The Preparation of N-Acetyl-1,3-dihydroxyisoindoline from *o*-Phthalaldehyde and Acetamide

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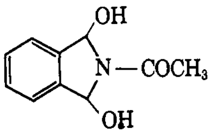
N-Acetyl-1,3-dihydroxyisoindoline has been synthesized *via* an unusual condensation of *o*-phthaldehyde with acetamide in the presence of sodium ethoxide. Physical and chemical properties of this isoindoline derivative have been examined in some detail.

More than 50 years ago Thiele and his co-workers[1] investigated a large number of reactions of *o*-phthalaldehyde (**1**). Their work conclusively demonstrated that **1** behaved as a normal dialdehyde in certain instances but more often reacted in atypical ways. More recent work[2] has provided examples of reactions of both types. The synthesis reported here is somewhat unusual in that it represents a kind of reaction of **1** which is presently rare.

Treatment of **1** with acetamide in the presence of sodium ethoxide at room temperature gave rise in good yields (73–78%) to a product, $C_{10}H_{11}NO_3$, labile to acid, base, and heat. Although ratios of starting materials, **1**-acetamide–sodium ethoxide, were varied from 1:1:1 to 1:2:2, only the 1:1 adduct of **1** and acetamide was obtained. No reaction took place in the absence of sodium ethoxide. The mode of formation of the adduct and its physical and chemical properties (*vide infra*) clearly required the assignment of the structure **2**, N-acetyl-1,3-dihydroxyisoindoline.



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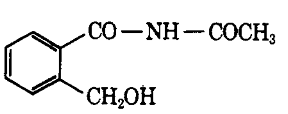

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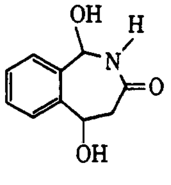

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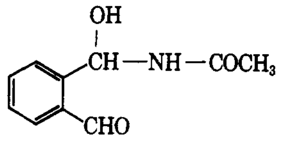

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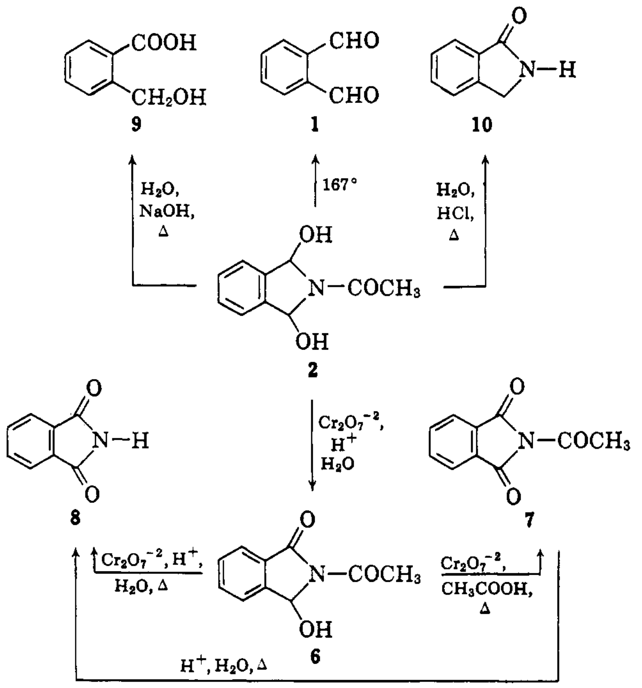
In assessing the evidence for structure **2**, the isomers **3** and **4**, which could conceivably arise from a base-catalyzed condensation of **1** with acetamide[1,2b,d,f,3] required consideration. A third possibility, **5**,[4] was dismissed since the product had no aldehydic properties. The presence of the isoindoline ring system was strongly suggested by oxidation of **2** with slightly acidic aqueous dichromate to N-acetyl-3-hydroxyphthalimidine (**6**). The identity of **6**, a previously unknown compound, was established from its infrared spectrum (*vide infra*), elemental analysis, and oxidation to the known compound, N-acetylphthalimide (**7**).[5] Conversion of **6** to **7** was effected by brief heating with sodium dichromate in a mixture of acetic acid and acetic anhydride. The use of a nonaqueous oxidizing system proved necessary since **7** was shown to undergo facile hydrolysis to phthalimide when heated briefly with aqueous acidic dichromate.



Thermal decomposition of **2** yielded phthalaldehyde in 25% yield, thereby allowing elimination of structures **3** and **4**. Base-catalyzed hydrolysis of **2** furnished α-hydroxy-*o*-toluic acid (**9**), apparently formed from reversal of the condensation to give **1** and subsequent characteristic disproportionation.[6]

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(1) (a) J. Thiele and O. Gunther, *Ann.*, **347**, 107 (1906); (b) J. Thiele and E. Weitz, *ibid.*, **377**, 1 (1910), and references therein.

(2) See, *e.g.*, (a) F. W. Lichtenhaler, *Tetrahedron Letters*, **No. 12**, 775 (1963); (b) W. Davey and H. Gottfried, *J. Org. Chem.*, **26**, 3699 (1961); (c) H. Baer and B. Achmatowicz, *ibid.*, **29**, 3180 (1964); (d) V. Anger, *Oesterr. Chemiker-Z.*, **62**, 354 (1961); (e) L. W. F. Kampschmidt and J. P. Wibaut, *Rec. trav. chim.*, **71**, 601 (1952); (f) L. F. Fieser and M. M. Pechet, *J. Am. Chem. Soc.*, **69**, 2577 (1946).

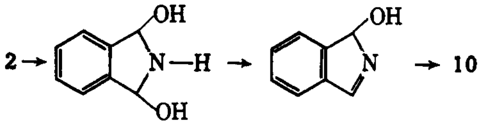
(3) S. Gabriel and G. Pinkus, *Ber.*, **26**, 2210 (1893).

(4) F. Feist, *ibid.*, **45**, 945 (1912).

(5) C. Graebe, *Ann.*, **247**, 288 (1888).

(6) Earlier workers (ref. 1a) reported that phthalide was the product isolated when **1** was subjected to the Cannizzaro reaction. We have found, as expected, that phthalide and/or **9** may be isolated from this reaction depending upon the conditions used for acidification. Concentrated acid and elevated temperatures favored phthalide formation whereas careful neutralization with dilute acid in the cold yielded only **9**.

Attempted acid hydrolysis of **2** gave a black tarry mixture from which a small amount of phthalimidine (**10**) was isolated; **10** could well have resulted from dehydration of an initially formed dihydroxyisoindoline (**11**) to the 1H-isoindole, **12**, and subsequent tautomerization. In view of the known instability of isoindoles in acid media[7] the formation of a large amount of tar in this reaction is scarcely surprising.



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Ultraviolet absorption spectra of **2**, benzyl alcohol, and **10** were determined in absolute ethanol. The spectrum of **2** in this region was very similar to that of benzyl alcohol and quite unlike the spectra of compounds in which a double bond is conjugated with a benzene ring.[8]

Certain solid-state infrared absorption maxima of **2**, **6**–**8**, and **10** are given in Table I. The infrared spectrum of **2** was completely consistent with the structural assignment.[9]

TABLE I

INFRARED ABSORPTION MAXIMA

	Cm.$^{-1}$			
Compd.	Bonded OH	Bonded NH	Amide CO	CH out-of-plane deformation
2	3247 (vs, br)	...	1621 (vs)	750 (vs)
6	3367 (m)	...	1710 (vs) 1678 (vs)	752 (vs)
7	...	...	1780–1660 (s)[a]	717 (vs)
8	...	3205 (s)	1700–1760 (vs)[a]	715 (vs)
10	...	3205 (m)	1666 (vs)	724 (vs)

[a] Multiple peaks occur in this area.

The n.m.r. spectrum of **2** in dimethyl sulfoxide-d_6 contained a three-proton singlet for CH_3CO (τ 7.78), a four-proton aryl singlet (τ 2.47), and a four-proton multiplet (τ 3.62–3.82). It has previously been shown that aromatic hydrogen atoms of benzene derivatives bearing identical *ortho* substituents which do not interact strongly with the ring can give rise to a single peak.[10] The chemical shift of the tertiary hydrogens in **2**, adjacent to oxygen and nitrogen atoms, would be expected to fall in the range of τ 3.5–4.0.[11] Further, Chapman[12] has recently reported that the proton hydroxyl resonance of the 6-OH in 6-hydroxycrinamine occurs as a doublet at τ 3.92 in dimethyl sulfoxide. This resonance arises from a proton in an environment similar to that of the hydroxyl protons of **2**, *i.e.*, -CHOH-N.[13]

The synthesis reported here appears to be the first successful preparation of a 1,3-dihydroxyisoindoline derivative. Earlier attempts to prepare such compounds by reduction of phthalimide derivatives have yielded only the corresponding phthalimidines.[14]

Reactions of **1** of the type reported here, in which the same atom of an attacking nucleophile has reacted with both formyl groups of **1** to yield a simple, symmetrical 1:1 adduct, were unknown until recently; one other example of such a reaction has been reported by Baer and Achmatowicz[2c] who prepared 1,3-dihydroxy-2-nitroindan by a base-catalyzed condensation of **1** and nitromethane.

The reactions of **1** with other amides are being investigated.

Experimental[15]

N-Acetyl-1,3-dihydroxyisoindole (**2**).[16]—Acetamide (3.54 g., 0.06 mole) was added in one portion to a solution of sodium ethoxide (1.38 g., 0.06 g.-atom, of sodium in 50 ml. of absolute ethanol) contained in a dropping funnel. After dilution to approximately 240 ml. and thorough mixing, the solution was added dropwise over a period of 3 hr. to a vigorously stirred alcoholic solution of *o*-phthalaldehyde (**1**,[17] 4.0 g., 0.03 mole in 750 ml. of absolute alcohol) protected from atmospheric moisture. The reaction mixture, after standing at room temperature for 24 hr., was treated with sufficient 5 *N* hydrochloric acid to effect approximate neutrality. Solvent was removed by allowing the mixture to stand in a moderate, dry air stream at room temperature. The resultant oily solid was filtered, dried, washed twice with water, and recrystallized from water or acetone to yield 4.37 g. (75%) of fine, white needles, m.p. 157.0–157.5°.

Anal. Calcd. for $C_{10}H_{11}NO_3$: C, 62.17; H, 5.70; N, 7.25; mol. wt., 193. Found: C, 61.93; H, 5.52; N, 7.21; mol. wt., 195 ± 3.

The ultraviolet absorption spectrum of **2** showed λ_{max}^{EtOH} in mμ (log ϵ) 222 (3.13), 243 s (2.82), 248 s (2.88), 255 (2.96), 260 s (2.98), 261.5 (3.08), and 268.5 (2.98); λ_{min}^{EtOH} in mμ (log ϵ) 239 (2.81), 258 (2.95), and 266 (2.88). Under the same conditions benzyl alcohol showed λ_{max}^{EtOH} in mμ (log ϵ) 222 (3.18), 243 s (2.75), 248 s (2.86), 254 (2.95), and 259 (3.00); λ_{min}^{EtOH} in mμ (log ϵ) 231 (2.61) and 256 (2.94). Further, **10** showed a less complex spectrum with λ_{max}^{EtOH} in mμ (log ϵ) 228 (3.80), 264 s (3.46), 271 (3.51), and 278 (3.50); and λ_{min}^{EtOH} in mμ (log ϵ) 260 (3.45) and 275 (3.44).

N-Acetyl-3-hydroxyphthalimidine (6). **Oxidation of 2.**—Sodium dichromate dihydrate (0.6 g., 0.002 mole) and concentrated sulfuric acid (1 drop) were added to an aqueous solution of **2** (0.6 g., 0.003 mole, dissolved in 25 ml. of hot water and cooled to room temperature). Reaction was evidenced by immediate darkening of the reaction mixture, evolution of heat, and formation of a white precipitate. The reaction mixture was filtered after standing overnight. The solid thus obtained, after washing with water and recrystallization from 95% ethanol, melted at 163.0–164.5° and weighed 0.3 g. (52%).

Anal. Calcd. for $C_{10}H_9NO_3$: C, 62.81; H, 4.71; N, 7.33. Found: C, 62.89; H, 4.88; N, 7.34.

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[15] Melting points were taken on a Büchi melting point apparatus calibrated against standard substances. Ultraviolet spectra were determined on a Bausch and Lomb Spectronic 505 spectrophotometer, and infrared spectra were determined in potassium bromide pellets (1–2 mg. of sample/400 mg. of potassium bromide) on a Beckman IR-8 spectrophotometer. A Varian A-60 spectrometer was used to determine n.m.r. spectra; tetramethylsilane was used as an external reference. Molecular weights were determined on a Mechrolab vapor pressure osmometer. Elemental analyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich.

[16] Data are given for a typical run; quantities of starting materials were varied (*vide supra*) with no effect on product identity and little effect on yield.

[17] *o*-Phthaldehyde was prepared by the method of J. C. Bill and D. S. Tarbell [*Org. Syn.*, **34**, 82 (1954)].

N-Acetylphthalimide (7). Oxidation of 6.—Excess sodium dichromate dihydrate (50 mg., 2.7×10^{-4} mole) was added to 6 (10 mg., 5.2×10^{-5} mole) dissolved in glacial acetic acid (2 ml.) and acetic anhydride (1 ml.). After brief heating on a steam bath, the reaction mixture was allowed to stand in a dry air stream. The semisolid mass remaining was filtered, washed with water, and recrystallized from benzene to yield 5 mg. (53%) of **7**, m.p. 134–135° (lit.[18] m.p. 132–135°). The infrared spectrum of **7** was identical with that of an authentic sample prepared by a usual method.[18]

Formation of Phthalimide (8) from 6 and from 7.—Treatment of **6** or of **7** with excess aqueous acidic sodium dichromate followed by brief heating on a steam bath resulted in deposition of **8** which, when recrystallized from benzene, had m.p. 235–236° (lit.[5] m.p. 233.5°). Phthalimide thus obtained was shown by identical infrared spectra and an undepressed mixture melting point to be identical with that of an authentic sample (Eastman Kodak Co.).

Thermal Decomposition of 2.—Heating of **2** (0.6 g., 0.003 mole) in a test tube immersed in an oil bath at 167° for 10 min. yielded a dark brown tarry mass which was extracted with ligroin (b.p. 66–75°). Removal of solvent left 0.1 g. (25%) of **1**, m.p. 53–54° (lit.[1a] m.p. 56°), identified by its infrared spectrum which was identical with that of an authentic sample.

α-Hydroxy-*o*-toluic Acid (9). Base-Catalyzed Hydrolysis of 2.—A mixture of **2** (1.0 g., 0.005 mole) and 40 ml. of aqueous sodium hydroxide (10% by weight) was heated at reflux for 3 hr. The hot solution was filtered, cooled in an ice bath, carefully acidified with 5 *N* hydrochloric acid, and extracted five times with ether. The ether extracts were dried over anhydrous sodium sulfate. Removal of the solvent on the steam bath left a white solid with a vinegar-like odor. Recrystallization from a benzene–ether mixture yielded 0.5 g. (66%) of **9**, m.p. 123.5–124.5° (lit.[19] m.p. 120°).

Anal. Calcd. for $C_8H_8O_3$: C, 63.16; H, 5.26; mol. wt., 152. Found: C, 63.34; H, 5.03; mol. wt., 150 ± 5.

An authentic sample of **9** was prepared using the method of Gardner and Naylor[20] for the preparation of the sodium salt of **9** and hydrolyzing this salt with 5 *N* hydrochloric acid at 0°. The product from base-catalyzed hydrolysis of **2** and the authentic sample of **9** were identical as shown by infrared spectra and mixture melting point behavior.

When **1** was allowed to react with 10% sodium hydroxide under the same conditions employed for base-catalyzed hydrolysis of **2**, **9** was obtained in nearly quantitative yield.

Phthalimidine (10). Acid-Catalyzed Hydrolysis of 2.—Treatment of **2** (1.34 g., 0.007 mole) with excess 3 *N* hydrochloric acid (30 ml.) at reflux for 30 hr. yielded a yellow solution containing a black semisolid. After filtration the mixture was reduced in volume on a rotary evaporator. The black gum remaining was recrystallized from acetone to yield 0.01 g. (11%) of **10**, m.p. 148–150° (lit.[21] m.p. 150°); **10** produced in this manner was shown to be identical with an authentic sample[21] by undepressed mixture melting point and identical infrared spectra.

Acknowledgment.—The authors wish to thank Mr. John C. Gilbert of Yale University for determination of the n.m.r. spectra.

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[19] E. Hjelt, *ibid.*, **25**, 524 (1892).

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A Novel Synthesis of 2,3-Disubstituted Indoles. A Study of the Reductive Cyclizations of Some 3-Substituted 2-(4,5-Dimethoxy-2-nitrophenyl)acrylonitriles[1a]

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The reductive cyclizations of 3-substituted 2-(4,5-dimethoxy-2-nitrophenyl)acrylonitriles with iron and acetic acid constitute a rapid and convenient synthesis for many novel 2,3-disubstituted indoles. A reaction mechanism and the general scope of the new synthesis are presented.

The intramolecular cyclizations of aminoalkyl cyanides[2-4] and the reductive cyclizations of nitrophenylalkyl cyanides[5,6] have been extensively investigated for the syntheses of quinolizidines, 2-aminoindolenine,[7] and 3-substituted indoles. Generally these reactions involve intramolecular amidine formation by addition of an amino group to a nitrile function. Subsequent deamination of the amidine can occur under forcing hydrogenation conditions as shown by Boekelheide,[3] Walker,[5] Kebrle,[4] Heacock,[8] and other investigators.[9]

In connection with similar studies in these laboratories we wish to report a new synthesis for 2-substituted 5,6-dimethoxyindole-3-carbonitriles (Table II). The essential steps of this synthesis are (1) the condensation of 5,6-dimethoxy-2-nitrophenylacetonitrile with various aldehydes, and (2) reductive cyclization of the resulting β-substituted α-(4,5-dimethoxy-2-nitrophenyl)acrylonitriles (Table I) with iron and acetic acid. The second step of this synthesis proceeds smoothly by reduction of the nitro group followed by intramolecular Michael addition of the resulting basic nitrogen function to the α,β-unsaturated nitrile system (it is to be noted that most reductive cyclizations have been reported under the conditions of catalytic hydrogenation).

The proposed reaction mechanism[10a] is illustrated for the case of 3-(*p*-chlorophenyl)-2-(4,5-dimethoxy-2-

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[1] (a) Presented at the 149th Meeting of the American Chemical Society, Detroit, Mich., April 1965. (b) To whom correspondence should be sent: Lakeside Laboratories, Division of Colgate-Palmolive Co., Milwaukee, Wis. 53201.

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[10] (a) Although complete reduction to the amine followed by cyclization and oxidative dehydrogenation of dihydroindole by ferric ion is conceivable, the isolation of ferrous acetate from the reaction mixture and the extremely lower yield of indoles when less than 2 moles of iron was used for the reductive cyclization favor our proposed mechanism. (b) C. S. Marvel and O. Kamm, *J. Am. Chem. Soc.*, **41**, 278 (1919).