The 'valence tautomers' of *o*-iodosobenzoic acid: the case of 4-pentyl-2-iodosobenzoic acid

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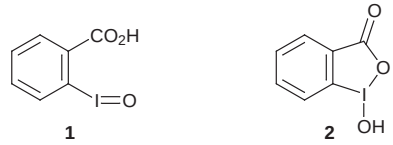
Contrary to a previous report, only the closed (iodoxolone) form of 4-pentyl-2-iodosobenzoic acid (3a) can be isolated; the previously assigned open (iodoso) form (3b) is actually 4-pentanoyl-2-iodobenzoic acid.

o-Iodosobenzoic acid (IBA, **1**) has long been known[1] to exist in the cyclic 1-hydroxy-1,2-benziodoxol-3(1*H*)-one form (**2**).[2,3] X-Ray crystal structure[4] and theoretical studies[5] agree that the cyclic form is the better representation, although the internal I–O bond is longer than a 'normal' single I–O bond, indicating significant 'open' character.[4b,c,5]

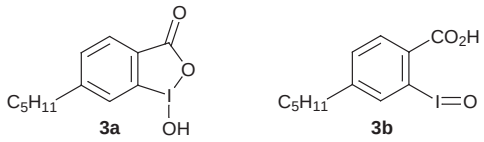
A valence tautomeric representation of IBA (**1** ⇌ **2**) suggests that both **1** and **2** can exist as separate entities. Such



1 **2**

representations have often appeared,[6] even if they were not intended to imply the simultaneous presence of interconverting open ('iodoso') and closed (iodoxolone) forms. Thus, in 1990, Panetta *et al*. reported the *separate isolation* of the iodoxolone and iodoso valence tautomers of 4-propyl- as well as 4-pentyl-2-iodosobenzoic acids.[7] These extraordinary results have been reiterated in a recent authoritative review,[3b] so that it becomes imperative to verify them, particularly because of the importance of IBA and its analogues as decontamination agents for toxic phosphonates and phosphates.[4b,c,5–8]

We have now reinvestigated the case of the 4-pentyl 'tautomers' (**3a** and **3b**), and report here that the previously described[7] compounds were misassigned; in fact, only a single 4-pentyl-2-iodosobenzoic acid can be isolated, and it is best represented as the 'closed' iodoxolone compound, **3a**.

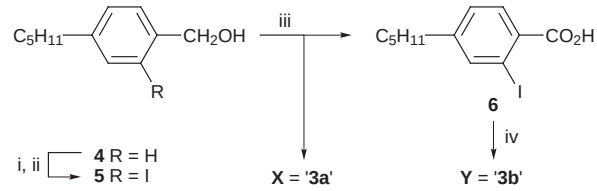


3a **3b**

The origin of the misassignments in ref. 7 lies in the synthetic sequence, which we summarize in Scheme 1. 4-Pentylbenzyl alcohol (**4**) was first regiospecifically iodinated to **5**.[7,9]

In the following and key step, iodo alcohol **5** was oxidized to 4-pentyl-2-iodobenzoic acid (**6**) using phase transfer catalysis in a $KMnO_4$–water–benzene system.[7,10] This reaction led not only to the desired **6**, in 63% yield, but also to a second, chromatographically-separated product, **X** (25%, mp 115–116 °C), assigned[7] as 4-pentyl-2-iodosobenzoic acid in its cyclic (iodoxolone) form, **3a**. A separate H_2O_2/Ac_2O oxidation[7,11] of **6** afforded 4-pentyl-2-iodosobenzoic acid **Y** (mp 188.5–189.5 °C) assigned[7] as the open (iodoso) valence tautomer, **3b**.

The assignments[7] of **X** and **Y** rest on acceptable elemental analyses for $C_{12}H_{15}IO_3$, suggestive of isomerism, as well as IR



Scheme 1 *Reagents and conditions*: i, BuLi, $Me_2NCH_2CH_2NMe_2$; ii, I_2; iii, $KMnO_4$–H_2O, C_6H_6, cat. $Bu_4P^+Cl^-$; iv, 30% H_2O_2, Ac_2O, 40 °C, 20 h

carbonyl bands for **X** at 1710 cm^{-1} and **Y** at 1650 cm^{-1}. The higher frequency C=O band of **X** was considered indicative of a 'lactone' structure as in **3a**.[7] However, it is known[2] that the carbonyl band of IBA, in its iodoxolone form, is at 1633 cm^{-1} (Nujol), so that the reported IR band of **X** at 1710 cm^{-1} is inconsistent with structure **3a**; it is **Y** (1650 cm^{-1}) that is more likely to merit this assignment.

We repeated the synthetic sequence of Scheme 1.[7] In particular, the permanganate oxidation of **5**, after chromatography of the product on silica gel (hexanes–EtOAc–HOAc, 79 : 20 : 1 to 28 : 70 : 2) afforded **6** (48%, mp 67.5–68.5 °C, lit.[7] 68.0–69.0 °C) and **X** (10%, mp 115–116 °C, lit.[7] 115–116 °C).

Our sample of **X** displayed the same mp, an experimentally comparable elemental analysis, and a similar IR C=O band (1707 cm^{-1}) relative to those reported[7] for '**3a**'. Nevertheless, several observations indicated that **X** was not **3a**. (1) The NMR spectrum of **X**‡ revealed only four sets of alkyl protons rather than the anticipated five. (2) The pentyl benzylic resonance of **5** (a triplet at δ 2.55) was missing in **X**, while a more deshielded triplet appeared at δ 3.1. (3) The IR spectrum (KBr) of **X** revealed two intense C=O absorptions at 1707 and 1686 cm^{-1}. The Supplementary Material for ref. 7 reports this band at 1685 cm^{-1}; it can be assigned to an aromatic CO_2H. The former band was assigned[7] to the carbonyl of **3a**, but the 'lactone' carbonyl group of (*e.g.*) **2** is known to absorb at 1633 cm^{-1} (Nujol).[2] (4) Compound **X** was kinetically inactive toward *p*-nitrophenyl diphenyl phosphate (PNPDPP) in aqueous micellar cetyltrimethylammonium chloride (CTACl) at pH 8 (see Table 1), whereas authentic benziodoxolones (*e.g.* **2**) rapidly cleave PNPDPP under these conditions.[8a,b] (5) Additionally, **X** did not oxidize iodide to iodine, a common property of iodosobenzoates.[8b]

Accordingly, an X-ray crystal structure determination was carried out for **X**,§ revealing it to be not an iodoso compound at all, but 4-pentanoyl-2-iodobenzoic acid (**7**) (Fig. 1). Clearly, the $KMnO_4$ oxidation of **5** to **6** must have been accompanied by overoxidation[12] at the benzylic position of the pentyl chain, affording (both) ketone **7** (and iodoterphthalic acid). Structure **7** immediately accounts for the spectral characteristics of **X** itemized above in points (1)–(3),¶ and, of course, **7** should also be inactive in the hydrolysis of PNPDPP or the oxidation of iodide [points (4) and (5)].

Compound **Y**, which we obtained from the peroxide oxidation of **6** (Scheme 1) had a mp identical to the compound previously obtained,[7] and is actually 4-pentyl-2-iodosobenzoic

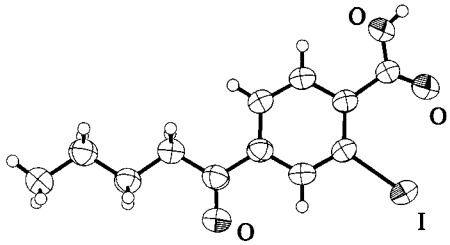


Fig. 1 ORTEP diagram of **X** (4-pentanoyl-2-iodobenzoic acid, **7**)

acid, best represented as **3a** (not **3b**[7]). Thus, **Y** (**3a**) gave both an appropriate elemental analysis [C, 43.l; H, 4.53; I, 38.0%) and NMR spectrum.‖ The IR (KBr) spectrum of **3a** displayed its C=O band at 1602 cm^{-1}, considerably lower than the reported[7] 1650 cm^{-1}. However, benziodoxolone carbonyl bands are very sensitive to conditions of their determination; the C=O absorption of **2** has been variously reported at 1633,[2] 1612,[6b] and 1605[6b] cm^{-1}. Additionally, **3a** showed the expected[2] (I)OH absorptions at 2928 and 2444 cm^{-1}. A standard iodometric titration[13] of **3a** gave 93% of I=O oxidative activity.

Most importantly, **3a** was very reactive toward PNPDPP. Its kinetic properties were assessed from a rate constant–[surfactant] profile for the cleavage of PNPDPP in micellar CTACl;[8b] conditions and results appear in Table 1. Not only is **Y** (**3a**) highly reactive toward PNPDPP, where **X** (**7**) is inactive (entry 2), but **3a** affords an acceleration of 1460 relative to micellar CTACl alone (entry 1), 4.6 times greater than the acceleration provided by the parent IBA (**2**) (entry 3). This reactivity advantage is an expected consequence of the hydrophobic pentyl group of **3a**, which affords better binding of **3a** to the micellar phase in which the phosphorolytic reaction occurs.[8b,c]

Table 1 Rate constants for the cleavage of PNPDPP[a]

Entry	Catalyst	$k_\psi/10^{-4}$ s^{-1}	k_{rel}
1	None[b]	2.05[c]	1.00
2	**X** (**7**)	2.00	0.98
3	**2**	640[d]	312
4	**Y** (**3a**)[e]	3000[f]	1460
5[g]	**2**	18.3	8.9
6[g]	**Y** (**3a**)	63.3	30.9

[a] For background, see ref. 8(*b*). Conditions for entries 1–4: [CTACl] = 1.0×10^{-3} M, [PNPDPP] = 1.0×10^{-5} M, [catalyst] = 1.0×10^{-4} M, pH 8, 0.02 M phosphate buffer, μ = 0.08 (NaCl), 25 °C. Rate constants were determined by monitoring the time dependent absorbance of the released *p*-nitrophenylate ion at 400 nm. [b] CTACl alone. [c] Given as 1.8×10^{-4} s^{-1} in ref. 6(*a*). [d] Ref. 8(*b*). [e] [PNPDPP] = 3.0×10^{-5} M, [Y] = 3.0×10^{-4} M. [f] Stopped-flow determination. [g] Microemulsion conditions:[7] 8% (w/w) CTABr, 8% *N*-methylpyrrolidinone, 4% toluene, 80% 0.03 M aqueous $Na_2B_4O_7 \cdot 10H_2O$ buffer, pH 9.4, 25 °C; [PNPDPP] = 3×10^{-5} M, [catalyst] = 3×10^{-4} M.

Although we could not obtain crystals of **3a** suitable for X-ray analysis, its closed, 'lactone' structure follows from the IR spectrum,[2] and from its kinetic properties toward PNPDPP (which link **3a** to other phosphorolytically reactive iodosobenzoates for which the closed structure has been established).[4–6,8] True 'iodoso' compounds, such as *m*-iodosobenzoic acid, show little esterolytic reactivity.[8a] Additionally, we determined the pK_a of **3a** as 6.8 from a pH–rate constant profile[4c,5,8b] for the cleavage of PNPDPP by **3a** in 0.02 M micellar CTACl and 0.02 M phosphate buffer over the pH range 5.35–7.68. A pK_a ~7 is appropriate for an *o*-iodosobenzoate in the iodoxolone form.[2,8]

Finally, **3a** was reported to be 477 times *less* reactive than IBA itself toward PNPDPP in a CTABr–*N*-methylpyrollidinone–toluene–aqueous borate microemulsion, a phenomenon attributed to incorporation of the more hydrophobic catalyst into the oily interior of the microemulsion.[7] However, we find **3a** to be quite reactive toward PNPDPP under these conditions (Table 1, entry 6); indeed, it is actually ~3.5 times more reactive than IBA (entry 5), paralleling the results in micellar CTACl (see above, and entries 3 and 4). Note (Table 1) that both IBA and **3a** are less reactive toward PNPDPP in the microemulsion than in micellar CTACl, an expected consequence of lessened mutual catalyst/substrate concentration in the microemulsion.[14]

In conclusion, only one 4-pentyl-2-iodosobenzoic acid can be isolated, and it is best represented as iodoxolone **3a**. A similar situation is likely to hold for 4-propyl-2-iodosobenzoic acid[7] as well.

We are grateful to the US Army Research Office for financial support.

Notes and References

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‡ δ_H[$(CD_3)_2CO$, 200 MHz] 0.92 (t, *J* 8, 3H), 1.4 (sext., *J* 8, 2H), 1.7 (pent., *J* 8, 2H), 3.1 (t, *J* 8, 2H), 7.9 (d, *J* 8, 1H), 8.1 (AB dd, *J* 8, 1.6, 1H), 8.5 (d, *J* 1.6, 1H).

§ *Crystal data* for **7**: $C_{12}H_{13}O_3I$, M = 332.12, colorless rods, 0.06 × 0.54 × 0.60 mm, monoclinic, space group $P2_1/n$, a = 4.2397(11), b = 29.477(5), c = 10.222(2) Å, β = 101.92(2)° U = 1249.9(5) $Å^3$, Z = 4, D_c = 1.765 g cm^{-3}, μ(Mo-Kα) = 25.52 cm^{-1}, F(000) = 648. The 2340 total data were collected at 20 °C using graphite monochromatized Mo-Kα radiation (λ = 0.71073 Å), and converged at R_1 = 0.0507, wR_2 = 0.0889 for all 2157 unique data. CCDC 182/910.

¶ Note too that the calculated elemental analysis of **7**, $C_{12}H_{13}IO_3$ [C, 43.4; H, 3.94; I, 38.2%] is nearly within accepted limits of the calculated analysis for **3**, $C_{12}H_{15}IO_3$ [C, 43.1; H, 4.52; I, 38.0%].

‖ δ[$[^2H_6]$DMSO, 200 MHz) 0.83 (t, *J* 8, 3H), 1.3 (m, $2CH_2$, 4H), 1.62 (pent., *J* 8, 2H), 2.75 (t, *J* 8, 2H), 7.5 (d, *J* 8, 1H), 7.6 (s, 1H), 7.9 (d, *J* 8, 2H), 7.95 (s, 1H, OH exchangeable with D_2O).

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Received in Corvallis, OR, USA, 17th April 1998; 8/02902D