J. Chem. Eng. Data **1988**, *33*, 532-534

Upon the Claimed Preparation of 2-Chloro-2,3-dihydrobenzimidazole, 2-Amino-2,3-dihydrobenzimidazole, and Related Compounds

John A. Barltrop and Terence C. Owen*

Department of Chemistry, University of South Florida, Tampa, Florida 33620

Reports by Studnicki claiming the preparation of 2-chloro-2,3-dihydrobenzimidazole, 2-amino-2,3-dihydrobenzimidazole, and related substances are mistaken. The substances obtained actually are unchanged starting material, *o*-phenylenediamine, and simple known derivatives of it.

Some little time ago there appeared in this Journal a report (*1*) by Marek Studnicki claiming the preparation of 2-chloro-2,3-dihydrobenzimidazole (*2*) (**1**, Table I) and from it the 2-mercapto and 2-amino compounds and sundry derivatives of them. Subsequent monographs (*3*) extended these claims and described supposed industrial applications also.

We observe that the preparation of these substances would constitute a truly remarkable and noteworthy achievement. Each is formally the product of addition of HX across a double bond of the imidazole ring of benzimidazole. Each, surely, would exhibit a pronounced proclivity toward loss of the addend and recovery of the considerable resonance stabilization of the benzimidazole system. That any of them should tolerate the experimental conditions described, viz., boiling in methanol, boiling with aqueous sodium sulfide, or fusion (sic) with potassium phthalimide, is totally outside the bounds of credibility.

Accordingly, having a considerable interest in unusual 2-substituted benzimidazoles (*4*), and wondering what exactly might be going on here, we found it necessary to consider closely the experimental information and structural evidence presented by Studnicki, and in due course to repeat almost all of the experiments described. We regret to have to report that it is all wrong.

The author did the experiments he describes, of that there is no doubt. The melting points reported are indeed observed. Where a pink precipitate is described, such a precipitate is indeed obtained. The mass spectra reported are indeed those of the substances produced, but they are totally incompatible with the assigned structures, and almost all of them are those of very simple substances, unchanged starting materials, and simple known conversion products of them, as shown in Table I.

Experimental Section

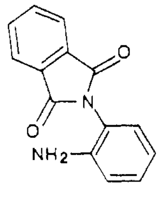
Compounds are discussed in the order in which they are described by Studnicki (*1*). Their claimed and actual structures and properties are presented in Table I.

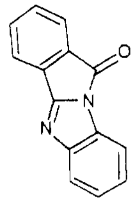
Compound 1. Supposed 2-Chloro-2,3-dihydrobenzimidazole. No reaction occurs between *o*-phenylenediamine and chloroform under any of the conditions described by Studnicki, or under any of several other conditions tried by us. When the reactants are *o*-phenylenediamine and its dihydrochloride in equimolar proportions, *o*-phenylenediamine monohydrochloride (*5*) is recovered essentially quantitatively. It melts at 204–206 °C, close to the value reported for **1**. When an excess of hydrogen chloride is used, the product is the dihydrochloride (mp 254–256 °C). Either, upon sublimation (the purification used by Studnicki), gives pure monohydrochloride, mp 210 °C. The mass spectrum reported for compound 1 (base peak *m/e* 108, M + 1 isotope peak *m/e* 109, 7.65%) is exactly that of *o*-phenylenediamine, MW 108, into which the hydrochloride dissociates upon introduction into the mass spectrometer. The minute peak, 0.08%, at *m/e* 118 corresponds to exactly that trace amount of benzimidazole (*6*), MW 118. The reported NMR spectrum in hexadeuterioacetone agrees with that of *o*-phenylenediamine monohydrochloride in that solvent, the somewhat unexpected characteristics being consistent with conformational and protolytic restrictions in that aprotic, poorly ionizing solvent. In deuterium oxide or in perdeuteriomethanol the spectrum is much simpler. Compound **1**, accordingly, is *o*-phenylenediamine monohydrochloride.

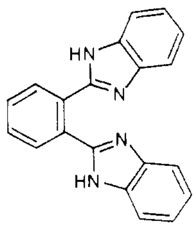
Compound 5′. Supposed 2,2-Iminobis(2,3-dihydrobenzimidazole). When the phenylenediamine hydrochloride (**1**) thus obtained is boiled with concentrated hydrochloric acid and the product is treated with excess ammonia, the free base, *o*-phenylenediamine, is of course, recovered. It melts at 102 °C, as indeed it should (lit. (*7*) 102–3 °C) and the mass spectrum reported is again that of *o*-phenylenediamine contaminated with a trace of benzimidazole. Compound **5′**, accordingly, is simply recovered *o*-phenylenediamine.

Compound 2. Supposed Sodium 2,3-Dihydrobenzimidazole-2-thiolate Double Salt with Sodium Sulfide. Phenylenediamine hydrochloride (**1**) reacts with sodium sulfide in hot water only to the extent of liberating hydrogen sulfide in a simple acid–base reaction. Upon cooling the hot solution, *o*-phenylenediamine (free base) and sodium sulfide nonahydrate crystallize out together in proportions governed by their relative amounts and concentrations (not specified in Studnicki's experimental directions). The melting point of the mixture varies with its composition and can be around the value of 166 °C reported. No mass spectrum, NMR, or other characterization is given for this "compound". When the material is leached with cold water, the sodium sulfide dissolves away and *o*-phenylenediamine is recovered in quite good yield. "Compound" **2**, accordingly, is a mixture of *o*-phenylenediamine and sodium sulfide nonahydrate.

Compound 3. Supposed 2-Phthalimidyl-2,3-dihydrobenzimidazole. When the above mixture (**2**) of *o*-phenylenediamine and sodium sulfide hydrate is fused with potassium phthalimide, some ammonia and phthalic acid are produced, some *o*-phenylenediamine and phthalimide are recovered, and, as the ancient literature (*8*) reveals, a veritable plethora of diamine–phthalate condensation products and polymers is obtained. Typical are



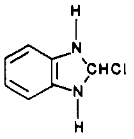
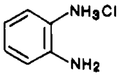
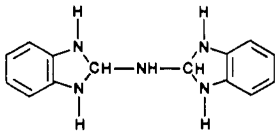
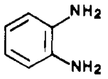
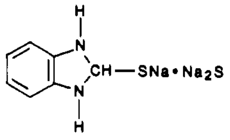
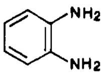
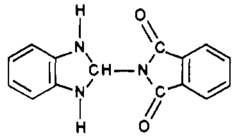
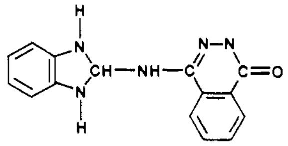
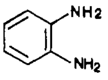
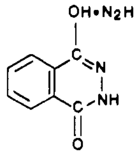
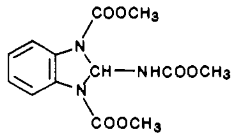
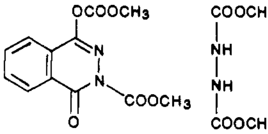
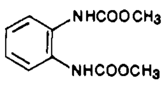
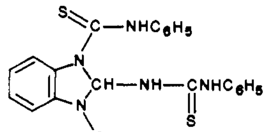
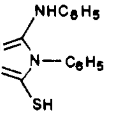




Two of these, *N*-(2-aminophenyl)phthalimide (MW 238) and its tetracyclic dehydration product (MW 220) account for the high-mass peaks (*m/e* 237 and 220) in the mass spectrum reported for **3**. We have prepared the third, 1,2-bis(2-benzimidazolyl)benzene, in good yield, by fusing *o*-phenylenediamine with phthalimide as well as by the literature procedure (*8*) using phthalic anhydride. All of these condensation products are

0021-9568/88/1733-0532$01.50/0

Table I. Supposed and Actual Structures of 2,3-Dihydrobenzimidazole Derivatives

structure claimed	reported mp, °C	actual identity	found mp, °C (lit.)
 1	210		204–6 (210)
 5′	102		102 (102)
 2	166	mixture of  and $Na_2S \cdot 9H_2O$	160–170
 3	340^a	mixture of phthalate–phenylenediamine condensation products (see Discussion)	280–340 (280–340)
 4	320^a	mixture of  and 	320^a (320)^a
 5‴	98	mixture of  and 	95–105
 6	211		(210)

^{a}Sublimes at this temperature.

high-melting (>280 °C), and bis(benzimidazolyl)benzene, like compound **3**, sublimes at 340 °C. The base peak at *m/e* 162 (isotope peak *m/e* 163, 10.19%) in the mass spectrum of **3** is puzzling. It corresponds to phthalhydrazide, which is unquestionably a major component of compound **4**, the product of hydrazinolysis of **3** (see next paragraph). In any event, the unpurified and ill-characterized "compound" **3**, claimed to be 2-phthalimidyl-2,3-dihydrobenzimidazole, actually is a mixture of phthalate–phenylenediamine condensation products and polymers along with some *o*-phenylenediamine, phthalic acid, and phthalimide.

Compound 4. Supposed 4-(2,3-Dihydrobenzimidazol-2-ylamino)-1-oxo-1,2-dihydrophthalazine. Complete hydrazinolysis of any set of phthalate–phenylenediamine condensation products, phthalimide, etc., such as comprise **3**, leads to the formation of phthalhydrazide and recovery of *o*-phenylenediamine. If the hydrazinolysis is conducted less vigorously, some bis(benzimidazolyl)benzimidazole survives and can be recovered. We find that phthalhydrazide, as prepared by hydrazinolysis of phthalate esters, phthalimide, and mixtures such as this one, always crystallizes as the hydrazine salt of the enolic form (dihydroxyphthalazine). Hydrazine is lost upon treating with acid or upon raising to the melting point, so that the sublimation behavior of free phthalhydrazide (320 °C) is observed. Acylation of the phthalhydrazide salt gives an equimolar mixture of the diacylphthalhydrazide and the corresponding diacylhydrazine. "Compound" **4** (sublimes 320 °C) thus is a mixture of *o*-phenylenediamine, the hydrazine salt of phthalhydrazide (sublimes 320 °C), and possibly small amounts of 1,2-bis(2-benzimidazolyl)benzene (sublimes 340 °C) and other phthalate–phenylene diamine condensation products.

Compound 5. Supposed 2-Amino-2,3-dihydrobenzimidazole Hydrochloride. As the preparation of this material is described by Studnicki, a hydrazinolysis product (**4**, 16.9 g) is boiled with dilute hydrochloric acid and filtered, the filtrate is neutralized with KOH and again filtered, the alkaline filtrate is concentrated and extracted with ether–benzene mixture, and the organic layer is evaporated to give **5** (1.1 g, 6.5% w/w). That a simple amine *salt* should survive, *as the salt*, neutralization with potash followed by extraction into a nonpolar organic solvent is hard to believe. The yield is low, and the reported mass spectrum again corresponds simply to *o*-phenylenediamine containing a trace of benzimidazole.

Compound 5‴. Supposed Dimethyl 2-[(Methoxycarbonyl)amino]-2,3-dihydrobenzimidazole-1,3-dicarboxylate. Consider the mass spectrum reported for this compound: *m/e* 296 (0.9%); 224 (84%) and 225 (10.5%); 192 (base peak) and 193 (18%); 148 (13%) and 147 (12.5%). It is claimed that the peak at 296 amu corresponds to the molecular ion of the supposed tris(methoxycarbonyl)-2-aminodihydrobenzimidazole. But the molecular weight of this substance, $C_{13}H_{15}N_3O_6$, actually is 309! In fact, *m/e* 296 corresponds to the bis(methoxycarbonyl) derivative of phthalhydrazide. This substance is the O,N bis derivative as structured in Table I. Old literature (*9*) reports the cognate structure for the diethyl homologue, and the NMR spectrum of the dimethyl compound prepared by us shows two clearly distinct methyl groups. The peak at *m/e* 224 (isotope peak at 225) is pictured by Studnicki as the bis(carbamate) of *o*-phenylenediamine. And that is exactly right, for that simple derivative of the original starting material is indeed a major component of "compound" **5‴**. But it is an actual constituent, and not just a mass spectroscopic ionization fragment. The peak at *m/e* 148 (M − 1 peak at 147) similarly corresponds to the presence of the bis(carbamate) of hydrazine in the mixture. The base peak at *m/e* 192 (isotope peak at 193) and the other major peaks at *m/e* 160 and 133 are characteristic fragments (224 − MeOH, 224 − 2MeOH, 148 − CH_3) of the components of the mixture.

Finally, consider melting point, the only characteristic we really have for Studnicki's material. Compound **5‴**, the crude, unrecrystallized substance obtained upon evaporation of volatiles from the methyl chloroformate digest of **4**, is reported to melt at 98 °C. We find, in fact, that the mixture produced by such digestion of an equimolar mixture of *o*-phenylenediamine and the hydrazine salt of phthalhydrazide does indeed melt at 95–105 °C, even though the individual components in pure form melt at considerably higher temperatures. Accordingly, Studnicki's compound **5‴**, reported to be the *N*,*N′*,*N″*-tris(methoxycarbonyl) derivative of 2-amino-2,3-dihydrobenzimidazole, is, in fact, an equimolar mixture of three compounds, the carbamates of phthalhydrazide, *o*-phenylenediamine, and hydrazine, as shown in Table I.

Compound 6. Supposed 2-[(Phenylthiocarbamoyl)amino]-2-chloro-2,3-dihydrobenzimidazole-1,3-dicarbothioamide. The molecular weight of this structure, 540 amu, once again is inconsistent with the reported mass spectrum in which the highest mass noted is an intense peak at *m/e* 268 (22.53%). In fact, the substance obtained here is 5-anilino-3-mercapto-4-phenyltriazole. The molecular weight of this substance is 268, and its melting point (*10*, *11*) is 210 °C, in agreement with the melting point (211 °C) reported for **6**. In the preparation of compound **6**, an unpurified extract of a hydrazinolysis mixture is treated directly with phenyl isothiocyanate. Under these conditions, unreacted hydrazine forms its *N*,*N′*-bis(thiocarbanilide) which cyclizes readily (*10*) with elimination of the elements of hydrogen sulfide to afford the mercaptotriazole structured in Table I, a compound known (*11*) since 1902. Compound **6** thus is 5-anilino-3-mercapto-4-phenyltriazole.

Registry No. **1**, 85354-90-1; **2**, 85355-01-7; **3**, 85354-91-2; **4**, 85354-92-3; $\mathbf{5}^{1}$, 86834-46-0; $\mathbf{5}^{111}$, 85354-94-5; **6**, 85354-95-6; Na_2S, 1313-82-2; $H_3COCO(NH)_2COOCH_3$, 17643-54-8; *o*-$MeOCONHC_6H_4NHCO_2Me$, 14803-74-8; *o*-phenylenediamine hydrochloride, 39145-59-0; *o*-phenylenediamine, 95-54-5; 4-hydroxy-1(2*H*)-phthalazinone hydrazine, 116054-32-1; 2-(methoxycarbonyl)-4-(methoxycarbonyloxy)-1-(2*H*)phthalazinone, 116054-33-2; 5-anilino-3-mercapto-4-phenyltriazole, 14132-84-4.

Literature Cited

(1) Studnicki, M. *J. Chem. Eng. Data* **1984**, *29*, 97–99.
(2) Studnicki, M. *Ind. Eng. Chem. Prod. Res. Dev.* **1983**, *22*, 482–487.
(3) Studnicki, M. *Hung. J. Ind. Chem.* **1984**, *12*, 287–296; **1985**, *13*, 347–361. *Przem. Chem.* **1985**, *64*, 190–193; **1985**, *64*, 424–425. *Ind. Eng. Chem. Prod. Res. Dev.* **1988**, *25*, 96–102.
(4) Owen, T. C.; Richards, A. *J. Am. Chem. Soc.* **1987**, *109*, 2520.
(5) Kuhn, R., Zumstein, F. *Ber.* **1926**, *59*, 488–498.
(6) Phillips, M. A. *J. Chem. Soc.* **1928**, 2392–2399.
(7) *Handbook of Chemistry and Physics*, 46th ed.; Chemical Rubber Co.: Cleveland, OH, 1965.
(8) Beilstein, Vol. 13, H., p 6.
(9) Beilstein, Vol. 25, II, p 10 (see also Vol. 25, II, p 546 and Vol. 24, II, p 197).
(10) Guha, P. C.; Sen, P. C. *J. Indian Chem. Soc.* **1927**, *4*, 43–50.
(11) Busch, M.; Ulmer, Th. *Ber.* **1902**, *35*, 1710–1716.

Received for review March 11, 1988. Accepted June 15, 1988. Work supported by National Cancer Institute Master Contract NO1-CM-437639.

Synthesis and Experimental Ionization Energies of Certain (*E*)-3-Arylpropenoic Acids and Their Methyl Esters

John R. Peterson,* Morley E. Russell,* and Irawan B. Surjasasmita

The Michael Faraday Laboratories, Department of Chemistry, Northern Illinois University, DeKalb, Illinois 60115

Ionization energies for several methoxy-substituted (*E*)-3-arylpropenoic acids and methyl (*E*)-3-arylpropenoates were experimentally determined by mass spectroscopy. The title compounds were prepared in excellent yield by Knoevenagel condensation of an aromatic aldehyde with malonic acid and by Fischer esterification of the acid with methanol.

In conjunction with our projected synthesis of the naturally occurring, antineoplastic podophyllotoxins by a transition-metal-mediated oxidative protocol, the need arose for ionization energy data for several methoxy-substituted (*E*)-3-arylpropenoic acids, **1**, and their methyl esters, **2**. Ionization energies for these compounds have not been reported in the literature to our knowledge except for a study (*1*) of the 2-substituted derivative. We now wish to report our experimentally determined ionization

0021-9568/88/1733-0534$01.50/0 © 1988 American Chemical Society