Reduction of 4-Arylidene-1,3-(2*H*,4*H*)isoquinolinediones

I. W. Elliott, Jr. and Y. Takekoshi*

Department of Chemistry, Fisk University, Nashville, Tennessee 37203

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Catalytic hydrogenation of some 4-arylidene-1,3-(2*H*,4*H*)isoquinolinediones (**1**) afforded the corresponding 4-arylmethyl-1,3-(2*H*,4*H*)isoquinolinediones (**2**), but reduction of **1** by sodium borohydride gave 4-arylmethyl-1(2*H*)isoquinolones (isocarbostyrils, **3**). Compounds of type **1** studied had aryl substituents phenyl, 3,4-dimethoxyphenyl, 3,4-methyleneoxyphenyl and 2-furyl. In one example of sodium borohydride reduction of an *N*-methylisoquinolinedione derivative (**1**) the heterocylic ring was opened, and 2-(1-hydroxymethyl-2-phenylethenyl)-*N*-methylbenzamide (**4**) was obtained from 4-benzylidene-2-methyl-1,3-(2*H*,4*H*)isoquinolinedione.

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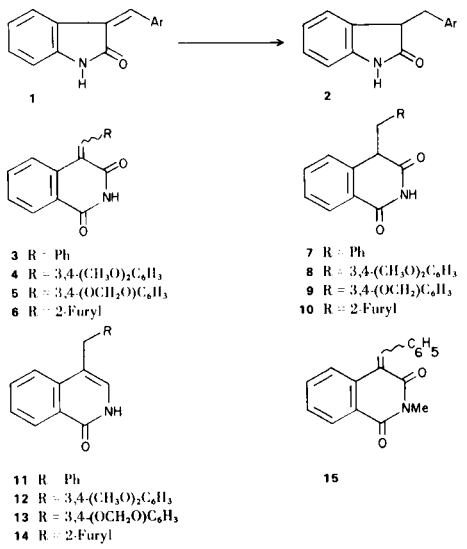
Similar chemical properties have previously been noted between structurally comparable derivatives of 1,3-(2*H*,4*H*)-isoquinolinedione (homophthalimide) and oxindole (1,2). We were interested in synthesizing 4-arylalkylhomophthalimides for other work, and the fact that 3-arylmethyleneoxindoles (**1**) are reduced at the carbon-carbon double bond to 3-arylmethyloxindoles (**2**) as well as by catalytic hydrogenation (3,4) suggested a fruitful parallel for the preparation of analogous homophthalimides.

The reduction of 4-alkylidenehomophthalimides is one of the few convenient ways in which 4-monoalkylated homophthalimides can be prepared (5). Marquardt and Nair (6) hydrogenated 4-benzylidenehomophthalimide (**3**) and obtained 4-benzylhomophthalimide (**7**), and Nair and Mehta similarly reduced 4-ethoxymethylenehomophthalimide to 4-methylhomophthalimide (7). Related reductions of other homophthalimide derivatives have been accomplished with zinc-acetic acid, sodium dithionite or stannous chloride (8).

In this paper, catalytic hydrogenation of four 4-arylidenehomophthalimides (**3-6**) is shown to afford the corresponding 4-arylmethyl derivatives (**7-10**), and similarly zinc dust in acetic acid reduced 4-benzylidenehomophthalimide (**3**) to 4-benzylhomophthalimide (**7**). In contrast, sodium borohydride reduced the same series of compounds (**3-6**) to the 4-arylmethyl-1-(2*H*)isoquinolones (**11-14**). The structural proofs for the products were based on elemental analysis and spectra. Compounds with the intact homophthalimide ring system show strong infrared absorption bands near 1710 and 1660-1680 cm^{-1}. The higher frequency band is associated with the carbonyl group at the 3-position and is not present in the 1-isoquinolone (isocarbostyril) derivatives. Also, the saturated homophthalimides (**7-10**) are distinguishable from the 1-isoquinolones (**11-14**) by the appearance of a long wavelength absorption band (345-348 nm) in the ultraviolet absorption spectra of the series of compounds **11** to **14**.

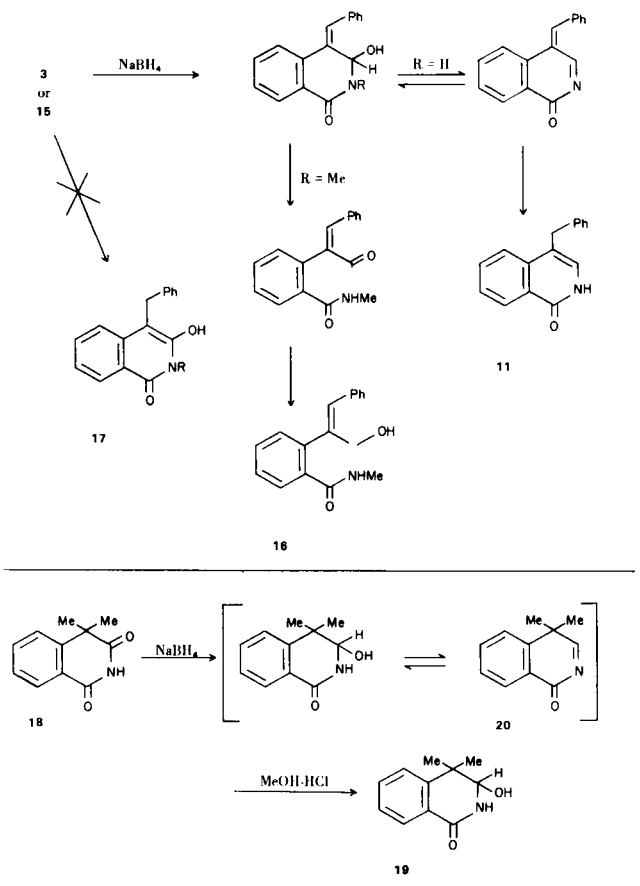
One example of borohydride reduction of an *N*-methylhomophthalimide was investigated, and a third kind of product was obtained. From 4-benzylidene-2-methylhomophthalimide (**15**), the ring-opened amido alcohol (**16**) was isolated as the principal reduction product. A possible explanation for the results with sodium borohydride is outlined in Chart I. The reduction of **3** to the 1-isoquinol-



one derivative (**11**) apparently does not occur by initial 1,4-addition of hydrogen to the C=C-C=O system in **3**, since the resulting enol **17** is tautomeric with 4-benzylhomophthalimide (**7**), and in our experience compound **7** is not reduced to **11** by sodium borohydride under these conditions.

Indirect evidence in support of this scheme can also be garnered from the effect of alkali borohydride on another non-enolizable homophthalimide. Ben-Ishai and co-workers (9) reported that reduction of 4,4-dimethylhomophthalimide (**18**) followed by treatment with acidic methanol afforded a 3-methoxyisoquinolone **19**. The intermediate formation of a reactive acylimine **20** was suggested by isolating a Diels-Alder adduct with 2,3-dimethyl-1,3-butadiene as well as a trimer of **20**.

Chart I



EXPERIMENTAL

General

Melting points were taken on a Mel-temp apparatus and are uncorrected. Ir spectra were recorded as Nujol mulls on a Perkin-Elmer 337 spectrophotometer, and uv spectra were recorded on a Cary 14 spectrophotometer. Analyses were by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

Condensation Reactions. General Procedure.

Homophthalimide, or *N*-methylhomophthalimide, (20 mmoles) was allowed to reflux one hour with an equimolar amount of aromatic aldehyde in acetic acid (100 ml.) and piperidine (2 ml.). The products (**3-6** and **15**) were isolated on cooling and recrystallized from alcohol. No attempt was made either to obtain a pure stereoisomer or to determine the isomeric composition of the following products.

Condensation Products. (a) 4-Benzylidenehomophthalimide (**3**).

Compound **3** (81% yield) had m.p. 185-186° (lit. (10) m.p. 173-174°).

(b) 4-(3,4-Dimethoxybenzylidene)homophthalidimide (**4**).

Compound **4** (75% yield) melted at 195-210°.

Anal. Calcd. for $C_{18}H_{15}NO_4$: C, 68.89; H, 4.89; N, 4.53. Found: C, 68.81; H, 4.99; N, 4.57.

(c) 4-(3,4-Methylenedioxybenzylidene)homophthalimide (**5**).

This compound was prepared in 87% yield and had m.p. 230-232° (lit. (11) m.p. 218-219°).

(d) 4-Furfurylidenehomophthalimide (**6**).

Compound **6** (92% yield) had m.p. 213-214° (lit. (11) m.p. 210°).

Anal. Calcd. for $C_{14}H_{19}NO_3$: C, 70.21; H, 3.79; N, 5.83. Found: C, 70.39; H, 4.05; N, 5.94.

(e) 2-Methyl-4-benzylidenehomophthalimide (**15**).

Compound **15** had m.p. 92-93° (lit. (12) m.p. 96°).

Hydrogenation Procedure. 4-Benzylhomophthalimide (**7**).

The compounds **3** and **6** were reduced at about 3 atmospheres pressure in acetic acid solution at room temperature with platinum oxide (Adam's) catalyst. By this method reduction of **3** afforded compound **7** in 40% yield, **7** had m.p. 176-177° (lit. (13) 176°). Compound **7** was also obtained by reduction of **3** with zinc dust in acetic acid.

Anal. Calcd. for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.21; N, 5.57. Found: C, 76.25; H, 5.10; N, 5.56.

4-(3,4-Dimethoxybenzyl)homophthalimide (**8**).

Hydrogenation of **4** afforded compound **8** (m.p. 149-150°) in 79% yield.

Anal. Calcd. for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50. Found: C, 69.49: H, 5.42.

4-(3,4-Methylenedioxybenzyl)homophthalimide (**9**).

Compound **9** (m.p. 157-158°) was obtained from hydrogenation of **5** in 80% yield.

Anal. Calcd. for $C_{17}H_{13}NO_4$: C, 69.15; H, 4.44; N, 4.74. Found: C, 68.89; H, 4.46; N, 4.72.

4-Furfurylhomophthalimide (**10**).

The title compound was prepared from **6** in 50% yield and had m.p. 172-173°.

Anal. Calcd. for $C_{14}H_{11}NO_3$: C, 69.70; H, 4.60; N, 5.81. Found: C, 69.57; H, 4.74; H, 5.56.

Reduction by Sodium Borohydride. General Procedure.

The 4-arylidenehomophthalimides (**3-6**) were suspended in methanol and treated with excess sodium borohydride. The products were isolated by diluting the reaction mixture with water, and the 1-isoquinolone derivatives (**11-14**) were recrystallized from

aqueous ethanol.

Products from Reduction by Sodium Borohydride.

(a) 4-Benzyl-1-isoquinolone (**11**).

Compound **11** was obtained from **3** in 53% yield and had m.p. 221-222°.

Anal. Calcd. for $C_{16}H_{13}NO$: C, 81.68; H, 5.57; N, 5.95. Found: C, 81.53; H, 5.73; N, 5.85.

(b) 4-(3,4-Dimethoxybenzyl)-1-isoquinolone (**12**).

Compound **12** (52% yield) had m.p. 208-210°.

Anal. Calcd. for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74. Found: C, 73.13; H, 5.90; N, 4.92.

(c) 4-(3,4-Methylenedioxybenzyl)-1-isoquinolone (**13**).

Compound **13** (m.p. 231-232°) was prepared from **5** in 63% yield.

Anal. Calcd. for $C_{17}H_{13}NO_3$: C, 73.11; H, 4.69; N, 5.01. Found: C, 72.96; H, 4.73; N, 5.07.

(d) 4-Furfuryl-1-isoquinolone (**14**).

Compound **14** (m.p. 201-201°) was isolated after reduction of **6** in 14% yield.

Anal. Calcd. for $C_{14}H_{11}NO_2$: C, 74.65; H, 4.92; N, 6.22. Found: C, 74.48; H, 4.70; N, 6.32.

2-(1-Hydroxymethyl-2-phenylethenyl)-*N*-methylbenzamide (**16**).

The title compound was obtained in 58% yield by reduction of **15** by sodium borohydride. The analytical sample had m.p. 152-154°; ir 1640 cm^{-1}; λ max (ethanol): 273 inflect., (log ε 3.16), 285 nm inflect., (log ε 3.02); mass spectrum: m/e 267 (M^+), 249 (M^+-H_2O), 208 (M^+-$CONCH_3$); nmr δ (deuteriochloroform): 8.07 (m, 1, ArH), 7.44-6.95 (m, 8, ArH), 4.83 (dd, J = 3.5 and 1.5 Hz, 1, CH=C), 2.88 (s, 3, CH_3), 3.25-3.40 (m, 2, CH_2), 2.78 (d, 1, OH).

Anal. Calcd. for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.25; H, 6.32; N, 5.16.

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