Raney Nickel-induced Alkylation Reactions *

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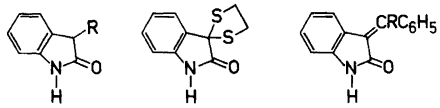
In connection with studies on the chemistry of oxindoles [2] it became important to develop a simple conversion of isatin (3-oxooxindole) into oxindole (*1a*)*** and hence an investigation of this transformation by the preparation of isatin ethylene thioketal (*2*) and its desulfurization was initiated. The thioketal could be prepared by standard means. Whereas Raney nickel treatment for sulfur removal in benzene or ethanol solution for short periods of time converted the thioketal (*2*) into the desired oxindole (*1a*), longer reaction times in ethanol led to high yields of 3-ethyloxindole (*1b*). Although the extraneous ethyl group could have originated *a priori* from the two-carbon moiety of the thioketal (*2*), its more likely derivation from the solvent was assured by the formation of the 3-alkyloxindoles *1c* and *1d* in the Raney nickel treatment of *2* in methanol and isopropyl alcohol, respectively. These results suggested that the desulfurization preceded the alkylation and that the two reactions were independent of each other. When, as a consequence, the ethylation of oxindole (*1a*) was attempted, *1b* was produced, but after longer reaction time.

It was now clear that the alkylations were identical in nature with the large number of reported Raney nickel-induced N-alkylation [3] and a few C-alkylations [4] and were mechanistically similar to the varied examples of known base-catalyzed alkylations with alcohols.[4] Thus, nickel acted as the oxidizing agent in the conversion of alcohol to aldehyde or ketone, as the base for the condensation of the carbonyl compound and oxindole and as the reducing agent in the reduction of the resultant 3-alkylideneoxindole. Since this view required the nickel surface to be in an intermediate state of oxidation for efficient promotion of the alkylation, it explained readily the more successful ethylation of the thioketal (*2*) than oxindole (*1a*). Presumably the desulfurization lowered the hydrogenation activity of the Raney nickel and hence made it a better agent for the dehydrogenation of ethanol, the first step in the alkylation. On this basis it was predicted, and thereafter verified, that the addition of mercaptans should increase the efficiency of the ethylation of oxindole (*1a*).



1a, R = H
1b, R = Et
1c, R = Me
1d, R = i-Pro
1e, R = $CH_2C_6H_5$

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3a, R = H
3b, R = Me

Dependence on heterogeneous catalysis for success of the alkylations could be predicted to make the results erratic. Hence it was no surprise that oxindole interaction with methanol gave sometimes 3-methyloxindole (*1c*) and often 3-methyleneoxindole polymer.[5] Reaction with benzyl alcohol led usually to 3-benzyloxindole (*1e*), but in one instance (with the use of old Raney nickel) to 3-benzaloxindole (*3a*). Reaction with α-phenylethanol yielded the alkylideneoxindole *3b*.

The alkylation of active methylene compounds other than oxindole also was investigated.[6] Treatment of ethyl acetoacetate with ethanol and Raney nickel gave merely ethyl β-hydroxybutyrate,[7] whereas similar reaction with nickel, which had been heated for 24 h in refluxing alcohol, yielded ethyl α-ethylacetate. Attempts to ethylate diethyl malonate or 2-tetralone were unsuccessful and a similar undertaking with deoxybenzoin yielded bibenzyl.[8,9]

In view of a reported oxidation of a 1,4-diol to a butyrolactone with Raney nickel [10] it was of interest to effect similar changes of 1,4-butanediol and 1,5-pentanediol. In one run the former was transformed to γ-butyrolactone, but usually low yields of 4-hydroxybutanal and 5-hydroxypentanal, respectively, were obtained.

Since completion of the present work there have been recorded various cases of Raney nickel-induced oxidation-reduction reactions on alcohols [11] and similarly catalyzed *N*-alkylations of amines with alcohols.[12] Furthermore, recent examples of *C*-alkylations with alcohols, albeit without nickel, related to the above alkylations of oxindoles also are on record.[13]

Experimental. Ultraviolet spectra of 95% ethanol solutions were recorded on Beckman DU and Cary 14 spectrophotometers and infrared spectra of

* For a preliminary account of part of this work, see Ref. 1. The present communication is based on H. E. Choulett, M.S. dissertation, Iowa State University, 1960.

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*** After the publication of the preliminary account of this work appeared,[1] Professor David A. H. Taylor (University College, Ibadan, Nigeria) kindly informed the authors that oxindole has been prepared in his laboratory for many years by Raney nickel-induced hydrogenation of isatin in ethanol at 150 °C.

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chloroform solutions on a Perkin-Elmer 137 Infracord spectrophotometer. Melting points were determined on a Fisher-Johns apparatus and are uncorrected. Alumina (80 – 200 mesh), activated by being agitated in ethyl acetate for 48 h, washed with water and methanol and dried under an infrared lamp for 48 h, was used for column chromatography. All 2,4-dinitrophenylhydrazones were purified by chromatography on a 4:1 Bentonite-Celite mixture.[14]

Isatin ethylene thioketal (2). A mixture of 500 mg of isatin, 0.5 ml of 1,2-ethanedithiol, 0.5 ml of boron trifluoride etherate in 4 ml of absolute methanol and 10 ml of glacial acetic acid was stirred at room temperature for 30 h. Vacuum removal of the solvents and trituration of the residue with water led to a solid, 630 mg (80%), whose sublimation gave colorless crystals of oxindole *2*, m.p. 200 – 201 °C. Anal. $C_{10}H_9ONS_2$: C, H, N.

General reduction and/or condensation procedure. A suspension of 1 – 5 g of Mozingo, W-2, Raney nickel[15] and 100 – 500 mg of oxindole *1a* or *2* in 20 – 50 ml of the appropriate solvent was refluxed with stirring for the indicated length of time. The catalyst was filtered through Supercel and the filtrate evaporated under vacuum. The residue was crystallized with or without prior alumina chromatography.

*Oxindole (*1a*).* Reduction of thioketal *2* in ethanol or benzene for 4 h gave oxindole (*1a*) (identical in all respects with an authentic sample) in 63 and 79% yield, respectively.

*3-Ethyloxindole (*1b*).* Reduction of thioketal *2* in ethanol for 24 h produced oxindole *1b* [m.p. mmp 104 °C (lit.[16] m.p. 104 °C)] in 83% yield. Nickel-induced ethylation of oxindole (*1a*) in ethanol for 72 h led to the same product in 90% yield, while 24 h nickel treatment of ethanol solutions of *1a*, *1a* and *p*-thiocresol, and *1a* and 1,2-ethanedithiol produced 3-ethyloxindole (*1b*) in 10, 20 and 50% yield, respectively.

*3-Methyloxindole (*1c*).* Reduction of thioketal *2* in methanol for 36 h and chromatography produced oxindoles *1a* and *1c* (identical in all respects with an authentic sample) in 43 and 16% yield, respectively. Nickel treatment of a methanol solution of *1a* for 84 h gave *1c* in 18% yield accompanied by polymer.

*3-Isopropyloxindole (*1d*).* Reduction of thioketal *2* in isopropyl alcohol for 84 h afforded oxindole *1d* [m.p. mmp 106 – 108 °C (lit.[5] m.p. 107 – 108 °C); identical in all respects with an authentic sample] in 32% yield.

*3-Benzyloxindole (*1e*).* A suspension of 500 mg of oxindole (*1a*) and 5.0 g of the nickel catalyst in 20 ml of benzyl alcohol was stirred at 105 °C for 72 h. The mixture was filtered and the filtrate evaporated under vacuum. Chromatography of a benzene solution of the residue on alumina and elution with ether – chloroform mixtures yielded 600 mg (72%) of colorless crystals of oxindole *1e*, m.p. 128 – 129 °C (lit.[17] m.p. 131 °C); IR: C=O 5.84 (s) μm; UV (log ε): 252 (3.95), 277 (sh, 3.13) nm. Anal. $C_{15}H_{13}ON$: C, H, N.

*3-Benzylideneoxindole (*3a*).* On one occasion the same experiment with aged catalyst gave an 81% yield of yellow, crystalline oxindole *3a*, m.p. mmp 177 – 177.5 °C (lit.[17] m.p. 175 – 176 °C); IR: C=O 5.87 (s), C=C 6.20 (m) μm; UV (log ε): 253 (4.14), 323 (4.05) nm (identical in all respects with an authentic specimen).

*3-(α-Methylbenzylidene-)oxindole (*3b*).* A reaction between oxindole (*1a*) and α-phenylethanol was carried out in the manner of the above preparation of *1e*. Elution of the alumina chromatogram with hexane – benzene mixtures yielded a liquid (in an amount equivalent to >10% of the excess alcohol used) whose 2,4-dinitrophenylhydrazone (m.p., mmp 253 – 255 °C) revealed it to be acetophenone. Final elution with chloroform led to 20% recovery of starting oxindole and earlier elution with ether yielded yellow, crystalline oxindole *3b*, m.p., mmp 196 – 197 °C (from hexane); IR: C=O 5.87 (s), C=C 6.20 (m) μm; UV (log ε): 255 (4.22), 260 (4.22), 302 (3.85) nm. Anal. $C_{16}H_{13}ON$: C, H, N.

Ethyl β-hydroxybutyrate. A suspension of 10.0 g of catalyst in 13.00 g of ethyl acetoacetate and 130 ml of absolute ethanol was refluxed with stirring for 72 h. The mixture was filtered and the filtrate evaporated. Distillation of the resultant residue afforded 10.70 g (81%) of liquid hydroxyester [b.p. 83 – 85 °C/10 kPa; IR (CCl_4): OH 2.77 (w), C=O 5.79 (s) μm], whose 3,5-dinitrobenzoate, m.p., mmp 82 – 83 °C (from aqueous ethanol) was identical in all respects with an authentic sample.

Ethyl α-ethylacetoacetate. A suspension of 10.0 g of catalyst in 130 ml of absolute ethanol was refluxed with stirring for 26 h, whereupon a solution of 13.0 g of ethyl acetoacetate in 20 ml of absolute ethanol was added over a 15 min period and the stirring and heating continued for 47 h. The mixture was filtered and the filtrate evaporated. Distillation of the residue gave colorless, liquid ketoester, b.p. 85 – 87 °C/12 kPa; IR (CCl_4): C=O 5.79 (s), 5.86 (s), C=C 6.18 (m) μm. Anal. $C_8H_{14}O_3$: C, H.

Ketonic cleavage of the β-ketoester by standard means and derivatization of the product yielded 2-pentanone 2,4-dinitrophenylhydrazone, m.p., mmp 143 – 144 °C.

Bibenzyl. A suspension of 15.0 g of the catalyst in a solution of 2.00 g of deoxybenzoin in 60 ml of absolute ethanol was refluxed with stirring for 72 h. The mixture was filtered and the filtrate evaporated. Chromatography of the residue on alumina and elution with hexane yielded 1.40 g (71%) of crystalline bibenzyl, m.p. mmp 51 – 52 °C (identical in all respects with an authentic sample).

4-Hydroxybutanal. A suspension of 10.0 g of the catalyst in 50 ml of absolute ethanol was refluxed for 24 h. The liquid then was decanted and the catalyst washed exhaustively with benzene. The solid was suspended in 20.0 g of 1,4-butanediol and the mixture stirred at 115 °C for 45 h. It then was filtered and the filtrate distilled fractionally, yielding 18.0 g of a colorless liquid, b.p. 114–116 °C/10 kPa. Treatment of 640 mg thereof with 2,4-dinitrophenylhydrazine gave 350 mg (20%) of orange, crystalline γ-hydroxybutyraldehyde 2,4-dinitrophenylhydrazone, m.p. 119–120 °C (lit.[15] m.p. 120 °C); IR: NH 3.02 (w), C=N 6.12 (s) μm. Anal. $C_{10}H_{12}O_5N_4$: C, H.

5-Hydroxypentanal. The same reaction and work-up with 10.0 g of catalyst and 20.0 g of 1,5-pentanediol yielded 17.0 g of colorless liquid, b.p. 120–122 °C/11 kPa, derivatization of 570 mg of which gave 200 mg (15%) of reddish orange, crystalline δ-hydroxyvaleraldehyde 2,4-dinitrophenylhydrazone, m.p. 105–106 °C (lit.[16] m.p. 119 °C); IR: NH 3.00 (w), C=N 6.14 (s) μm. Anal. $C_{11}H_{14}O_5N_4$: C, H, N.

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