 6.21; N, 4.18.

Hydrogenation of 5-Methyl-1-phenylisoquinolin-3(2H)-one (1c).

A solution of 1c (2.25 g, 9.6 mmoles) [6] in 99.5% acetic acid (130 ml) was hydrogenated in the presence of 10% palladium-on-charcoal (Engelhardt) catalyst (0.8 g) until the absorption of hydrogen ceased. The catalyst was removed by filtration and the filtrate evaporated to dryness. Rubbing of the residual oil with dilute (1:1) ammonium hydroxide gave a solid. It was filtered off, dried and the components were separated on a column of aluminum oxide, using chloroform and chloroform-methanol (9:1) as the eluents. The products were:

5-Methyl-1-phenyl-1,4-dihydroisoquinolin-3(2H)-one (3c).

Compound 3c was obtained upon elution with chloroform, yield 1.55 g (68%), mp 177-178° (from ethyl acetate) (lit [4] mp 177°).

5-Methyl-1-phenyl-5,6,7,8-tetrahydroisoquinolin-3(2H)-one (2c).

Compound 2c was obtained upon elution with chloroform-methanol (9:1), yield 0.45 g (20%), mp 178-179° (from ethyl acetate); ir (potassium bromide): ν C=O 1650 cm⁻¹; ¹H nmr (deuteriochloroform): MeCH(CH₂)₂CH₂ 1.28 d (3), 2.77 sextet (1), 1.3-2.0 m (4), 2.41 t (2), =CH 6.38 d (1), ⁴J = 1.2 Hz, ArH 7.42 s (5), NH 10.96 (broad) (1).

Anal. Calcd. for $C_{16}H_{17}NO$: C, 80.30; H, 7.16; N, 5.85. Found: C, 80.38; H, 7.18; N, 5.89.

4-(4-Picolinyl)-1-(4-pyridyl)-1,4-dihydroisoquinolin-3(2H)-one (3d).

4-(4-Picolinyl)-1-(4-pyridyl)-isoquinolin-3(2H)-one (1d) (7.4 g, 23.6 mmoles) [8] was dissolved in 99.5% acetic acid (170 ml). Engelhardt's catalyst (10% palladium-on-charcoal) (2 g) was added and the mixture was hydrogenated until the absorption of hydrogen stopped. After removal of the catalyst, the filtrate was evaporated to dryness and the residue rubbed with acetone to give homogeneous 3d (1.5 g, 29%), mp 195-197° (from ethanol); ir (potassium bromide): ν C=O 1670 cm⁻¹; ms: m/z (I%) 315 (100), M.

Anal. Calcd. for $C_{20}H_{17}N_3O$: C, 76.15; H, 5.43; N, 13.32. Found: C, 76.14; H, 5.60; N, 13.49.

Hydrogenation 1-Phenylbenzo[f]isoquinolin-3(2H)-one (1e).

A solution of 1e (0.6 g, 2.2 mmoles) [6] in acetic acid (100 ml) was hydrogenated in the presence of 10% palladium-on-charcoal (Engelhardt) catalyst (0.2 g) until no more hydrogen was absorbed. After removal of the catalyst, the filtrate was evaporated to dryness and the residual oil was rubbed with acetone to give product 4 (0.35 g, 58%), mp 259-260°; ir (potassium bromide): ν C=O 1640 cm⁻¹; ¹H nmr (deuteriochloroform): δ CH₂CH₂ 2.68 m (4), H-4, 6.88 s (1), H-5 7.75 m (1), ArH 7.1-7.4 m (3), Ph-1 7.49 s (5).

Anal. Calcd. for $C_{19}H_{15}NO$: C, 83.49; H, 5.53; N, 5.12. Found: C, 83.33; H, 5.58; N, 5.17.

The acetone mother liquor was evaporated to dryness and the residue was chromatographed on a column of alumina. Elution with chloroform gave 0.1 g (17%) of the 1,4-dihydro derivative 3e, mp 220-221° (lit [5] mp 223-225°).

Hydrogenation of 1-Phenyl-4-benzylbenzo[f]isoquinolin-3(2H)-one (1f).

Compound 1f (0.3 g, 0.83 mmole) [6] was hydrogenated in 99.5% acetic acid (100 ml) in the presence of 10% palladium-on-charcoal (Engelhardt) catalyst (0.1 g) until the absorption of hydrogen had ceased. The catalyst was removed and the filtrate evaporated to dryness. Rubbing of the residue with acetone gave a solid that was filtered off and dried to yield 0.15 g (50%) of the 9,10-dihydro compound 5, mp 217-219°; ir (potassium bromide): ν C=O 1635 cm⁻¹; ¹H nmr (deuteriochloroform): δ CH₂CH₂ 2.62 m (4), ArCH₂ 4.18 s (2), ArH 7.0-7.6 m (14).

Anal. Calcd. for $C_{26}H_{21}NO$: C, 85.92; H, 5.82; N, 3.85. Found: C, 85.55; H, 5.86; N, 3.55.

The acetone mother liquor was evaporated to dryness and the residue rubbed with dilute (1:1) ammonium hydroxide. The resulting solid was a mixture of 5 and 3f that could not be separated either by crystallization or chromatography. The presence of the 1,4-dihydro derivative 3f occurring together with 5 was supported by the ν C=O 1665 cm⁻¹ ir band besides the ν C=O 1635 cm⁻¹ band of 5. Further evidence was supplied by the ¹H nmr data; in addition to the ArCH₂ and (CH₂)₂ signals at 4.21 and 2.62 ppm, respectively, of compound 5, there were also the lines of CH₂CH at 3.34 m (2) and 4.58 t (1), indicating the presence of 3f. On the basis of these signals the yield of 3f was 21%.

Hydrogenation of 4-Benzyl-1-phenylbenzo[h]isoquinolin-3(2H)-one (1g).

A solution of 1g (3.25 g, 8.9 mmoles) [6] in 99.5% acetic acid (200 ml) was hydrogenated in the presence of 10% palladium-on-charcoal (Engelhardt) catalyst (0.75 g) until no more hydrogen was absorbed. After removal of the catalyst, the filtrate was evaporated to dryness and the residue rubbed with acetone. The resulting solid was filtered off and dried to give 2.2 g (67.3%) of the 5,6-dihydro derivative 6, mp 261-263° (from ethyl acetate); ir (potassium bromide): ν C=O 1630 cm⁻¹; ¹H nmr (deuteriochloroform): δ CH₂CH₂ 2.86 s (4), ArCH₂ 4.03 s (2), ArH 6.70 dd (1) (the Ph-1 group is nearly perpendicular to the aromatic ring), 6.98 td (1), 6.76 td (1) and ArH 7.0-7.5 m (11).

Anal. Calcd. for $C_{26}H_{21}NO$: C, 85.92; H, 5.82; N, 3.85. Found: C, 85.80; H, 6.01; N, 3.70.

The acetone mother liquor was evaporated to dryness. The residue was rubbed with dilute (1:1) ammonium hydroxide, and the resulting solid was filtered off. In this way a mixture of 6 and 3g was obtained that could be separated neither by crystallization, nor by chromatographic methods. The presence of 3g was supported by the ir spectrum; besides the ν C=O 1630 cm⁻¹ band of 6, also the ν C=O 1660 cm⁻¹ band, characteristic of 1,4-dihydroisoquinolin-3(2H)-ones was seen. Further, in the ¹H nmr spectrum, in addition to the ArCH₂ 4.07 and CH₂CH₂ 2.75 m signals due to 6, also the H-peri (6.30 d) and H-1 (5.67) lines could be well identified and assigned to 3g. Their evaluation shows that

the yield of **3g** was 10%.

Acknowledgements.

REFERENCES AND NOTES

[1] G. Tóth, L. Hazai, Gy. Deák, H. Duddeck, H. Kühne and M. Hricovini, *Tetrahedron*, **44**, 6861 (1988).

[2] L. Hazai, Gy. Deák, A. Schnitta, J. Haskó-Breuer and E. Horváth, *Acta Chim. Hung.*, **116**, 303 (1984).

[3] Gy. Deák, L. Hazai and G. Tóth, *J. Heterocyclic Chem.*, **14**, 583 (1977).

[4] Z. Csűrös, Gy. Deák, I. Hoffmann and A. Török-Kalmár, *Acta Chim. Acad. Sci. Hung.*, **60**, 177 (1969).

[5] L. Hazai, Gy. Deák and M. Dóda, *Acta Chim. Acad. Sci. Hung.*, **108**, 255 (1981).

[6] L. Hazai, Gy. Deák, G. Tóth, J. Volford and J. Tamás, *J. Heterocyclic Chem.*, **19**, 49 (1982).

[7] Gy. Deák, K. Gáll-Istók, L. Hazai and L. Sterk, *Synthesis*, 393 (1975).

[8] L. Hazai, Gy. Deák, G. Szabó and E. Koltai, *Acta Chim. Acad. Sci. Hung.*, **102**, 305 (1979).