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RESEARCHES ON OXAZOLES

II. Halogen Derivatives of Phenyloxazoles*

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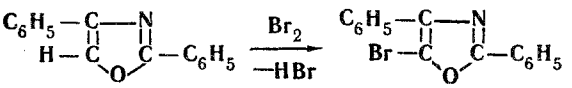
Bromine, and, for the first time, iodine, are inserted at various positions in the 1, 3-oxazole ring by halogenating mercury derivatives of oxazole. Thus, unlike what is obtained by direct halogenation, halogen derivatives of oxazole are available independently of alkyl or phenyl substituents already present in the ring. Direct halogenation of phenyl-substituted oxazoles is reviewed, and in this connection 2, 4-diphenyloxazole is brominated directly. α-Bromo derivatives of 1, 3-oxazole are also synthesized.

Halogen derivatives of oxazole are of interest as fluorescent compounds, or as starting materials for synthesizing other fluorescent compounds containing the oxazole ring.

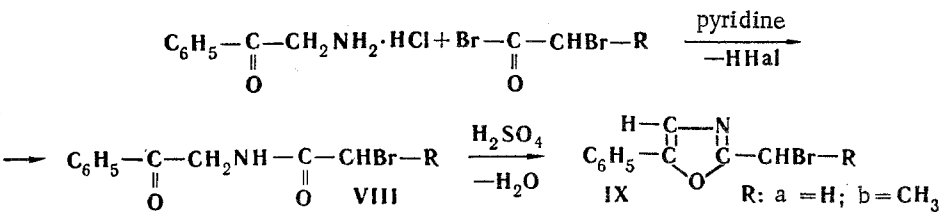
Chlorination [2] and bromination [3, 4] of oxazole derivatives were studied by Gompper and coworkers. They showed that chlorination leads to decomposition of the oxazole, or addition of chlorine to the oxazole ring [3], while bromination, depending on the reaction conditions, results in formation of bromine-oxazole adducts, bromination of the oxazole ring, or alkyl side-chain bromination. Bromination of oxazole phenyl groups was never observed.

By indirect halogenation we have prepared a number of oxazole halogen derivatives with halogen in the oxazole ring, in the alkyl side chain or in the aryl substituent. Halogenation (bromination derivatives or iodination) of previously synthesized [1] mercury derivatives of oxazole, in aqueous (analogous to [5]) or carbon tetrachloride solution led to insertion of bromine, and, for the first time, of iodine, at various positions in the 1, 3-oxazole ring, among them positions inaccessible by direct bromination. Thus it is possible to halogenate position 2, at which, according to [4], direct electrophilic halogenation reactions do not take place. According to the literature [3], and work done by us, 2, 5-diphenyloxazole does not undergo direct bromination, but gives only bromine adducts, though 2-methyl-5-phenyl-1, 3-oxazole can be brominated directly to give a good yield of the 2-bromo derivative; the present method of indirect bromination can be used to prepare 4-bromo- and 4-iodo derivatives (III and IV, see table) of the former. In this connection it was of interest to ascertain the effects of phenyl groups at positions 2 and 4 and on the direct bromination of the 1, 3-oxazole ring. As direct halogenation of 2, 4-diphenyl-1-3-oxazole had not been studied, we undertook bromination of their compound, and found that unlike 2, 5-diphenyl-1, 3-oxazole, reaction at position 5 was rapid, and the yield of product good:



Here, as with other oxazole derivatives [3], reaction is initially followed by formation of adducts between the bromine-substituted oxazole and bromine, and decomposition of these adducts with water or ammonia gives a free bromine compound which is identical with that obtained by reacting the corresponding oxazole mercury derivative with bromine (I, table). Such response of phenoxazoles to bromination may be due to different electron density distributions in the heterocyclic ring caused by substituents [6].

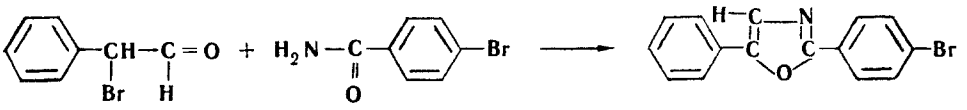
Our route to 2-(α-bromoalkyl)-5-phenyl-1, 3-oxazoles, which gave good yields, was [7]



* For Part I see [1].

The amidoketones VIII were generally prepared by heating together the starting materials dissolved in pyridine, which functioned as an acceptor of the hydrogen halide. However, when synthesizing VIIIa, the actual precise amount of pyridine required was one-third of what was needed to combine with the two molecules of halogen hydride liberated in the reaction. If less pyridine was used, reaction was incomplete, while larger amounts gave oily material and the yield of IXa was greatly reduced. But even in preparing the homolog VIIIb, such close control over the quantity of pyridine proved superfluous, and the reaction followed one course even when considerable excess pyridine was used.

2-(p-Bromophenyl)-5-phenyl-1,3-oxazole can be obtained in good yield according to the equation [8]



Experimental

Preparation of halogenoxazoles from mercurioxazole compounds. The appropriate oxazolemercuriacetate was prepared as described in [1], and 0.01 mole was suspended in 30–40 ml CCl_4, stirred, and 0.011 mole bromine (or 0.01 mole iodine) added dropwise at such a rate that decolorization ensued. After the halogen had been added, the reaction products were boiled for 1 hr, cooled, the precipitate of inorganic mercury salt filtered off, and the mother liquor vacuum-evaporated. The resultant yellow, usually oily product, was purified by recrystallizing from 80–90% aqueous MeOH, the solution being filtered through a layer of aluminum oxide plus one of activated carbon. Then the material was recrystallized from petrol ether or vacuum-fractionated.

Halogenoxazoles can also be obtained in good yield by adding, over a period of 2 hr, to a stirred suspension of 0.01 mole oxazolemercuriacetate in 50 ml water, a solution of 0.02 mole iodine and 0.1 mole KI in 35 ml water. In the case of iodine, the reaction was run at room temperature, while with bromine plus KBr in water, it was run at 0° C. At the end of the reaction, the products were decolorized with $Na_2S_2O_3$, extracted with $CHCl_3$, the bulked extracts dried over $CaCl_2$, the solvent vacuum-distilled off, and the reaction product purified as described above.

The oxazoles substituted in the ring were colorless crystalline compounds melting higher than the corresponding unsubstituted compounds, and soluble in organic solvents, insoluble in water.

The table gives the properties of the halogenoxazoles obtained from oxazolemercuriacetates.

Bromination of 2,4-diphenyl-1,3-oxazole. 0.44 g (0.002 mole) 2,4-diphenyl-1,3-oxazole was dissolved in 9 ml CCl_4, the solution stirred, and 0.48 g (0.006 mole) Br_2 in 5 ml CCl_4 added, when a copious reddish-brown precipitate (mp about 125° C) separated, and the solution turned dark-red. If the precipitate was filtered off and treated with aqueous ammonia, 2,4-diphenyl-5-bromo-1,3-oxazole was obtained. Further, boiling the same mixture, with stirring, on a water bath for 30 min caused the solid to dissolve, and on cooling a fresh precipitate of an orange material (mp about 160°, decomp) was obtained, and filtered off. On standing in air it gradually decomposed, while on treatment with aqueous ammonia this took place rapidly, the product being 2,4-diphenyl-5-bromo-1,3-oxazole (0.35 g), mp 79°–80°, undepressed mixed mp with I (see table). Evaporation of the CCl_4 mother liquor gave a further quantity (0.05 g) of the same compound, total yield 0.4 g (68%).

Bromoacetamidoacetophenone (VIIIa). 1.7 g (0.01 mole) ω-aminoacetophenone hydrochloride was suspended in a solution of 2.4 g (0.012 mole) bromoacetylbromide in 12 ml dioxane, and about 6 ml of a 10% solution of pyridine in dioxane added to the boiling solution until the solid disappeared. Hydrogen bromide was evolved, the mixture turned yellow, and cleared. When reaction was finished, there might be a small amount of oily material on the bottom of the vessel, solidifying on cooling, and readily soluble in water. The amount of it increased with increase in excess pyridine used, the yield of the main product being lowered. Hence it was important to determine just when the suspended solid had all dissolved, since that determined the end of the reaction and termination of pyridine addition. When reaction was complete the products were allowed to cool to room temperature, and then poured, with stirring, into 70 ml water. The almost colorless precipitate was filtered off and dried, yield of technical material 1.28 g. Recrystallized from EtOH it formed colorless flaky crystals, soluble in benzene and dioxane, less soluble in petrol ether and EtOH, insoluble in water. Yield 50%, mp 147°–149° C. Found: Br 31.60; N 5.90%. Calculated for $C_{10}H_{10}BrNO_2$: Br 31.21; N 5.46%.

2-Bromoethyl-5-phenyl-1,3-oxazole (IXa). 4.2 g (0.0164 mole) VIIa was dissolved in 10 ml concentrated H_2SO_4 at room temperature, the solution stirred for 3–4 hr, and then poured into ice water. Yield of technical product

Halogenoxazoles Synthesized from Mercury Derivatives of Oxazoles

Compound number	1,3-Oxazole	Mp (recrystallization solvent), °C	Formula	Found, %				Calculated, %				Yield, %
				C	H	Hal	N	C	H	Hal	N	
I	2,4-Diphenyl-5-bromo	80 (petrol ether)	$C_{15}H_{10}BrNO$	59.68	3.40	26.59 26.92	4.66	60.00	3.33	26.60	4.66	72
II	2,4-Diphenyl-5-iodo	90 (90% MeOH)	$C_{15}H_{10}INO$	51.88	2.88	36.38 36.82	4.17 4.51	51.87	2.87	36.59	4.04	64
III	2,5-Diphenyl-4-bromo	66 (after vacuum-distilling)	$C_{15}H_{10}BrNO$	59.93	3.03	26.48 26.62	4.39 4.51	60.00	3.33	26.60	4.66	80
IV	2,5-Diphenyl-4-iodo	94 (90% MeOH)	$C_{15}H_{10}INO$	51.41 51.35	2.78 2.64	36.41 36.79	4.34 3.94	51.87	2.87	36.59	4.04	85
V	2-Methyl-5-phenyl-4-bromo	68–70 (80% MeOH) 67 [3]	$C_{10}H_8BrNO$	50.42	3.36	33.50	5.74	50.42	3.36	33.61	5.88	65
VI	2-Methyl-5-phenyl-4-iodo-	57 (80% MeOH)	$C_{10}H_8INO$	42.48	2.80	44.58 44.48	4.70 4.51	42.10	2.80	44.60	4.91	55
VII	4,5-Diphenyl-2-iodo	85 (petrol ether)	$C_{15}H_{10}INO$	51.63	3.05	36.90 36.98	3.80	51.87	2.87	36.59	4.04	60

3.4 g (87%). Recrystallized from EtOH it formed colorless crystals, readily soluble in the usual organic solvents, insoluble in water; it had an irritating action on the skin; mp 79°–81° C. Found: Br 33.58; N 6.05%. Calculated for $C_{10}H_8BrNO$: Br 33.61; N 5.88%.

α-Bromopropionamidoacetophenone (VIIIb). A suspension of 6.8 g (0.04 mole) ω-aminoacetophenone hydrochloride in a mixture of 6 ml dioxane and 8 ml pyridine was stirred at room temperature, and 10.8 g (0.05 mole) α-bromopropionamide in 6 ml dioxane added. Then the mixture was heated for 20 min on a boiling water bath, cooled, and poured into water, yield 7.5 g (75%) technical product, recrystallized from petrol ether to give colorless crystals mp 86° C. Found: Br 29.91; N 5.50%. Calculated for $C_{11}H_{12}BrNO_2$: Br 29.62; N 5.18%.

2-(α-Bromoethyl)-5-phenyl-1,3-oxazole (IXb). 1.1 g (0.004 mole) VIIIb was dissolved in 6 ml concentrated H_2SO_4, and the solution heated for 10 min on a boiling water bath, after which the products were left for 24 hr, and poured into 100 ml ice water, when an oily material separated, and crystallized after a time (1 g, 97%). Recrystallized from 25 ml petrol ether it formed colorless crystals mp 69° C, soluble in the usual organic solvents, insoluble in water. Found: Br 31.78; N 5.54%. Calculated for $C_{11}H_{10}BrNO$: Br 31.80; N 5.55%.

2-(p-Bromophenyl)-5-phenyl-1,3-oxazole. Equimolecular amounts of α-bromophenylacetaldehyde and p-bromobenzamide were fused together with stirring, by heating in a glycerol bath at 110°–120° C. The initially liquid reactants solidified. 200 ml benzene was carefully added, with stirring, to the products while still hot, the mixture cooled and filtered. The precipitate was washed with benzene until pale green, and then dried. The resultant technical product was treated with boiling water, and the mixture filtered. Unreacted amide separated from the aqueous mother liquor. The precipitate was recrystallized from EtOH, using decolorizing charcoal. Yield 50%, mp 118° (115°–116° [9]).

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