

Acid-catalysed Cyclization of α -Oxo-anilides to 1,3-Dihydro-3-hydroxyindol-2-ones

By **Hiroumi Aoyama*** and **Yoshimori Omote**, Department of Chemistry, The University of Tsukuba, Sakuramura, Niihari, Ibaraki, Japan

Tadashi Hasegawa and Hiroaki Shiraiishi, Department of Chemistry, Tokyo Kyoiku University, Otsuka, Tokyo, Japan.

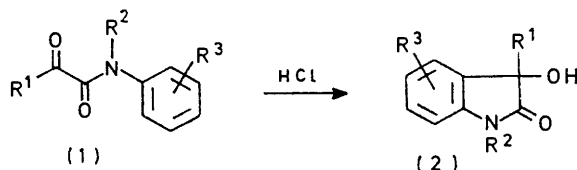
N-Alkyl- α -oxo-anilides undergo acid-catalysed cyclization at 25 °C to give the corresponding 1,3-dialkyl-1,3-dihydro-3-hydroxyindol-2-ones in high yields. The same anilides give 1,3-dialkyl-3-chloro-1,3-dihydroindol-2-ones, when treated with concentrated hydrochloric acid at 80 °C. Reduction of the hydroxyindolones yields 1,3-dialkylindoles.

DURING an investigation of the photochemical reactions of amides,¹ *N*-alkyl- α -oxo-anilides were found to afford 1,3-dihydro-3-hydroxyindol-2-ones on treatment with concentrated hydrochloric acid.

When *N*-methylpyruvanilide (1a) was treated with concentrated hydrochloric acid for 5 min at 25 °C, 1,3-dimethyl-1,3-dihydro-3-hydroxyindol-2-one (2a), identical with an authentic sample,² was obtained in

can be explained in terms of protonation on the ketone carbonyl oxygen followed by cyclization and deprotonation (*cf.* the mechanism of the Bischler synthesis of indoles³).

On the other hand, when the anilides (1a—d) were treated with concentrated hydrochloric acid at 85 °C, the corresponding 1,3-dialkyl-3-chloro-1,3-dihydroindol-2-ones (3a—d) were obtained, accompanied by small



a; $R^1 = R^2 = \text{Me}, R^3 = \text{H}$
 b; $R^1 = \text{Me}, R^2 = \text{Et}, R^3 = \text{H}$
 c; $R^1 = R^2 = \text{Me}, R^3 = p\text{-Me}$
 d; $R^1 = R^2 = \text{Me}, R^3 = p\text{-Cl}$
 e; $R^1 = R^2 = \text{Me}, R^3 = p\text{-OMe}$
 f; $R^1 = R^2 = \text{Me}, R^3 = o\text{-Me}$
 g; $R^1 = R^2 = \text{Me}, R^3 = m\text{-Me}$
 h; $R^1 = \text{Et}, R^2 = \text{Me}, R^3 = \text{H}$

a; $R^1 = R^2 = \text{Me}, R^3 = \text{H}$
 b; $R^1 = \text{Me}, R^2 = \text{Et}, R^3 = \text{H}$
 c; $R^1 = R^2 = \text{Me}, R^3 = 5\text{-Me}$
 d; $R^1 = R^2 = \text{Me}, R^3 = 5\text{-Cl}$
 e; $R^1 = R^2 = \text{Me}, R^3 = 5\text{-OMe}$
 f; $R^1 = R^2 = \text{Me}, R^3 = 7\text{-Me}$
 g; $R^1 = R^2 = \text{Me}, R^3 = 6\text{-Me}$
 g'; $R^1 = R^2 = \text{Me}, R^3 = 4\text{-Me}$
 h; $R^1 = \text{Et}, R^2 = \text{Me}, R^3 = \text{H}$

96% yield. The anilides (1b—h) also gave the corresponding 1,3-dialkyl-1,3-dihydro-3-hydroxyindol-2-ones (2b—h) in high yields. In the case of the *meta*-substituted anilide (1g) the product was a 2 : 3 mixture of two positional isomers, (2g) and (2g'). The results are summarized in Table 1. The indoles (2b—h) were

amounts of 1,3-dihydro-3-hydroxyindol-2-ones (2a—d) (see Table 2). Compounds (3a—d) were apparently

TABLE 1

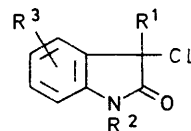
Cyclization of the oxo-anilides (1) to the chloroindolones (2)

| Reactant | Reaction time (min) | Reaction temp. (°C) | Yields (%) |
|----------|---------------------|---------------------|------------|
| (1a) | 5 | 25 | 96 |
| (1b) | 5 | 25 | 94 |
| (1c) | 5 | 25 | 91 |
| (1d) | 4 | 80 | 80 |
| (1e) | 5 | 25 | 96 |
| (1f) | 20 | 25 | 73 |
| (1g) | 5 | 25 | 94 |
| (1h) | 5 | 25 | 93 |

identified on the basis of spectral data and elemental analyses.

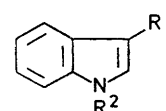
The formation of the 3-hydroxyindol-2-ones (2a—h)

¹ T. Hasegawa and H. Aoyama, *J.C.S. Chem. Comm.*, 1974, 743; T. Hasegawa, H. Aoyama, and Y. Omote, *Tetrahedron Letters*, 1975, 1901.



(3)

a; $R^1 = R^2 = \text{Me}, R^3 = \text{H}$
 b; $R^1 = \text{Me}, R^2 = \text{Et}, R^3 = \text{H}$
 c; $R^1 = R^2 = \text{Me}, R^3 = 5\text{-Me}$
 d; $R^1 = R^2 = \text{Me}, R^3 = 5\text{-Cl}$



(4)

a; $R^1 = R^2 = \text{Me}$
 b; $R^1 = \text{Me}, R^2 = \text{Et}$
 c; $R^1 = \text{Et}, R^2 = \text{Me}$

formed by reactions of the products (2a—d) with chloride anion; this was confirmed by the fact that the treatment of compounds (2a—d) with concentrated hydrochloric acid under the same conditions gave the chloro-derivatives (3a—d) in similar yields.

² E. Giovanninni and J. Rosales, *Helv. Chim. Acta*, 1963, 46, 1332.

³ R. J. Sundburg, 'The Chemistry of Indoles,' Academic Press, New York, 1970.

Since 1,3-dihydro-3-hydroxyindol-2-ones can be converted into the corresponding indoles by reduction with lithium aluminium hydride,⁴ the cyclization of α -oxo-anilides was expected to be useful for the synthesis of

TABLE 2

Cyclization of the oxo-anilides (1) to the chloroindolones (3)

| Reactant | Reaction time (min) | Reaction temp. (°C) | Yields (%) |
|----------|---------------------|---------------------|------------------|
| (1a) | 3 | 85 | (3a) 83; (2a) 15 |
| (1b) | 3 | 85 | (3b) 81; (2b) 16 |
| (1c) | 3 | 85 | (3c) 80; (2c) 15 |
| (1d) | 20 | 85 | (3d) 71; (2d) 25 |

some indoles. When the anilide (1a) was treated with concentrated hydrochloric acid and the crude product was reduced with lithium aluminium hydride, 1,3-dimethylindole⁵ (4a) was obtained in 78% yield. The anilides (1b and h) similarly afforded 1-ethyl-3-methylindole⁵ (4b) (82%) and 3-ethyl-1-methylindole (4h) (74%), respectively.

EXPERIMENTAL

General Procedure for Cyclization of the α -Oxo-anilides (1a—1i) to the Hydroxyindolones (2a—h).—A solution of the anilide (1) (500 mg) in concentrated hydrochloric acid (10 ml) was kept for 5—20 min at 25 °C (or 80 °C). After addition of water the solution was extracted with ethyl acetate three times. The organic layer was washed with sodium hydrogen carbonate solution and water, dried (MgSO₄), and evaporated, and the crude product was purified by chromatography or recrystallization.

(i) 1,3-Dihydro-3-hydroxy-1,3-dimethylindol-2-one (2a) was identical with authentic material.

(ii) 1-Ethyl-1,3-dihydro-3-hydroxy-3-methylindol-2-one (2b) had m.p. 139—140.5°; ν_{\max} (KBr) 3 330 and 1 690 cm⁻¹; δ (CDCl₃) 1.26 (3 H, t, *J* 7.2 Hz, CH₂CH₃), 1.59 (3 H, s, 3-CH₃), 3.44 (1 H, s, OH), 3.84 (2 H, q, *J* 7.2 Hz, CH₂), and 6.80—7.50 (4 H, m, aromatic) (Found: C, 69.2; H, 6.85; N, 7.25. C₁₁H₁₃NO₂ requires C, 69.1; H, 6.85; N, 7.35%).

(iii) 1,3-Dihydro-3-hydroxy-1,3,5-trimethylindol-2-one (2c) had m.p. 158—160°; ν_{\max} (KBr) 3 330 and 1 690 cm⁻¹; δ (CDCl₃) 1.59 (3 H, s, 3-CH₃), 2.47 (3 H, s, 5-CH₃), 3.18 (3 H, s, NCH₃), 3.76 (1 H, s, OH), 6.74br (1 H, d, *J* 8.0 Hz, 7-H), 7.16br (1 H, d of d, *J* 8.0 and 2.0 Hz, 6-H), and 7.28br (1 H, d, *J* 2.0 Hz, 4-H) (Found: C, 68.9; H, 6.85; N, 7.25. C₁₁H₁₃NO₂ requires C, 69.1; H, 6.85; N, 7.35%).

(iv) 5-Chloro-1,3-dihydro-3-hydroxy-1,3-dimethylindol-2-one (2d) had m.p. 144.5—146°; ν_{\max} (KBr) 3 300 and 1 700 cm⁻¹; δ (CDCl₃) 1.58 (3 H, s, 3-CH₃), 3.17 (3 H, s, NCH₃), 3.40br (1 H, s, OH), 6.75br (1 H, d, *J* 9.0 Hz, 7-H), 7.29br (1 H, d of d, *J* 9.0 and 2.0 Hz, 6-H), and 7.37br (1 H, d, *J* 2.0 Hz, 4-H) (Found: C, 57.2; H, 4.75; N, 6.6. C₁₀H₉ClNO₂ requires C, 56.75; H, 4.75; N, 6.7%).

(v) 1,3-Dihydro-3-hydroxy-5-methoxy-1,3-dimethylindol-2-one (2e) had m.p. 151—153°; ν_{\max} (KBr) 3 300 and 1 690 cm⁻¹; δ (CDCl₃) 1.57 (3 H, s, 3-CH₃), 3.16 (3 H, s, NCH₃), 3.82 (3 H, s, O-CH₃), 6.80 (2 H, m, 6- and 7-H), and 7.10 (1 H, m, 4-H) (Found: C, 63.7; H, 6.3; N, 6.85. C₁₁H₁₃NO₃ requires C, 63.75; H, 6.3; N, 6.75%).

(vi) 1,3-Dihydro-3-hydroxy-1,3,7-trimethylindol-2-one (2f)

had m.p. 140—141°; ν_{\max} (KBr) 3 330 and 1 690 cm⁻¹; δ (CDCl₃) 1.55 (3 H, s, 3-CH₃), 2.55 (3 H, s, 7-CH₃), 3.47 (3 H, s, N-CH₃), and 7.00—7.40 (3 H, m, aromatic) (Found: C, 69.0; H, 6.9; N, 7.25. C₁₁H₁₃NO₂ requires C, 69.1; H, 6.85; N, 7.35%).

(vii) 1,3-Dihydro-3-hydroxy-1,3,6-trimethylindol-2-one (2g), isolated from a mixture of (2g) and 1,3-dihydro-3-hydroxy-1,3,4-trimethylindol-2-one (2g') by fractional recrystallization [compound (2g') was not completely purified], had m.p. 173—175.5°; ν_{\max} (KBr) 3 330 and 1 690 cm⁻¹; δ (CDCl₃) 1.55 (3 H, s, 3-CH₃), 2.36 (3 H, s, 6-CH₃), 3.14 (3 H, s, NCH₃), 3.37 (1 H, s, OH), 6.65br (1 H, s, 7-H), 6.86br (1 H, d, *J* 8.0 Hz, 5-H), and 7.27br (1 H, d, *J* 8.0 Hz, 4-H) (Found: C, 69.5; H, 6.9; N, 7.35. C₁₁H₁₃NO₂ requires C, 69.1; H, 6.85; N, 7.35%); compound (2g') showed δ (CDCl₃) 1.63 (3 H, s, 3-CH₃), 2.47 (3 H, s, 4-CH₃), 3.14 (3 H, s, N-CH₃), and 6.41—7.42 (3 H, m, aromatic).

(viii) 3-Ethyl-1,3-dihydro-3-hydroxy-1-methylindol-2-one (2h) had m.p. 183—184°; ν_{\max} (KBr) 3 350 and 1 690 cm⁻¹; δ [(CD₂)₂SO] 0.58 (3 H, t, *J* 7.5 Hz, CH₂CH₃), 1.81 (2 H, q, *J* 7.5 Hz, CH₂), 3.08 (3 H, s, NCH₃), 3.35br (1 H, s, OH), and 6.85—7.41 (4 H, m, aromatic) (Found: C, 68.8; H, 6.85; N, 7.25. C₁₁H₁₃NO₂ requires C, 69.1; H, 6.85; N, 7.35%).

General Procedure for Cyclization of the Oxo-anilides (1a—d) to the Chloroindolones (3a—d).—A solution of the anilide (1) (500 mg) in concentrated hydrochloric acid (10 ml) was heated to 85 °C for 3—20 min. After addition of water, the mixture was extracted with ethyl acetate three times and the organic layer was washed with sodium hydrogen carbonate solution and water, and evaporated. The residue was chromatographed on silica gel to yield the products (3) accompanied by small amounts of the hydroxyindolones (2).

(i) 3-Chloro-1,3-dihydro-1,3-dimethylindol-2-one (3a) had b.p. 162—167° at 3 mmHg; ν_{\max} (film) 1 730 cm⁻¹; δ (CDCl₃) 1.88 (3 H, s, 3-CH₃), 3.22 (3 H, s, NCH₃), and 6.81—7.53 (4 H, m, aromatic) (Found: C, 61.1; H, 5.15; N, 7.15. C₁₀H₁₀ClNO requires C, 61.4; H, 5.15; N, 7.15%).

(ii) 3-Chloro-1-ethyl-1,3-dihydro-3-methylindol-2-one (3b) had b.p. 168—173° at 3 mmHg; ν_{\max} (film) 1 730 cm⁻¹; δ (CDCl₃) 1.30 (3 H, t, *J* 8.0 Hz, CH₂CH₃), 1.91 (3 H, s, 3-CH₃), 3.81 (2 H, q, *J* 8.0 Hz, CH₂), and 6.85—7.60 (4 H, m, aromatic) (Found: C, 62.8; H, 5.75; N, 6.65. C₁₁H₁₂ClNO requires C, 63.0; H, 5.75; N, 6.7%).

(iii) 3-Chloro-1,3-dihydro-1,3,5-trimethylindol-2-one (3c) had m.p. 100—102°; ν_{\max} (KBr) 1 728 cm⁻¹; δ (CDCl₃) 1.86 (3 H, s, 3-CH₃), 2.34 (3 H, s, 5-CH₃), 3.19 (3 H, s, NCH₃), 6.74br (1 H, d, *J* 8.0 Hz, 7-H), 7.15br (1 H, d of d, *J* 8.0 and 1.5 Hz, 6-H), and 7.26br (1 H, d, *J* 1.5 Hz, 4-H) (Found: C, 63.2; H, 5.75; N, 6.75. C₁₁H₁₂ClNO requires C, 63.0; H, 5.75; N, 6.85%).

(iv) 3,5-Dichloro-1,3-dihydro-1,3-dimethylindol-2-one (3d) had m.p. 106—108°; ν_{\max} (KBr) 1 730 cm⁻¹; δ (CDCl₃) 1.85 (3 H, s, 3-CH₃), 3.20 (3 H, s, NCH₃), 6.72br (1 H, d, *J* 9.0 Hz, 7-H), 7.26br (1 H, d of d, *J* 9.0 and 2.0 Hz, 6-H), and 7.34br (1 H, d, *J* 2.0 Hz, 4-H) (Found: C, 52.5; H, 3.95; N, 6.3. C₁₀H₉Cl₂NO requires C, 52.2; H, 3.95; N, 6.1%).

General Procedure for Syntheses of the 1,3-Dialkylindoles (4a, b, and h) from the Oxo-anilides (1a, b, and h).—A

⁴ J. Bergman, *Acta Chem. Scand.*, 1971, **25**, 1277.

⁵ E. F. J. Janetzky and P. E. Verkade, *Rec. Trav. chim.*, 1945, **65**, 691.

solution of the anilide (1) (1.0 g) in concentrated hydrochloric acid (20 ml) was kept for 5 min at 25 °C. After addition of water, the solution was extracted with ethyl acetate three times and the organic layer was worked up as usual. The crude product was dissolved in dry ether (60 ml). Lithium aluminium hydride (600 mg) was added, and the mixture was refluxed for 4 h, worked up as usual,

and chromatographed on silica gel. Elution with benzene gave the indole (4).

The indoles (4a and b) were identical with authentic materials: compound (4h) had b.p. 118—121° at 4 mmHg (lit.,⁵ 96—97° at 0.6 mmHg), ν_{max} (film) 3 050, 1 612, and 727 cm^{-1} .

[6/152 Received, 23rd January, 1976]
