

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

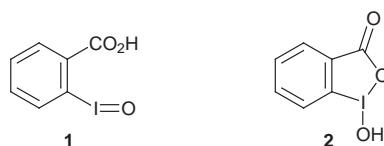
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Contrary to a previous report, only the closed (iodoxolone) form of 4-pentyl-2-iodosobenzoic acid (**3a**) can be isolated; the previously assigned open (iodoso) form (**3b**) is actually 4-pentanoyl-2-iodobenzoic acid.

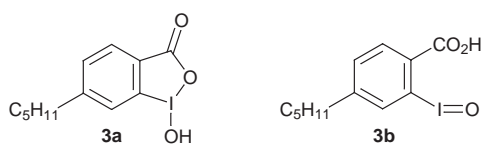
o-Iodosobenzoic acid (IBA, **1**) has long been known¹ to exist in the cyclic 1-hydroxy-1,2-benziodoxol-3(1*H*)-one form (**2**).^{2,3} X-Ray crystal structure⁴ and theoretical studies⁵ agree that the cyclic form is the better representation, although the internal I–O bond is longer than a 'normal' single 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



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}

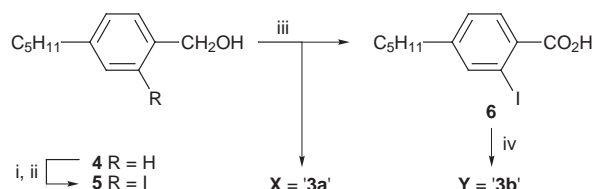
We have now reinvestigated the case of the 4-pentyl 'tautomers' (**3a** and **3b**), and report here that the previously described⁷ compounds were misassigned; in fact, only a single 4-pentyl-2-iodosobenzoic acid can be isolated, and it is best represented as the 'closed' iodoxolone compound, **3a**.



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), assigned⁷ as 4-pentyl-2-iodosobenzoic acid in its cyclic (iodoxolone) form, **3a**. A separate $\text{H}_2\text{O}_2/\text{Ac}_2\text{O}$ oxidation^{7,11} of **6** afforded 4-pentyl-2-iodosobenzoic acid **Y** (mp 188.5–189.5 °C) assigned⁷ as the open (iodoso) valence tautomer, **3b**.

The assignments⁷ of **X** and **Y** rest on acceptable elemental analyses for $\text{C}_{12}\text{H}_{15}\text{IO}_3$, suggestive of isomerism, as well as IR



Scheme 1 Reagents and conditions: i, BuLi, $\text{Me}_2\text{NCH}_2\text{CH}_2\text{NMe}_2$; ii, I_2 ; iii, KMnO_4 – H_2O , C_6H_6 , cat. $\text{Bu}_4\text{P}^+\text{Cl}^-$; 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 known² 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 reported⁷ 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 assigned⁷ 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 overoxidation¹² at the benzylic position of the pentyl chain, affording (both) ketone **7** (and iodo-terephthalic 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

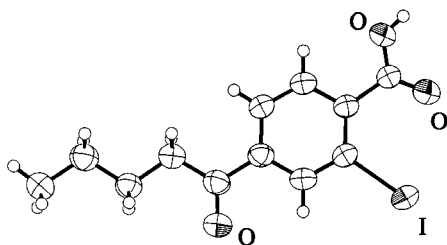


Fig. 1 ORTEP diagram of **X** (4-pentanoil-2-iodobenzoic acid, **7**)

acid, best represented as **3a** (not **3b**⁷). Thus, **Y** (**3a**) gave both an appropriate elemental analysis [C, 43.1; 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 reported⁷ 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 expected² (I)OH absorptions at 2928 and 2444 cm⁻¹. A standard iodometric titration¹³ of **3a** gave 93% of I=O oxidative activity.

Most importantly, **3a** was very reactive toward PNPDP. Its kinetic properties were assessed from a rate constant–[surfactant] profile for the cleavage of PNPDP in micellar CTACl;^{8b} conditions and results appear in Table 1. Not only is **Y** (**3a**) highly reactive toward PNPDP, 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 PNPDP^a

Entry	Catalyst	$k_p/10^{-4} \text{ s}^{-1}$	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] = $1.0 \times 10^{-3} \text{ M}$, [PNPDP] = $1.0 \times 10^{-5} \text{ M}$, [catalyst] = $1.0 \times 10^{-4} \text{ M}$, pH 8, 0.02 M phosphate buffer, $\mu = 0.08$ (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 $1.8 \times 10^{-4} \text{ s}^{-1}$ in ref. 6(a). ^d Ref. 8(b). ^e [PNPDP] = $3.0 \times 10^{-5} \text{ M}$, [Y] = $3.0 \times 10^{-4} \text{ M}$. ^f Stopped-flow determination. ^g Microemulsion conditions:⁷ 8% (w/w) CTABr, 8% *N*-methylpyrrolidinone, 4% toluene, 80% 0.03 M aqueous Na₂B₄O₇·10H₂O buffer, pH 9.4, 25 °C; [PNPDP] = $3 \times 10^{-5} \text{ M}$, [catalyst] = $3 \times 10^{-4} \text{ M}$.

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 PNPDP (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 PNPDP by **3a** in 0.02 M micellar CTACl and 0.02 M phosphate buffer over the pH range 5.35–7.68. A $pK_a \sim 7$ 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 PNPDP in a CTABr–*N*-methylpyrrolidinone–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 PNPDP 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 PNPDP 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 acid⁷ as well.

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Notes and References

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‡ $\delta_{\text{H}}[(\text{CD}_3)_2\text{CO}, 200 \text{ MHz}]$ 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**: C₁₂H₁₃O₃I, *M* = 332.12, colorless rods, 0.06 × 0.54 × 0.60 mm, monoclinic, space group *P*2₁/*n*, *a* = 4.2397(11), *b* = 29.477(5), *c* = 10.222(2) Å, β = 101.92(2)°, *U* = 1249.9(5) Å³, *Z* = 4, *D_c* = 1.765 g cm⁻³, $\mu(\text{Mo-K}\alpha)$ = 25.52 cm⁻¹, *F*(000) = 648. The 2340 total data were collected at 20 °C using graphite monochromatized Mo-K α 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**, C₁₂H₁₃O₃I [C, 43.4; H, 3.94; I, 38.2%] is nearly within accepted limits of the calculated analysis for **3**, C₁₂H₁₃O₃I [C, 43.1; H, 4.52; I, 38.0%].

|| $\delta[{}^2\text{H}_6]\text{DMSO}, 200 \text{ MHz}]$ 0.83 (t, *J* 8, 3H), 1.3 (m, 2CH₂, 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 D₂O).

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