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OXIDATIVE CYCLIZATION OF HALOBENZOPHENONE OXIMES TO 4,2'-IODONIA-3-PHENYL-1,2-BENZISOXAZOLE SALTS

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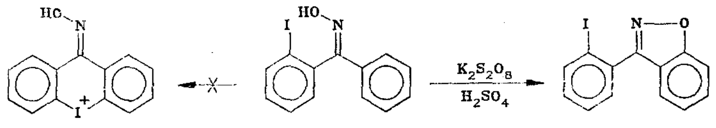
It is shown that the syn oximes of o-iodo- and o-, m-, and p-bromobenzophenones, under the influence of $K_2S_2O_8$ in concentrated H_2SO_4, form the corresponding 3-aryl-1,2-benzisoxazoles as a result of oxidative cyclization. 3-(2-Iodophenyl)-1,2-benzisoxazole is oxidized by peracetic acid to the iodoso derivative which, upon heating in concentrated H_2SO_4, undergoes cyclization to the 4,2'-iodonia-3-phenyl-1,2-benzisoxazole cation. The iodide, bromide, and tetrafluoroborate of this cation were isolated.

It is known that oximes of ketones are key compounds in the synthesis of a number of heterocycles, including isoxazoles and 1,2-benzisoxazoles [1]. Recently a great deal of attention has been directed to the oxidation of oximes and, chiefly, oxidative deoximation [2-4]. Several examples of the oxidative cyclization of the oximes of some not completely trivial ketones have also been described. Thus, oximes of ketones that contain a hydroxyphenyl group in the α position, under the influence of brominating agents [5], Mn^{3+} salts [6], or $Tl(NO_3)_3$ [7], give spiroisoxazolines, whereas the isomeric oximes of 2-arylidene-3-oxoquinuclidines, under the influence of Ag_2O, undergo cyclization to give five- or seven-membered heterocycles, depending on the configuration [8].

In the present paper we report a new oxidative cyclization reaction in which halobenzophenone oximes participate and describe salts of an iodonium cation that is a new heterocyclic system made up of four fused rings and is obtained as a result of double oxidative cyclization of 2-iodobenzophenone oxime.

We have previously synthesized 10-oxodibenz[b,e]iodinium salts and showed that they do not form an oxime at the carbonyl group [9]. In order to study the Beckmann rearrangement in a series of cyclic iodonium compounds we attempted to obtain 10-oximinodibenz[b,e]iodinium salts by alternative synthesis, viz., by oxidative cyclization of 2-iodobenzophenone syn-oxime (I). However, upon treatment of the latter with $K_2S_2O_8$ in concentrated H_2SO_4 cyclization pro-



HSO_4^- I II

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ceeded in another direction, and 3-(2-iodophenyl)-1,2-benzisoxazole (II) was formed in 70% yield instead of the expected cyclic iodonium salt.

The structure of II was established on the basis of the mass spectrum,* which, in addition to a molecular ion at 321 $[C_{13}H_8INO]^+$, contained peaks at 293 $[C_{12}H_8IN]^+$, 203 $[C_6H_4I]^+$, and 76 $[C_6H_4]^+$, which unambiguously prove that the iodine atom is located in the 3-phenyl substituent. Fragmentation of the molecular ion with the ejection of a CO fragment is characteristic for benzisoxazoles [10].

2-Bromobenzophenone syn-oxime behaves similarly under the same conditions and is converted in 60% yield to 3-(2-bromophenyl)-1,2-benzisoxazole (III), the structure of which was also confirmed by the mass spectrum (see the experimental section). We found that the yields of the benzisoxazoles in our reaction are determined both by the nature of the halogen and its position in the benzophenone ring. Thus 2-chlorobenzophenone syn-oxime does not undergo this reaction, and 4- and 3-bromobenzophenone syn-oximes undergo cyclization with considerably greater difficulty than the corresponding 2-bromo isomer. In both cases the cyclization gives the product in only about 12% yield. In addition to 3-(4-bromophenyl)- (IV) and 3-(3-bromophenyl)-1,2-benzisoxazole (VI), the corresponding bromobenzophenones (21% of the 4-bromo isomer and 6.5% of the 3-bromo isomer), 20% and 13%, respectively, of the starting oximes were recovered. The reactions are accompanied by pronounced resinification. Compounds III, IV, and VI were characterized by the UV spectra, which were similar to the spectrum of unsubstituted 3-phenyl-1,2-benzisoxazole.

We found that our reaction is characteristic only for oximes of iodo- and bromobenzophenones. The oxime of benzophenone itself is oxidized by potassium persulfate in concentrated H_2SO_4 to benzoic acid, whereas, under milder conditions, viz., by the action of peracetic acid on it, we were able to isolate also intermediate oxidation products, viz., phenyl benzoate and benzophenone, in low yields. Thus, under our conditions, benzophenone oxime evidently initially undergoes oxidative deoximation, and the resulting benzophenone then undergoes Baeyer—Villiger oxidation.

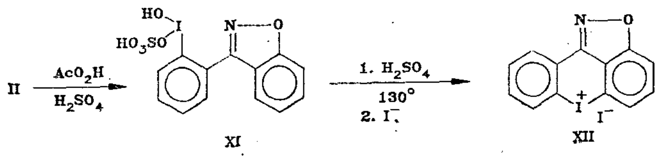
The oximes of benzophenones with electron-donor substituents (4-methoxy and 2-methoxy) undergo complete resinification under the conditions that we tested. However, the oximes of 2-nitro- (60%) and 4,4'-dinitrobenzophenone (94%) are basically recovered unchanged.

In the case of 2-iodobenzophenone syn-oxime we showed that the presence of both reagents, viz., the oxidizing agent and sulfuric acid, is necessary for successful realization of the cyclization. In the absence of sulfuric acid cyclization does not take place. We also showed that the presence of only concentrated H_2SO_4 without an oxidizing agent does not give rise to syn-anti isomerization of the oxime.

We assume that the oxidative cyclization of the oximes begins with protonation of the oxime, which is followed by attack by the oxidizing agent on the nitrogen atom and cyclization in the ortho position of the less electron deficient of the two benzene rings, which leads, with splitting out of water and a proton, to the formation of the benzisoxazole ring.

It is known that the Beckmann rearrangement of oximes of o-substituted acetophenones proceeds considerably more rapidly than the rearrangement of oximes of the corresponding para isomers [11]. It is assumed that the reason for this is destabilization of the o-substituted oxime as a consequence of disruption of the coplanarity of the oxime group and the benzene ring. Evidently, the same reason, viz., stabilization of the oxime by conversion to the sterically unhindered aromatic system, in our case leads to especially facile cyclization of the syn oximes of 2-iodo- and 2-bromobenzophenone.

3-(2-Iodophenyl)-1,2-benzisoxazole is readily oxidized by peracetic acid in the presence of concentrated H_2SO_4 to the corresponding iodoso derivative, which is isolated from the re-



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*Here and subsequently, the m/z values are given for the ion peaks.

TABLE 1. Characteristics of the Synthesized Compounds

Compound	mp,* °C	Found, %			Empirical formula	Calc., %			Yield, %
		C	H	N(I)		C	H	N(I)	
II	92—93	48,5	2,4	4,4	$C_{13}H_8INO$	48,6	2,5	4,4	70
III	49,5—51	57,1	2,9	5,1	$C_{13}H_8BrNO$	57,0	2,9	5,1	60
VI	93—94	56,9	3,0	5,1	$C_{13}H_8BrNO$	57,0	2,9	5,1	12
XI	159—161	35,3	2,3	3,2	$C_{13}H_{10}INO_6S$	35,8	2,3	3,2	85
XII	140	35,2	1,7	3,1	$C_{13}H_7I_2NO$	34,9	1,6	3,1	81
XIII	251—252	38,5	2,0	3,3	$C_{13}H_7INO \cdot BF_4$	38,4	1,7	3,4	80
XIV	190,5—193	38,9	1,6	3,3	$C_{13}H_7BrINO$	39,0	1,8	3,5	44
XV	142—143	34,9	1,5	3,3 (56,7)	$C_{13}H_7I_2NO$	34,9	1,6	3,1 (56,8)	98

*Compound II was crystallized from n-butanol, and III, VI, and XV were crystallized from hexane; XI-XIV decomposed.

action in the form of the hydroxybisulfate. The latter undergoes cyclization in concentrated H_2SO_4 at 130°C to give the 4,2'-iodonia-3-phenyl-1,2-benzisoxazole cation, which is isolated in the form of the iodide (XII), which is only slightly soluble in water.

The corresponding tetrafluoroborate and bromide were obtained from it by exchange reactions. According to the results of x-ray diffraction analysis,* regarding which more details will be reported separately, the four-ring 4,2'-iodonia-3-phenyl-1,2-benzisoxazole tetrafluoroborate is almost planar, whereas the iodonium ring has a slightly expressed sofa conformation (the iodine atom deviates 0.11 Å from the plane of the five coplanar carbon atoms) with 4.6° bending along the line connecting the two carbon atoms bonded to the iodonium atom.

The thermal decomposition of 4,2'-iodonia-3-phenyl-1,2-benzoxazole iodide proceeds surprisingly cleanly leading to 4,2'-diodo-3-phenyl-1,2-benzisoxazole in 98% yield. However, the thermolysis of the corresponding bromide, judging from the mass spectrum of the reaction products, led, as expected, to a mixture of 4-iodo-2'-bromo- and 4-bromo-2'-iodo-1,2-benzisoxazoles, as well as small amounts of 4,2'-diiodo- and 4,2'-dibromo-3-phenyl-1,2-benzisoxazoles. It should be noted that the formation of fluoreno[9,1-c,d]isoxazole is not observed in the thermolysis of both of our salts, in contrast to the thermolysis of other iodonium cations with iodine in the six-membered ring, which leads not only to the formation of dihalo derivatives but also to the formation of the corresponding five-membered ring with the liberation of iodine [12-14]. The yields, constants, and analytical data for all of the compounds described for the first time are presented in Table 1.

EXPERIMENTAL

2-Iodobenzophenone syn-Oxime (I). A 2-ml sample of concentrated H_2SO_4 was added to a solution of 11 g (36 mmole) of 2-iodobenzophenone, obtained by the method in [15], and 7.92 g (114 mmole) of $NH_2OH \cdot HCl$ in 250 ml of isoamyl alcohol, and the mixture was refluxed for 23 h with periodic removal of the resulting water by distillation, after which it was cooled and poured into 200 ml of water. The organic layer was evaporated *in vacuo* to a small volume and treated with excess petroleum ether. The precipitated oxime I was washed with petroleum ether and dried *in vacuo* to give 8.58 g (74%) of a product with mp 151-153°C (from 50% aqueous alcohol) (according to [15], this compound had mp 152°C).

3-(2-Iodophenyl)-1,2-benzisoxazole (II). A 1.25-g (5 mmole) sample of finely ground $K_2 \cdot S_2O_8$ was added gradually with stirring at −15°C to a solution of 1 g (3 mmole) of oxime I in 25 ml of concentrated H_2SO_4, and the mixture was maintained at −15°C for 3 h. It was then poured over 150 g of ice, and the aqueous mixture was treated with excess Na_2SO_3. Extraction with ether gave 0.71 g (70%) of II.

3-(2-Bromophenyl)-1,2-benzisoxazole (III). A procedure similar to that used to prepare oxime I gave 2.06 g (68%) of 2-bromobenzophenone syn-oxime, with mp 132°C (mp 132-133°C [17]), from 2.88 g (11 mmole) of 2-bromobenzophenone, synthesized by the method in [16], and 2.45 g

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*The x-ray diffraction analysis was carried out by A. S. Batsanov, V. N. Petrov, and Yu. T. Struchkov in the Institute of Heteroorganic Compounds of the Academy of Sciences of the USSR, for which we express our thanks.

(35.5 mmole) of $NH_2OH \cdot HCl$ in 30 ml of isoamyl alcohol. A 2.5-g (9.2 mmole) sample of finely ground $K_2S_2O_8$ was then added in small portions with stirring at −15°C to a solution of 0.84 g (3 mmole) of the oxime in 25 ml of concentrated H_2SO_4, and the mixture was maintained at −15°C for 2 h, 7 days at 20°C, and poured over 100 g of ice. The reaction products were extracted with ether, the ether was removed, and 0.49 g (60%) of isoxazole III was isolated from the residue in ascending chromatography on silica gel (5/40 μ) in CCl_4. Mass spectrum: 273 + 275 $[C_{13}H_8BrNO]^+$, 245 + 247 $[C_{12}H_8BrN]^+$, 194 $[C_{13}H_8NO]^+$, 166 $[C_{12}H_8N]^+$, 155 + 157 $[C_6H_4Br]^+$, and 76 $[C_6H_4]^+$.

3-(4-Bromophenyl)-1,2-benzisoxazole (IV). A 1.5-g (5 mmole) sample of $K_2S_2O_8$ was added in portions at −15°C to a solution of 1 g (3.6 mmole) of 4-bromobenzophenone syn-oxime (V) {obtained by the method in [18], mp 170-172°C (mp 168-170°C [18])}, and the mixture was maintained at −15°C for 2.5 h and at 20°C for 9 days, during which time three 1.5-g portions of $K_2S_2O_8$ were added. The mixture was then poured over 100 g of ice, and the reaction products were extracted with ether. From the residue after removal of the ether, we used ascending chromatography with a column packed with silica gel (5/40 μ) in CCl_4 to give 0.09 g (11.5%) of IV {mp 127-129°C (mp 132-133°C [19])} and 0.16 g (21%) of 4-bromobenzophenone {mp 79-80°C (mp 81.5-82°C [20])}, after which elution with benzene gave 0.2 g of oxime V.

3-(3-Bromophenyl)-1,2-benzisoxazole (VI). This compound was obtained in a manner similar to that in the preceding experiment from 1 g (3.6 mmole) of 3-bromobenzophenone syn-oxime (VII) (synthesized by the method in [21], mp 175°C). The yield of VI was 0.1 g (12%); also isolated were 0.05 g (6.5%) of 3-bromobenzophenone with mp 76-78°C (mp 77°C [21]) and 0.13 g of oxime VII.

Oxidation of Benzophenone Oxime (VIII). A) With Potassium Persulfate: A 4.6-g (17 mmole) sample of $K_2S_2O_8$ was added in portions at −10°C to a solution of 2.28 g (11.5 mmole) of oxime VIII in 95 ml of concentrated H_2SO_4, and the mixture was maintained at −18°C for 3 h and at 20°C for 12 h and then poured over 200 g of ice. The aqueous mixture was extracted with ether, and the ether was removed by distillation to give 1.26 g (90%) of benzoic acid with mp 122°C.

B) With Peracetic Acid: A 2.2-ml sample 29% H_2O_2 (21 mmole) and 1.5 ml of concentrated H_2SO_4 were added dropwise at −25°C to a solution of 0.69 g (3.5 mmole) of oxime in 6.5 ml of acetic anhydride, and the mixture was maintained at −20°C for 3 h, at 20°C for 4 days, and at 60°C for 32 h and then poured over 50 g of ice. The dark solution was extracted with CCl_4, and the extract was distilled to give 0.38 g of a residual colored oily substance. Chromatography with a column packed with silica gel (5/40 μ) in benzene yielded 0.08 g (11%) of phenyl benzoate with mp 68-69°C (mp 69°C [22]) and 0.03 g (4%) of benzophenone, which was identified by TLC. Benzoic acid was not eluted.

Attempt to Oxidize the Nitrobenzophenone Oximes. A) 2-Nitrobenzophenone syn-Oxime (IX): As in the case of oxime I, 1.45 g (6.4 mmole) of 2-nitrobenzophenone, obtained by the method in [23], yielded 1.54 g (99%) of oxime IX with mp 123-125°C (mp 122-123°C [24]). A 0.85-g (3.5 mmole) sample of IX was treated as in the preparation of isoxazole IV, and the reaction mixture was maintained at 20°C for 5 days. The markedly darkened mass was poured over 100 g of ice, and the aqueous mixture was extracted with ether to give 0.5 g (59% of the amount used) of oxime IX with mp 123°C.

B) 4,4'-Dinitrobenzophenone Oxime (X): A 1.03-g (3.6 mmole) sample of X, synthesized by the method in [25] and having mp 193-195°C (mp 195° [25]), was treated as in the preparation of isoxazole IV, and the reaction mixture was maintained at 20°C for 4 months. It was then poured over 100 g of ice, and the aqueous mixture was extracted with ether to give 0.97 g (94% of the amount used) of oxime X with mp 195°C.

3-(2-Iodosophenyl)-1,2-benzisoxazole Hydroxybisulfate (XI). A solution of 0.5 g (1.6 mmole) of isoxazole II in 8 ml of acetic anhydride and 3 ml of 29% H_2O_2 (30 mmole) were added dropwise successively to 13 ml of H_2SO_4 at −15°C, and the mixture was maintained at −15°C and at 20°C for 1 day and then poured over 50 g of ice. The iodoso compound X that precipitated after standing in a refrigerator was removed by filtration, and the filtrate was extracted with ether to give 0.09 g of isoxazole II, which was washed with acetone and dried *in vacuo* to give 0.59 g (85%) of XI.

4,2'-Iodonia-3-phenyl-1,2-benzisoxazole Salts. A) Iodide (XII): A solution of 0.45 g of XI in 30 ml of concentrated H_2SO_4 was maintained at 130°C for 1 h and then poured over 200 g of ice. The resulting aqueous solution of 4,2'-iodonia-3-phenyl-1,2-benzisoxazole bisulfate was washed with ether to remove the nonsaltlike substances, and iodide XII was precipitated by the addition of NaI, washed with acetone and ether, and dried. The yield was 0.36 g (81%).

B) Tetrafluoroborate (XIII): A 0.35-g sample of XII was treated with excess triethyloxonoium tetrafluoroborate in nitromethane by the method in [9] to give 0.26 g (80%) of tetrafluoroborate XIII.

C) Bromide (XIV): A 0.3-g (0.7 mmole) sample of tetrafluoroborate XIII in 100 ml of water was dissolved by heating, after which the addition of NaBr precipitated 0.13 g (44%) of bromide XIV.

Thermolysis of XII. A 0.1-g (0.2 mmole) of iodide XII was heated in a sealed ampul at 145°C for 10 min, after which it was cooled, and the contents of the ampul were dissolved in $CHCl_3$, and the liberated iodine (2%) was titrated with thiosulfate. Removal of the $CHCl_3$ gave 0.098 g (98%) of 4,2'-diiodo-3-phenyl-1,2-benzisoxazole (XV) with mp 142-143°C (from hexane).

Thermolysis of XIV. A 0.1-g (0.25 mmole) sample of bromide XIV was heated in a sealed ampul at 200°C for 10 min, after which it was cooled, and the contents of the ampul were dissolved in $CHCl_3$, and the solution was decolorized with thiosulfate. The $CHCl_3$ was removed to give 0.09 g (90%) of a mixture of 4,2'-dihalo-3-phenyl-1,2-benzisoxazoles, which melted over the 90-95° range. Mass spectrum: 447 $[C_{13}H_7I_2NO]^+$, 401 + 399 $[C_{13}H_7BrINO]^+$, 373 + 371 $[C_{12}H_7BrIN]^+$, 355 + 353 + 351 $[C_{13}H_7Br_2NO]^+$, 320 $[C_{13}H_7INO]^+$, 292 $[C_{12}H_7IN]^+$, 274 + 272 $[C_{13}H_7BrNO]^+$, 246 + 244 $[C_{12}H_7BrN]^+$, 203 $[C_6H_4I]^+$, 193 $[C_{13}H_7NO]^+$, 165 $[C_{12}H_7N]^+$, and 157 + 155 $[C_6H_4Br]^+$.

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