Benziodazoles: Synthesis for Bioactivity Studies

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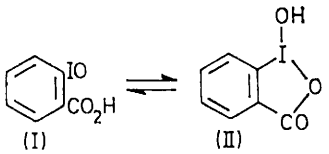
Some new members of the benziodazole series that contain trivalent iodine have been prepared from the appropriate *ortho*-iodobenzamides by oxidation with either chlorine, t-butyl hypochlorite, or peracetic acid. None of the compounds had any worthwhile biological activity.

TRIVALENT organic iodine compounds seem to have received comparatively little attention in the context of possible chemotherapeutic use except for sporadic reports [1-3] on *in vitro* antimicrobial activity of a few aryl iodonium salts. This paper describes the preparation of certain novel benziodazoles for bioactivity tests; the selection of this heterocycle stemmed from the following considerations. The pharmacology of *ortho*-iodo-, *ortho*-iodosyl-, and *ortho*-iodyl-benzoic acids was studied around 1910 by Loevenhart and Grove [4,5] and the antibacterial activity was investigated by Arkin.[6] This activity, and the view current in 1926 that chronic arthritis was probably due to an infection, led Young and Youmans [7] to suggest the trial of *o*-iodylbenzoic acid for such conditions. This was evidently successful by contemporary criteria and certain salts of *o*-iodylbenzoic acid were on the market in the 1930's.

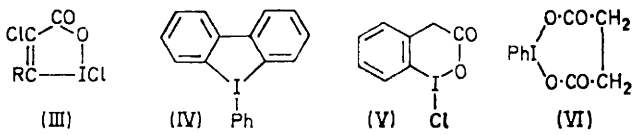
More recently Chinard [8] suggested, on the basis of



(I) (II)

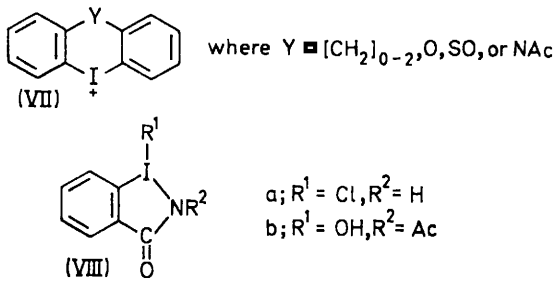
some exploratory animal experiments, that *o*-iodosylbenzoic acid might be tried as a tropical bactericide for wounds. *o*-Iodosylbenzoic acid (I), which embodies iodine in the trivalent oxidation state, was described in 1892 by Meyer and Wachter,[9] who suggested that it might exist in tautomeric equilibrium with the cyclic form (II). Later, Willgerodt [10] summarised the evidence in favour of this structure.

Baker, Mann, Sheppard, and Tetlow [11] have recently adduced chemical and i.r. spectral evidence in support of this early speculation and have reviewed the status



(III) (IV) (V) (VI)

of the iodoxolen and other kindred ring systems, (III)—(VI), containing iodine as a hetero atom. The heterocyclic iodonium salts (VII) have been described by



(VII) (VIII)

Wen-Kuei Hwang and his co-workers [12-14] and Beringer, Kravetz, and Topliss.[15]

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[12] Wen-Kuei Hwang, *Sci. Sinica*, 1957, **6**, 123 (*Chem. Abs.*, 1957, **51**, 16476b).
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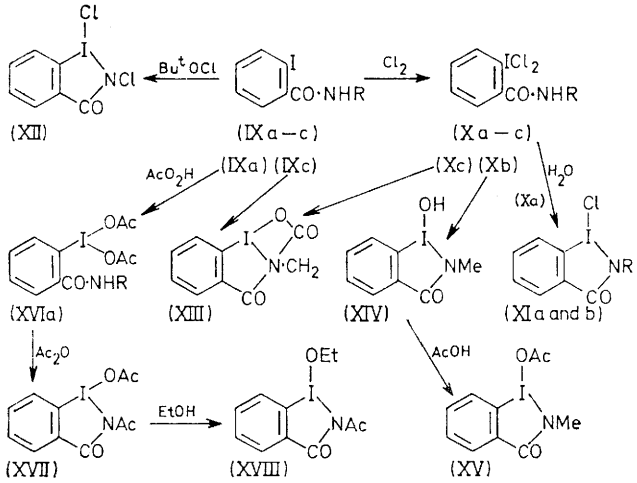
The recent report by Wolff and Steinberg [16] on the benziodazole compounds (VIIIa and b) interested us because this novel heterocyclic system can be regarded as the nitrogen analogue of the heterocyclic iodoxole form (II) of *o*-iodosylbenzoic acid, for which some antibacterial activity had been claimed. Though it seemed probable that this activity was of a non-specific character and was merely associated with the oxidative power of the trivalent iodine, we thought the benziodazole system merited some scrutiny. Accordingly, we attempted the preparation of a few representative compounds for wide exploratory screening for bioactivity. However, since these benziodazoles were very insoluble in water, acetone, and other solvents acceptable in biological test systems, we attempted to confer solubility by introduction of suitable substituents, including basic and acid groups with salt-forming characteristics. However, the chemistry proved unfavourable for such operations and the biological results were discouragingly negative, so we abandoned the programme and now report the few points of chemical interest. The compounds containing trivalent iodine often proved difficult to purify, since solubilities limited the choice of solvent and during crystallisation some decomposition was liable to occur. Moreover the vigorous or near explosive decomposition upon heating that frequently occurred often made elemental analysis difficult and inexact.

The oxidising agents used for conversion of the monovalent iodine in *ortho*-iodobenzamides were elemental chlorine in chlorinated hydrocarbon solvents,[16] acetic acid, t-butyl hypochlorite,[17] and peracetic acid.[18]



SCHEME

a; R = H. b; R = Me. c; R = $CH_2 \cdot CO_2H$

The reaction Scheme is illustrated. The chlorination of *o*-iodobenzamide (IX) with elemental chlorine has been described by Wolf and Steinberg,[16] who presumed the formation of the dichloride (Xa) but did not characterise it before converting it into the benziodazole (XI). We have confirmed the identity of both these compounds, obtained by Wolf and Steinberg's method,[16] and have extended the reaction to the *N*-substituted benzamides (IXb and c), the latter with the idea of providing a carboxy-group which would give soluble salts. The reactions of the *N*-methylbenzamide followed more or less the expected courses save that we were able to isolate the *N*-methylbenziodazole (XIV), whereas we failed with the compound (Xc). The *N*-methyl compound (XIV) was acylated smoothly to give the acetate (XV). The hydrolysis of the iodochlorides was affected by the character of the substituent on the amide nitrogen.

According to Altenkirk and Israelstam,[17] chlorination of *o*-iodobenzamide (IXa) with t-butyl hypochlorite gives *N*-chloro-2-iodobenzamide, described as a white crystalline compound, m.p. 176—177°. In our hands this procedure gave a bright yellow, crystalline compound (40%), m.p. 178—181°, together with much unchanged *o*-iodobenzamide. The elemental analysis corresponded to the empirical formula $C_7H_4Cl_2INO$ and the i.r. spectrum showed no OH or NH peaks and C=O at 1660 cm.$^{-1}$; when the quantity of t-butyl hypochlorite used was increased to that stoicheiometrically required for the introduction of two chlorine atoms, the yield of this compound was increased to 84%. These observations are wholly consistent with the structure (XII). The discrepancy between our results and those of Altenkirk and Israelstam [17] was not further investigated as the introduction of a chloro-substituent on the nitrogen atom was not of interest for our study.

When the *ortho*-iodobenzamides were oxidised with peracetic acid, a different pattern emerged. The *o*-iodobenzamide (IXa) readily gave the diacetoxy-iodo-compound (XVIa), whereas the *N*-methyl compound (IXb) did not react. The *N*-acetic acid (IXc) gave the tricyclic compound (XIII), which was also obtained readily by hydrolysis of the dichloro compound (Xc). The diacetate (XVIa) was cyclised by treatment with acetic anhydride to the benziodazole (XVII), which reacted readily with ethanol to give the ethoxy-compound (XVIII), analogous to the iodoxole compound reported by Baker and his co-workers.[11] However, extension of this reaction to the use of diethylaminoethanol produced unidentified and unattractive products.

All the trivalent iodine compounds in this series liberated two atoms of iodine from potassium iodide solution; titration of this with standard thiosulphate confirmed the identity of the products.

The products (XIa), (XIb), (XV), (XII), (XIII), (XVII), and (XVIII) were tested against a range of viral, bacterial, fungal, protozoal, and helminth

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organisms but none showed an interesting level or type of activity; work in these series was therefore discontinued.

EXPERIMENTAL

o-(*Dichloroiodo*)-N-*methylbenzamide* (Xb).—*o*-Iodo-*N*-methylbenzamide (13 g., 0·05 mole) in 1,1,2,2-tetrachloroethane (125 ml.) was treated with a stream of dry chlorine at 0° for 4 hr. The resulting yellow precipitate of the *dichloride* was washed with the same solvent, then with ether, and dried *in vacuo* at room temp.; the yellow amorphous powder (14·8 g., 89%) had m.p. 154° (Found: C, 28·4; H, 2·5; I, 37·3. $C_8H_8Cl_2INO$ requires C, 28·9; H, 2·4; I, 38·3%).

1-*Chloro*-2-*methyl*-1,2-*benziodazol*-3(2H)-*one* (XIb).—Thorough grinding of the dichloride with water gave the *benziodazole*, a pale cream powder (58%), m.p. 176—177° (decomp.) (Found: C, 32·7; H, 2·4; I, 43·0. C_8H_7ClINO required C, 32·5; H, 2·4; I, 42·9%).

N-[o-(*Dichloroiodo*)*benzoyl*]*glycine* (Xc).—Chlorine was passed into a filtered solution of *o*-iodobenzoylglycine (15·25 g., 0·05 mole) in glacial acetic acid (450 ml.), with stirring, for 4 hr. at room temp. The precipitate of the *dichloride* was washed successively with acetic acid and ether to give a bright yellow powder (14·7 g., 78%), m.p. 138° (Found: C, 29·4; H, 2·2; I, 33·2. $C_9H_8Cl_2INO_3$ required C, 28·7; H, 2·1; I, 33·8%).

5H-[1,2,5]*Iodoxazolo*[1,5-a][1,2]*benziodazole*-2(3H),5-*dione* (XIII).—Trituration of the dichloride with water gave the *lactone*, a white powder (91%), m.p. 234° (decomp.) (Found: C, 35·7; H, 2·0; I, 41·7. $C_9H_6INO_3$ requires C, 35·7; H, 2·0; I, 41·9%).

1,2-*Dichloro*-1,2-*benziodazole*-3(2H)-*one* (XII).—*o*-Iodobenzamide (4·9 g., 0·02 mole) dissolved in methanol (90 ml.) was treated with t-butyl hypochlorite (7·7 g., 0·07 mole) and stirred at room temp. The bright yellow precipitate of the *dichlorobenziodazole* which was formed almost at once, was filtered off, and washed with methanol. It formed bright yellow plates (84%), m.p. 184° (decomp.) (Found: C, 26·9; H, 1·3; I, 40·7. $C_7H_4Cl_2INO$ requires C, 26·6; H, 1·3; I, 40·3%).

1-*Hydroxy*-2-*methyl*-1,2-*benziodazol*-3(2H)-*one* (XIV).—*o*-Dichloro-*N*-methylbenzamide (33·2 g.), anhydrous sodium carbonate (25 g.), and crushed ice (50 g.) were ground together in a glass mortar (chilled in ice) until the ice had melted and a thick cream-coloured paste was formed. 5N-Sodium hydroxide (70 ml.) was then added in portions of 10 ml. with external cooling and trituration after each addition; water (150 ml.) was then added and the white slurry was kept at 0° overnight. The precipitate was washed with water, dried *in vacuo* (P_2O_5), and then washed with chloroform to remove unchanged amide. The crude benziodazole, a white powder (15 g., 54%), m.p. 166° (slight detonation), was used directly for conversion into the acetyl derivative.

1-*Acetoxy*-2-*methyl*-1,2-*benziodazol*-3(2H)-*one* (XV).—The hydroxy-compound (XIV) (13 g., 0·05 mole) was warmed with glacial acetic acid (25 ml.) until a solution was obtained. This was filtered while hot, then cooled, and the *acetoxy*-derivative was precipitated with ether, as a white amorphous solid (13·1 g., 88%), m.p. 168° (decomp.) (Found: C, 37·0; H, 3·2; N, 4·3. $C_{10}H_{10}INO_3$ requires C, 37·6; H, 3·1; N, 4·2%).

o-*Iodobenzamide Diacetate* (XVIa).—A suspension of *o*-iodobenzamide (24·8 g., 0·1 mole) in glacial acetic acid (80 ml.) was heated to 50—60°. Peracetic acid (Laporte) (40%; 24·8 ml.) was added gradually with stirring, whereupon the solid dissolved. The solution was heated at 50—60° for a further 15 min. and then cooled to give the *diacetate*, colourless needles (16·6 g., 46%), m.p. 198—200° (decomp.) (Found: C, 36·2; H, 3·1; I, 35·2. $C_{11}H_{12}INO_5$ requires C, 36·2; H, 3·3; I, 34·8%).

1-*Acetoxy*-2-*acetyl*-1,2-*benziodazol*-3(2H)-*one* (XVII).—The diacetate (XVIa) (35·4 g., 0·097 mole) was heated with acetic anhydride (250 ml.) to just below the b.p.; the solid then dissolved. The solution was filtered immediately (prolonged heating leads to decomposition of the product) and cooled to give the *product* (35·6 g., 100%) as lustrous plates, m.p. 192—193° (decomp.) (Found: C, 38·1; H, 2·8; I, 36·8. $C_{11}H_{10}INO_4$ requires C, 38·1; H, 2·9; I, 36·6%).

2-*Acetyl*-1-*ethoxy*-1,2-*benziodazol*-3(2H)-*one* (XVIII).—The acetoxy-derivative (XVII) (10 g.) was refluxed gently with ethanol (120 ml.) for 30 min. The hot solution was filtered and cooled to give the *ethoxybenziodazole* as colourless needles (7·5 g., 78%), m.p. 195° (Found: I, 38·2; N, 4·3. $C_{11}H_{16}INO_3$ requires I, 38·2; N, 4·2%).

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