Mild and Safe Procedure for Hydrolyzing Oximes: Improved Synthesis of 1,2-Indandione

SURENDRA K. GUPTA and SURESH A. MARATHE ˣ

Abstract □ Four ketoximes were hydrolyzed to the corresponding ketones in 66–91% yields using 75% sulfuric acid and 37% formaldehyde at room temperature. An earlier procedure involving hydrochloric acid and 37% formaldehyde is extremely hazardous because it leads to the formation of bis(chloromethyl) ether, a potent carcinogen.

Keyphrases □ Oximes—hydrolysis, synthesis of 1,2-indandione and other ketones □ Hydrolysis—oximes to ketones, synthesis of 1,2-indandione □ 1,2-Indandione—synthesis by hydrolysis of 2-oximino-1-indanone

The hydrolysis of oximes can be accomplished using various reagents and conditions (1–4). Many procedures employ strong acids and elevated temperatures or long reaction times.

DISCUSSION

One of the mildest procedures used for hydrolyzing oximes was reported by Cava *et al.* (5). These investigators hydrolyzed 2-oximino-1-indanone using 36% formaldehyde and concentrated hydrochloric acid (Scheme I). The most serious drawback of this procedure is the formation of bis(chloromethyl) ether as a by-product.

According to Frankel *et al.* (6), formaldehyde and hydrochloric acid react at ambient temperatures in moist air, forming bis(chloromethyl) ether spontaneously in yields of about 0.01 mole %. Their studies showed that even formalin slurries containing Friedel–Crafts salts resulted in bis(chloromethyl) ether concentrations of 250–1500 ppb.

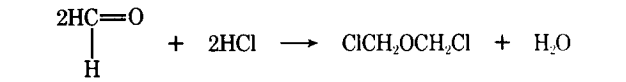
Bis(chloromethyl) ether has been shown (7, 8) to be an extremely potent carcinogen. For example, squamous cell carcinomas of the lung and esthesioneuroepitheliomas of the olfactory epithelium were produced in high incidence in rats following inhalation of 0.1 ppm of bis(chloromethyl) ether (7). A later report (8) indicated that repeated mouse skin application of bis(chloromethyl) ether produced papillomas and carcinomas, whereas subcutaneous injection in rats resulted in fibrosarcomas. As a result of these findings, the Occupational Safety and Health Administration (OSHA) included bis(chloromethyl) ether as one of the 14 carcinogens considered to be extremely hazardous to health (9).

The main purpose of this article is to emphasize the health hazards involved in the literature procedure (5) for preparing 1,2-indandione. In addition, a minor modification is described which offers a relatively safe and mild method for hydrolyzing oximes. The modified procedure consists of adding 75% sulfuric acid to a slurry or solution of the oxime in 37% formaldehyde at room temperature (Scheme II).

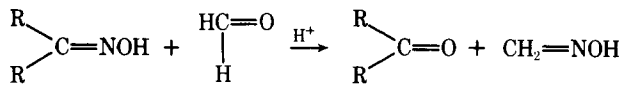
The hydrolysis of the oximes reported here was completed within 1 hr. When using this procedure, the hydrolysis of 2-oximino-1-indanone to 1,2-indandione was accomplished in 80% yield. The earlier conversion (5) of 2-oximino-1-indanone to 1,2-indandione was 55%. The general applicability of this procedure was demonstrated by hydrolyzing oximes from one heterocyclic and two commercially available ketones (Table I).

Table I—Hydrolysis of Oximes

Oxime	Hydrolysis Product	Workup Procedure	Yield, %
2-Oximino-1-indanone	1,2-Indandione	A	80
2-Piperidinoacetophenone oxime	2-Piperidinoacetophenone	B	91
p-Nitroacetophenone oxime	*p*-Nitroacetophenone	A	66
Benzophenone oxime	Benzophenone	A	80



Scheme I



Scheme II

EXPERIMENTAL[1]

Starting Materials—2-Oximino-1-indanone was prepared from 1-indanone using *n*-butyl nitrite and concentrated hydrochloric acid according to the literature procedure (5). 2-Piperidinoacetophenone oxime was prepared by treating 2-piperidinoacetophenone (10) with hydroxylamine hydrochloride and potassium hydroxide using the procedure of Cromwell and Hoeksema (11). Benzophenone oxime and *p*-nitroacetophenone oxime were prepared by using the standard procedure (12).

General Procedure for Hydrolyzing Oximes—Sulfuric acid (200 ml, 75%) was added, cautiously, to a vigorously stirred solution or slurry of the oxime (0.31 mole) in formaldehyde (100 ml, 37%) at room temperature. The reaction became slightly exothermic. The suspension (or solution) was stirred for 45–60 min without any external heating or cooling. The mixture was poured over crushed ice (~1500 ml) with stirring, and the ketone was isolated by either of the following procedures.

Procedure A—This procedure is applicable for isolating ketones insoluble in aqueous mineral acids.

A precipitate was formed from which the desired ketone was isolated by filtration, washing with water, and drying. The following ketones were isolated from hydrolysis of the corresponding oximes.

1,2-Indandione was isolated in an 80% yield, mp 98–110°. The analytical sample was obtained by recrystallization from acetone, mp 105–118° [lit. (5) mp 95–115°]; IR: ν_{max} (mineral oil) 2930, 2899, 2825, 1761, 1701, 1661, 1600, 1585, 1570, 1460, 1380, 1320, 1300, 1250, 1200, 1180, 1150, 1110, 1080, 960, 940, 920, 770, 740, 710, and 630 cm^{-1}; UV: λ_{max} (ϵ) 248 (11,857), 290 (2763), and 300 (2482) nm.

Anal.—Calc. for $C_9H_6O_2$: C, 73.97; H, 4.14; O, 21.89. Found: C, 74.04; H, 4.10; O, 22.05.

Benzophenone was obtained in an 85% yield, mp 45–47° [lit. (13) mp 48°].

p-Nitroacetophenone was isolated in a 66% yield, mp 76–78° (after one recrystallization from ethanol) [lit. (13) mp 80–82°].

Procedure B—This procedure is applicable for isolating ketones soluble in aqueous mineral acids.

The solution was made alkaline (pH ≈ 10) by adding cold (0°) aqueous (10%) sodium hydroxide. The basic solution was extracted with ether, the ether extracts were washed with water and dried

[1] Melting points were determined using a Fischer-Johns melting-point apparatus and are corrected. Elemental analyses were performed by Enviro Analytical Laboratory, Knoxville, Tenn. Elemental analyses on commercially available materials were considered unnecessary. The purity and identity of the hydrolysis products were established by comparison with authentic samples. A Beckman IR-33 spectrophotometer was used for recording the IR spectra of the compounds. UV spectra were obtained using a Beckman ACTA CV spectrophotometer.

(magnesium sulfate), and the solvent was removed by evaporation under reduced pressure, giving the desired ketone.

This procedure was used to isolate 2-piperidinoacetophenone and gave a yield of 91%, bp 102–104° (0.2 mm Hg) [lit. (10) bp 180–181° (26 mm Hg)]; IR: ν_{max} (neat) 3050, 2925, 2840, 2790, 2747, 1684, 1672, 1590, 1570, 1440, 1374, 1290, 1274, 1250, 1230, 1210, 1190, 1168, 1150, 1120, 1100, 1069, 1030, 1012, 985, 955, 850, 740, 705, and 680 cm^{-1}; UV: λ_{max} 243 nm (ϵ 9670).

Anal.—Calc. for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89. Found: C, 76.63; H, 8.40; N, 6.78.

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Synthesis of 5-Hydroxy-1-[[5-(*p*-nitrophenyl)furfurylidene]-amino]hydantoin, a Metabolite of Dantrolene

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Abstract □ The synthesis and structural elucidation of 5-hydroxy-1-[[5-(*p*-nitrophenyl)furfurylidene]amino]hydantoin, a compound proposed as a metabolite of dantrolene sodium, are reported. In addition, a chromatographic comparison of the biological and synthesized materials is made.

Keyphrases □ Dantrolene metabolite—synthesis and structural elucidation of 5-hydroxy-1-[[5-(*p*-nitrophenyl)furfurylidene]amino]hydantoin □ 5-Hydroxy-1-[[5-(*p*-nitrophenyl)furfurylidene]-amino]hydantoin—dantrolene metabolite, synthesis and structural elucidation

Dantrolene sodium, 1-[[5-(*p*-nitrophenyl)furfurylidene]amino]hydantoin sodium salt hydrate[1], is a peripherally acting, novel, skeletal muscle relaxant (1–4). Metabolism of dantrolene sodium was reported to proceed through both reductive and nonreductive pathways (5). A polarographic method was developed for simultaneous determination of dantrolene (I) with its reduced and nonreduced metabolites (5).

Subsequently, a procedure was described for determining dantrolene alone and for estimating the amounts of two metabolites (6). One of these metabolites was referred to as Metabolite A (5, 6). Metabolite A now has been isolated, and evidence accumulated in these laboratories suggests that its structure is 5-hydroxy-1-[[5-(*p*-nitrophenyl)furfurylidene]amino]hydantoin (II) (Scheme I). This paper is concerned with the synthesis and structural elucidation of II and its subsequent chromatographic comparison with the isolated Metabolite A.

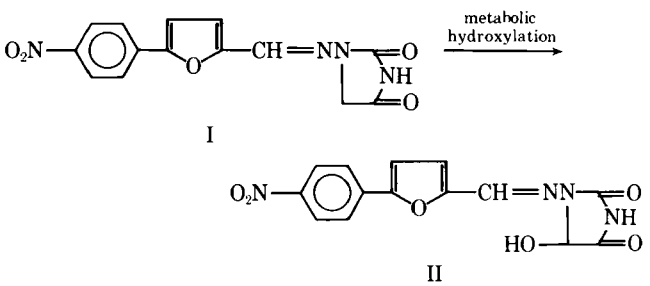
[1] Dantrium, Eaton Laboratories, Division of Morton-Norwich Products, Inc.

DISCUSSION

Cyclization of benzaldehyde semicarbazone (III) with oxalyl chloride (IV) allowed isolation of 1-(benzylideneamino)parabanic acid (V). By a combined catalytic hydrogenation and hydrogenolysis of V to 1-amino-5-hydroxyhydantoin (VI) and subsequent condensation of VI *in situ* with 5-(*p*-nitrophenyl)furfural (VII), II was prepared (Scheme II).

The NMR signal of the N_3—H proton (11.3 ppm) of II compared favorably with the N_3—H proton of dantrolene (11.3 ppm). In contrast, the N_1—H proton of the positional isomer 3-[[5-(*p*-nitrophenyl)furfurylidene]amino]hydantoin was observed at 8.3 ppm, close to the phenyl protons (7). Thus, the NMR spectrum of II supports catalytic reduction of the carbonyl of V in the 5-position rather than the 4-position; *i.e.*, II is a 1-amino-5-hydroxyhydantoin rather than a 3-amino-5-hydroxyhydantoin.

Compound II was unstable in the presence of base. When II was



Scheme I