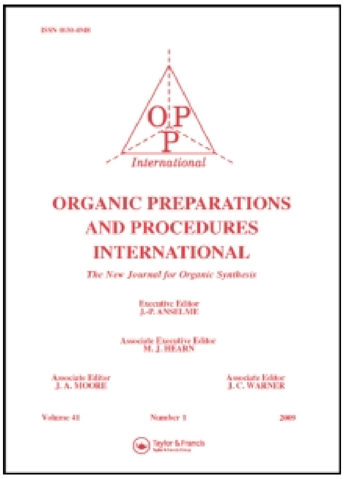

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THE REACTION OF NINHYDRIN WITH ACETIC ACID

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combined extracts dried ($MgSO_4$) and concentrated. The thick, partially opaque residue was distilled through a short-path Claisen head to give the desired product (3.90 g, 63%) bp. 46-48°/0.05 torr, that solidified as a white solid, mp. 48-50°, lit.[1] bp. 97-98°/8 torr, mp. 48-50°.

Anal. Calcd. for $C_7H_{13}NS$: C, 58.64; H, 9.02; N, 9.64; S, 22.20
Found: C, 58.69; H, 9.15; N, 9.79; S, 22.38

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3. The Kjedahl flask was obtained from an unknown manufacturer but appears to be the same as the Wheaton pressure bottle and stopper assembly (mfr. no. 223077) with rated pressure capability of 150 psi. In a separate experiment, the quinuclidinone and hydrogen sulfide in isopropanol were reacted in the described proportions in a 250 mL glass-lined steel bomb equipped with pressure gauge. Maximum pressure observed after 20 min at 40° was 77 psi. Since the experimental pressures are sufficiently close to the pressure limits of the vessel, increasing the scale of this reaction is not recommended with this flask.

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THE REACTION OF NINHYDRIN WITH ACETIC ACID

Submitted by (04/03/91)
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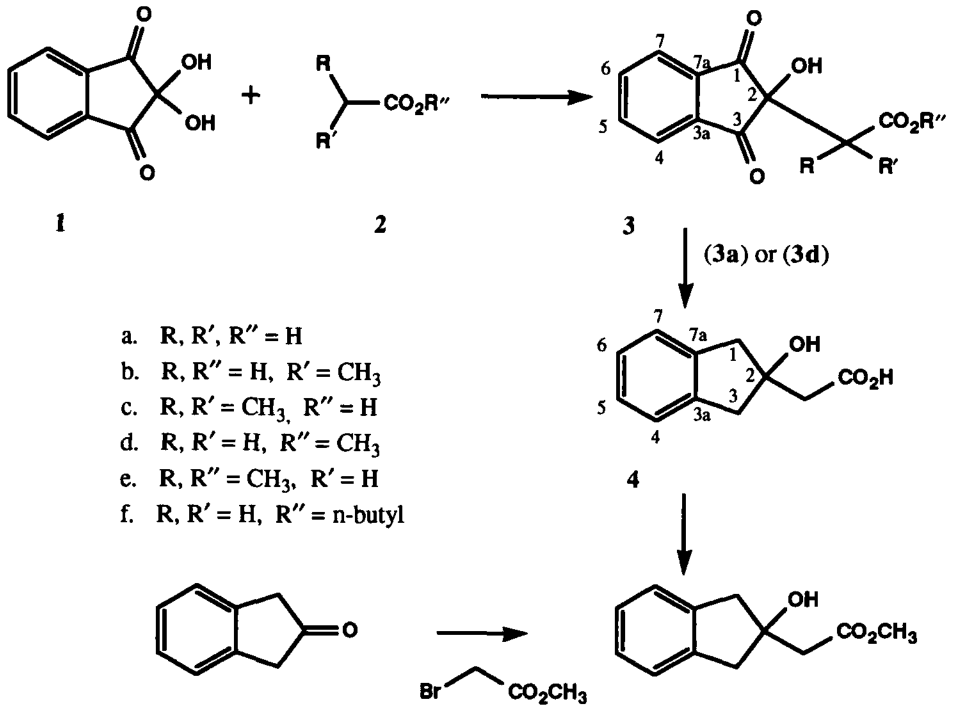
Ninhydrin (**1**) is a versatile chemical that undergoes a large number of reactions that lead to useful chemical intermediates. Indeed the chemistry of **1** is quite extensive having been the subject of three reviews.[1] Compound **1** reacts with many active methylene compounds such as malonic ester,[2] nitromethane,[2] and acetophenone[3] producing aldol products. Many of these condensations are carried out in acetic acid as solvent. It was therefore very surprising to us to discover that **1** will react with acetic acid. For example when **1** is refluxed for 8 days in acetic acid the aldol product **3a** is generated in 41% yield. By this procedure **3a** can be prepared in generous quantities and is easily purified. The reaction of **1** with propionic acid (**2b**) and isobutyric acid (**2c**) proceeds less readily giving only 22% and 5% yields of **3b** and **3c** respectively. It was of interest to determine if **1** would react with ethyl acetate on long refluxing. When this reaction was attempted, no new product could be detected;



1 2 3 4 6 5

a. R, R', R'' = H
b. R, R'' = H, R' = CH_3
c. R, R' = CH_3, R'' = H
d. R, R' = H, R'' = CH_3
e. R, R'' = CH_3, R' = H
f. R, R' = H, R'' = n-butyl

however when **1** was refluxed in n-butyl acetate for 9 days a 20% yield of the ester **3f** was obtained.

The carbonyl groups at positions 1 and 3 of **3a** or its methyl ester **3d** can be hydrogenolyzed to the indane **4**. The methyl ester **5** was prepared from **4** and was found to be identical to the ester **5** obtained from the Reformatsky reaction of methyl bromoacetate and 2-indanone(**6**).

EXPERIMENTAL SECTION

Melting points are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a General Electric QE-300 spectrometer; chemical shifts are reported in δ units relative to internal tetramethylsilane. HPLC separations were performed on a Waters Associates prep LC system 500. Mass spectra were determined on a CEC 21-110 spectrometer at an ionizing voltage of 70 eV. FD mass spectra were obtained using a Finnigan-MAT model 731 spectrometer using carbon dendrite emitters. FAB spectra were obtained on a VG ZAB-3 spectrometer using zenon atom bombardment.

2,3-Dihydro-2-hydroxy-1,3-dioxo-1H-indene-2-acetic Acid (**3a**).- A solution of ninhydrin hydrate (178.1 g, 1.0 mol) in 1 L of glacial acetic acid was refluxed for eight days. At the end of this time, there was only a small amount of ninhydrin remaining in the reaction mixture as determined by tlc (SiO_2, EtOAc, UV). The dark solution was concentrated to a solid which was triturated in ether, collected, and washed with ether providing 107 g of crude **3a** as a light gray solid. Recrystallization from 1.2 L of ethyl acetate using decolorizing carbon, and addition of an equal volume of hexanes, and chilling in a refrigerator overnight gave 89.3 g (41%) of **3a** as white crystals, mp. 178-180°.

FD MS: M$^+$ 220, ^{1}H NMR (DMSO-d$_6$): δ 3.04 (s, 2H, -CH$_2$-), 6,74 (bs, 1H, OH), 8.02 (s, 4H, Ar), 12.62 (bs, 1H, COOH). ^{13}C NMR (DMSO-d$_6$): δ 38.31 (-CH$_2$COOH), 71.61 (C2), 123.38 (C4/7), 136.25 (C5/6), 140.76 (C3a/7a), 170.89 (COOH), 199.12 (C1/3).

Anal. Calcd. for $C_{11}H_8O_5$: C, 60.01; H, 3.66. Found: C, 60.25; H, 3.80

The dicyclohexylamine salt of **3a** was prepared by dissolving **3a** in ethanol and adding an equivalent of dicyclohexylamine. After 1 hr, the white crystals were collected, washed with ether and dried, mp. 202-204°.

Anal. Calcd for $C_{23}H_{31}NO_5$: C, 68.80; H, 7.78; N, 3.49. Found: C, 68.82; H, 7.55; N, 3.52

2,3-Dihydro-2-hydroxy-α-methyl-1,3-dioxo-1H-indene-2-acetic Acid (**3b**).- A mixture of 17.8 g (0.1 mol) of **1** and 74 g (1 mol) of propionic acid was refluxed for 3.5 days. The reaction mixture was concentrated to a thick oil which was dissolved in 100 mL of warm toluene and then cooled in an ice bath for several hours. The crystals that separated were collected, washed with cold toluene, and dried to yield 15.1g of brown colored crude **3b**. This material was slurried in 50 mL of methylene chloride and collected and washed with methylene chloride.Two recrystallizations from ethyl acetate provided 5.2 g (22%) of **3b** as white crystals, mp. 140-141°.
MS: M$^+$ 234. ^{1}H NMR (DMSO-d$_6$): δ 1.48 (d, 3H, CH$_3$), 3.15 (q, 1H, CH), 6.68 (s, 1H, OH), 7.98 (s, 4H, Ar), 12.64 (bs, 1H, COOH).

Anal. Calcd for $C_{12}H_{10}O_5$: C, 61.54; H, 4.30. Found: C, 61.44; H, 4.28

2,3-Dihydro-2-hydroxy-α,α-dimethyl-1,3-dioxo-1H-indene-2-acetic Acid (**3c**).- A mixture of 17.8 g (0.1 mol) of **1** and 150 mL of isobutyric acid was refluxed under nitrogen for 9 days. Tlc (SiO$_2$, EtOAc, UV) indicated that only a small amount of **1** remained in the reaction mixture.The excess isobutyric acid was removed under reduced pressure to give a dark brown gum which was slurried in methylene chloride and shaken with 1N NaOH. The aqueous layer was separated and extracted 3 times with methylene chloride. Concentration of the methylene chloride extracts afforded 5.3 g of an off white solid. This crude **3c** was recrystallized 3 times from ethyl acetate-hexanes to provide 1.2 g (5%) of **3c** mp. 103-105°.
MS: M$^+$ 248. ^{1}H NMR (DMSO-d$_6$): δ 1.39 (s, 6H, C-(CMe$_2$)$_2$), 6.45 (bs, 1H, OH), 7.94 (s, 4H, Ar),12.5 (bs, 1H, COOH).

Anal. Calcd. for $C_{13}H_{12}O_5$: C, 62.90; H, 4.87. Found: C, 62.94; H, 4.88

2,3-Dihydro-2-hydroxy-1,3-dioxo-1H-indene-2-acetic Acid, Methyl Ester (**3d**).- This ester was prepared using the general procedure outlined in reference 4. A mixture of 0.08 mol (17.6 g) of **3a** and 24 mL of chlorotrimethylsilane was stirred for 48 hrs at room temperature in 800 mL of methanol. The reaction mixture was concentrated to a residue that crystallized. Upon recrystallization from ethyl acetate-hexanes there was obtained 14.7 g (78%) of **3d** with mp. 92-94°. Tlc (SiO_2, EtOAc, UV): one spot.

MS: M^+ 234. ^1H NMR ($CDCl_3$): δ 3.08 (s, 2H, $-CH_2-$), 3.61 (s, 3H, CH_3), 4.24 (s, 1H, OH), 7.92 (m, 2H, Ar), 8.05 (m, 2H, Ar).

^{13}C NMR ($CDCl_3$): δ 36.88 (CH_2COOH), 51.36 ($-OCH_3$), 72.00 (C2), 123.31 (C4/7), 135.62 (C5/6), 139.70 (C 3a/7a), 169.46 (CO_2-), 197.04 (C1/3).

Anal. Calcd. for $C_{12}H_{10}O_5$: C, 61.54; H, 4.30. Found: C, 61.31; H, 4.03

2,3-Dihydro-2-hydroxy-α-methyl-1,3-dioxo-1H-indene-2-acetic Acid, Methyl Ester (**3e**).- A mixture of 2.0 g of **3b** and 2.5 mL of chlorotrimethylsilane was stirred in 100 mL of methanol at room temperature overnight. The solution was concentrated and the residue taken up in 60 mL of methylene chloride. This solution was washed with saturated sodium bicarbonate solution and dried over anhydrous sodium sulfate. Upon concentration there was obtained a residue that gradually crystallized. Recrystallization from ethyl acetate-hexanes gave 1.3 g (61%) of **3e** as white crystals, mp. 78-80°.[5]

MS: M^+ 248. Tlc (SiO_2, toluene: EtOAC 3:1, UV) one spot. ^1H NMR ($CDCl_3$): δ 1.30 (d, 3H, CH_3), 3.14 (q, 1H, CH), 3.69 (s, 3H, OCH_3), 4.52 (s, 1H, OH), 7.98 (m, 4H, Ar).

Anal. Calcd. for $C_{13}H_{12}O_5$: C, 62.90; H, 4.80. Found: C, 63.16; H, 5.15

2,3-Dihydro-2-hydroxy-1,3-dioxo-1H-indene-2-acetic Acid, n-Butyl Ester (**3f**).- A mixture of 17.8 g (0.1 mol) of **1**, 350 mL of n-butyl acetate, and 1 g of p-toluenesulfonic acid was refluxed for 9 days. The reaction mixture was concentrated to a semi-solid residue that was triturated in ether. The solid was collected (2.5 g) and was identified as recovered **1**. The ether filtrate was concentrated to an oil weighing 23.7 g. Tlc (SiO_2, toluene:EtOAc 3:1, UV) indicated that some **1** was still present along with 3 other components. Preparative HPLC separated the main component and after recrystallizing from ethyl acetate-hexanes, there was obtained 5.5 g (20%) of **3f** as white crystals, mp. 68-70°.

MS: M^+ 276. ^1H NMR (DMSO): δ 0.84 (t, 3H, $-CH_3$), 1.10 (sextet, 2H, $-C\underline{H}_2CH_3$), 1.22 (quintet, 2H, $-CH_2CH_2CH_3$), 3.08 (s, 2H, $-CH_2CO$), 3.77 (t, 2H, $-OCH_2-$), 6.84 (s, 1H, OH), 8.04 (s, 4H, Ar).

Anal. Calcd. for $C_{15}H_{16}O_5$: C, 65.45; H, 5.49. Found: C, 65.63; H, 5.69

2,3-Dihydro-2-hydroxy-1H-indene-2-acetic Acid (**4**).- A solution of 10 g (0.045 mol) of **3a** in 140 mL of acetic acid was hydrogenated at 50° and at an initial hydrogen pressure of 60 psi in the presence of 1 g of 5% Pd/C. The theoretical hydrogen uptake was achieved in 6 hrs. The catalyst was removed by filtration and the filtrate was concentrated to a residue that crystallized when triturated in ethanol. Recrystallization from ethanol afforded 5.0 g (58%) of white crystals, mp.128-130°.

MS: M^+ 192. ^1H NMR (DMSO): δ 2.63 (s, 2H, $-CH_2-$), 2.91 (d, 2H, $-CH_2Ar$), 3.12 (d, 2H, $-CH_2Ar$), 7.10 (m, 2H, Ar), 7.17 (m, 2H, AR). ^{13}C NMR (DMSO): δ 45.09 ($-CH_2COOH$), 46.16 (C1/3), 78.70 (C2), 124.41 (C5/6), 125.93 (C4/7), 141.68 (C3a/7a), 172.58 (COOH).

Anal. Calcd. for $C_{11}H_{12}O_3$: C, 68.74; H, 6.29; O, 24.97. Found: C, 68.54; H, 6.16; O, 24.71

The dicyclohexylamine salt was prepared by dissolving **4** in warm ethanol and adding an equivalent of dicyclohexylamine. The white crystals obtained were recrystallized from ethanol-ether, mp.166-168°.

Anal. Calcd. for $C_{23}H_{33}NO_3$: C, 74.36; H, 8.95; N, 3.77. Found: C, 74.57; H, 9.15; N, 3.71

Preparation of **4** from **3d**.- A mixture of 13g (0.055 mol) of **3d** in 130 mL of acetic acid was hydrogenated at 60 psi at 40° in the presence of 7.0 g of 5% Pd/C for 16 hrs.The catalyst was removed by filtration and the filtrate concentrated to a white solid (9.3 g). Recrystallization from ethyl acetate gave 4.2 g (40%) of **4** , mp. 126-128°.

FD MS: MH$^+$ 193. ^{1}H NMR (DMSO-d_6): δ 2.61 (s, 2H, $-CH_2CO$), 2.90 (d, 2H, CH_2Ar), 3.11 (d, 2H, $-CH_2Ar$), 4.81 (bs, 1H, OH), 7.08 (m, 2H, Ar), 7.16 (m, 2H, Ar), 12.08 (bs, 1H, COOH).

Anal. Calcd. for $C_{11}H_{12}O_3$: C, 68.74; H, 6.29. Found: C, 68.67; H, 6.41

2,3-Dihydro-2-hydroxy-1H-indene-2-acetic Acid, Methyl Ester (**5**).- A solution of 7.2g (0.0375 mol) of **4**, 100 mL of ethylene dichloride, 30 mL of methanol, and 2 mL of con. H_2SO_4, was refluxed for 16 hrs. The reaction mixture was then washed successively with H_2O, $NaHCO_3$ solution, and H_2O. After drying over $MgSO_4$, the organic layer was concentrated to a viscous liquid (4.2 g). Tlc (SiO_2, EtOAc, UV) was one spot. The liquid solidified after storing in the refrigerator for 48 hrs. The solid was triturated in hexanes and the white crystals collected, mp. 36-38°.

FAB MS. MH$^+$ 207; ^{1}H NMR ($CDCl_3$): δ 2.76 (s, 2H, $-CH_2CO$), 3.02 (d, 2H, CH_2Ar), 3.16 (d, 2H, CH_2Ar), 3.61 (s, 1H, OH), 3.76 (s, 3H, $-OCH_3$), 7.12-7.22 (m, 4H, Ar).

Anal. Calcd. for $C_{12}H_{14}O_3$: C, 69.89; H, 6.84. Found: C, 69.77; H, 6.89

Preparation of **5** from **6**.- Powdered zinc (5 g) was slurried in 50 mL of benzene and 10g (0.076 mol) of 2-indanone in 50 mL of benzene added. The reaction mixture was stirred for 15 minutes and then 11.6g (0.076 mol) of methyl bromoacetate was added all at once. The reaction mixture was then stirred for 24 hrs at room temperature. Most of the zinc at this time had been consumed. The reaction mixture was concentrated and the residue slurried in 200 mL of 1N HCl for 2 hrs and then extracted twice with 100 mL portions of ether. Some insoluble material collected at this time had a mass spectrum that was in agreement with data for 1,3-di-(2-indanylidene) indane, a compound isolated from the Reformatsky reaction of 2-indanone and ethyl bromoacetate.[6] The ether extracts were concentrated to an oil (4.9 g) which was purified by preparative HPLC to give 2.14 g of an oil that was one spot on tlc at the same rf as **5**. This oil instantly crystallized on seeding with **5**. A small

amount was recrystallized from hexanes to provide white crystals, mp. 38-40°.
FAB MS. MH$^+$ 207. ^{1}H NMR (CDCl$_3$): δ 2.78 (s, 2H, -CH$_2$CO-), 3.03 (d, 2H, -CH$_2$Ar), 3.15 (d, 2H, -CH$_2$Ar), 3.61 (s, 1H, OH), 3.77 (s, 3H, OCH$_3$), 7.13-7.24 (m, 4H, Ar).

Anal. Calcd. for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 70.18; H, 6.84

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FACILE CHROMONE RING-OPENING OF KHELLIN

Submitted by (05/24/91)

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The natural furochromone, khellin (**1**) has long attracted attention on account of vasodilator action, and more recently lipid-altering and antiatherosclerotic activity has been discovered.[1]

We have found that under very mild conditions (chloroform solution containing trifluoroacetic acid at room temperature), khellin (**1**) is transformed quantitatively into a bright yellow crystalline product whose ^{1}H NMR spectrum retained all proton functionality of the starting furochromone. The diketone enol trifluoroacetate structure (**2**) assigned to this product is supported by empirical analysis ($C_{16}H_{13}F_3O_7$) and ^{1}H and ^{13}C spectra.[2] Enhancement of the 6-H and 7-Me