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STUDIES OF OXAZOLES

I. Mercuration of 1, 3-Oxazole Derivatives

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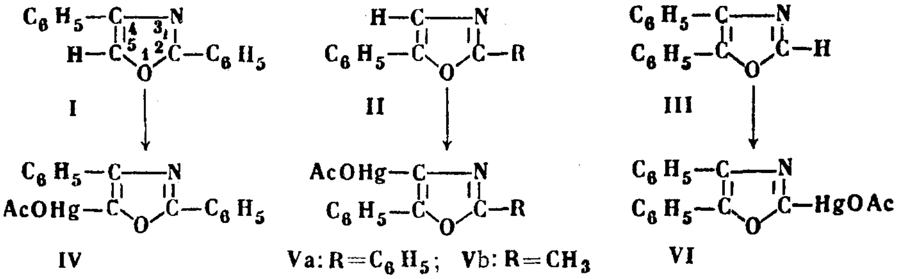
Mercuration of oxazole derivatives is studied. As a result mono- and disubstituted mercury derivatives, hitherto not described in the literature, are obtained. The ability of the oxazole ring to undergo mercuration decreases in the order C−5 > C−4 ≥ C−2. It is shown that phenyl-substituted oxazoles are mercurated solely, or mainly at least, at an unsubstituted carbon atom in the heterocyclic ring, actual phenyl substituents in the oxazoles remaining inert towards mercuration.

Oxazole derivatives find wide application as scintillating materials [1]. Their chemical study is the subject of a number of papers. The literature describes reactions taking place in the side chain of an oxazole ring [2-4], accompanied by scission and rearrangement of the latter [5, 6]. Save for bromation [7, 8], other reactions leading to substitution of the oxazole ring are so far unknown.

In the present work various substituted oxazoles with substituents at the 2, 4-, 2, 5- and 4, 5- positions in the oxazole ring have been mercurated for the first time. The mercuration was effected by fusing together the oxazole and mercuric acetate, or by heating them together in glacial acetic acid or ethanol. This gives the corresponding mercury-substituted compounds, with a mercury atom in the oxazole ring, in accordance with the equations below, and there is not a single case where the mercury atom enters the phenyl substituents:

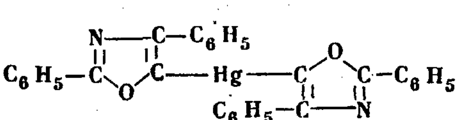


Va: $R=C_6H_5$; Vb: $R=CH_3$

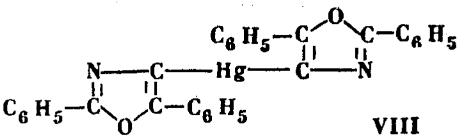
It is shown that these compounds contain a mercury atom directly linked to the oxazole ring, by the following circumstantial evidence. Halogenation of the mercuration products IV-VI gave the corresponding halogenated oxazoles, with the halogen in the heterocyclic ring [9], and not in the substituents, and they were identical with the compounds prepared by direct synthesis, or described in the literature [8], but they differed from the phenyloxazoles with halogen in the phenyl substituents [1]. Furthermore, as was previously shown [10], 2, 5-diphenyloxadiazole, which is an analog of the oxazoles but which is without a hydrogen atom in the heterocyclic ring, cannot be mercurated, and this is indirect evidence of the inertness of the phenyl substituents in systems I-III. Phenyl substituted derivatives of other 5-membered aromatic heterocyclic compounds, furan, thiophene, selenophene, pyrrole [11], isoxazole [12], pyrazole [13], isoxadiazole [14] are also mercurated similarly to oxazoles and oxadiazoles. In all these cases mercuration also leaves the phenyl substituents unmercurated, the mercury atom entering solely into the heterocyclic ring of the molecule, as previously explained [15].

Mercuration of oxazoles under the given conditions is an electrophilic reaction [15]. As in the case of bromination [8, 15], another electrophilic reaction known to take place with oxazoles, I is mercurated most easily, mercuration of oxazoles of types II and III requiring more drastic conditions. However, while IIa and III cannot in general be brominated [7], they are mercurated.

Reaction of the mercury oxazloes IV, Va with sodium stannite gives the corresponding oxazolyl-substituted mercury derivatives VII, VIII:



VII



VIII

Like oxazolylmercuracetates and dioxazolyl-substituted mercuries, mineral acids hydrolyze them to the starting oxazoles.

Experimental

(2, 4-Diphenyl-1, 3-oxazole-5-yl) mercuracetate (IV). A mixture of 4.4 g (0.02 mole) 2, 4-diphenyl-1, 3-oxazole and 6.35 g (0.02 mole) mercuric acetate in 8 ml glacial acetic acid was stirred and heated for 20 min at 60-70°. The reaction mixture was converted from a suspension to a bulky porridge-like mass, which was cooled, filtered, the solid washed with ether and dried, to give 9 g (94%) colorless crystalline product mp 170-171°. After boiling with water to wash off traces of mercuric acetate, the material was dissolved in benzene (about 250 ml), any insoluble residue filtered off, and the filtrate run through a column of alumina and then evaporated under reduced pressure to incipient crystallization. The purification was repeated, to give colorless crystals, soluble in benzene, dioxane, ethanol, less soluble in acetone, slightly soluble in carbon tetrachloride, insoluble in petrol ether or water. Mp 187°. Found: Hg 41.46; N 3.15%. Calculated for $C_{17}H_{13}HgNO_3$; Hg 41.74; N 2.92%.

IV can also be made by boiling the starting materials together in methanol.

Bis(2, 4-diphenyl-1, 3-oxazole-5-yl) mercury (VII). a) 1 g (0.0021 mole) IV was dissolved in a mixture of 15 ml water and 120 ml acetone, and a freshly prepared solution of sodium stannite (prepared from 0.66 g sodium hydroxide and 0.54 g (0.0028 mole) stannous chloride in 6.5 ml water) stirred into the hot solution. Immediately mercury was observed to separate, and the solution to form two layers. After holding for an hour at room temperature, the reaction mixture was heated to boiling, then filtered. The solid was washed with hot acetone and dissolved in benzene. The benzene-insoluble inorganic part of the precipitate was filtered off, washed with hot benzene, and VII precipitated from the benzene filtrate with petrol ether. Yield 0.4 g (60%), mp 232-234°. Recrystallization from benzene gave colorless crystals, soluble in benzene, and dioxane, slightly soluble in ethanol or acetone, insoluble in cyclohexane or water, mp 236°. Found: Hg 32.22%. Calculated for $C_{30}H_{20}HgN_2O_2$: Hg 31.25%.

b) 0.45 g (0.0027 mole) KI in 10 ml 90% aqueous dioxane. Separation into liquid layers took place. The mixture was refluxed and stirred for 3 hr, 60 ml water added, and after cooling the precipitate (~ 1 g), which turned red in air, was filtered off. It was extracted with benzene, and the benzene extract passed through a column of alumina, after which it was evaporated to incipient crystallization. The colorless crystals obtained had mp 235° (ex benzene—petrol ether), undepressed mixed mp with the compound prepared in the previous synthesis.

(2, 5-Diphenyl-1, 3-oxazole-4-yl) mercuracetate (Va). 22.1 g (0.1 mole) 2, 5-diphenyl-1,3-oxazole and 31.8 g (0.1 mole) mercuric acetate in 40 ml glacial acetic acid were stirred and refluxed for 2 hr. The reaction products were cooled, the precipitate filtered off, washed on the filter with 10 ml 60% acetic acid, and dried. Yield 38-43 g (80-90%), mp 154-158°. The material was dissolved in 800 ml boiling benzene, and the hot solution containing a small amount of insoluble material, filtered through an alumina column. The precipitate obtained on cooling (~30 g, 63%, mp 171-173°) was recrystallized from benzene to give colorless crystals soluble in dioxane, benzene, ethanol, less soluble in acetone, slightly soluble in CCl_4, insoluble in petrol ether and water, mp 192-193°. Found: Hg 41.51; N 2.81%. Calculated for $C_{17}H_{13}HgNO_3$: Hg 41.74; N 2.92%.

The crude Va obtained when the reaction is carried out by fusing the reactants together (~ 190°, 15 min) is not easy to purify.

Bis(2, 5-diphenyl-1, 3-oxazole-4-yl) mercury (VIII). A freshly-prepared alkaline solution of sodium stannite (prepared by mixing 1.98 g sodium hydroxide in 9 ml water with 1.62 g (0.0085 mole) stannous chloride in 10 ml water) was added to a solution of 3 g (0.0063 mole) Va in a mixture of 45 ml water and 360 ml acetone. After 2 hr the precipitate was filtered off, and washed with hot acetone. Water precipitated from the acetone solution 1.7 g VIII, mp 170-220°, yield 1.4 g (68%), mp 218-220° (ex benzene). Repeated recrystallization followed by vacuum-drying at 100° gave colorless crystals, soluble in benzene, dioxane, and acetone, less soluble in alcohols, insoluble in cyclohexane or water, mp 223-225°. Found: Hg 30.98%. Calculated for $C_{30}H_{20}HgN_2O_2$: Hg 31.25%.

The same compound was synthesized by boiling Va with potassium iodide in 80% aqueous dioxane for 3 hr, followed by precipitation of the reaction product with water.

(2-Methyl-5-phenyl-1, 3-oxazol-4-yl) mercuracetate (Vb). 3.2 g (0.02 mole) 2-methyl-5-phenyl-1, 3-oxazole and 6.36 g (0.02 mole) mercuric acetate in 5 ml isobutanol and 0.5 ml glacial acetic acid were refluxed for 1 hr, when a copious precipitate was formed. This was filtered off, and it weighed 1.3 g; it was extracted with benzene, and evaporation of the benzene solution gave 0.6 g colorless crystalline material. Strong cooling of the alcoholic mother liquor precipitated a further 1.2 g Vb, mixed mp with the previous compound undepressed. Total yield 1.8 g (22%), mp 160-162°. Vb was soluble in benzene, dioxane, and alcohols, insoluble in cyclohexane and water. Found: Hg 47.71; N 3.68%. Calculated for $C_{12}H_{11}HgNO_3$: Hg 47.95; N 3.36%.

Fusing the reactants together in the above proportions by heating on a water bath for 45 min, or heating them together in glacial acetic acid gave the reaction product as an oil which was difficult to purify further.

(4, 5-Diphenyl-1, 3-oxazol-2-yl) mercuracetate (VI). A mixture of 16.4 g (0.075 mole) 4, 5-diphenyl-1, 3-oxazole and 23.6 g (0.075 mole) mercuric acetate was heated and stirred on a water bath at 80-85°, for 10-15 min. The reaction mixture thickened. 125 ml diethyl ether was added carefully to the still warm reaction mixture, the whole well stirred, filtered, and washed with ether. Yield 28.5 g (80%), mp 168°. The material was dissolved in 300 ml benzene, undissolved mercury salt filtered off (~ 2.9 g), the hot benzene mother liquor filtered through an alumina layer and then cooled, when 13.1 g (47%) VI, mp 178°, was precipitated. Approximately a further 7 g crude VI was isolated from the benzene mother liquor. Further purification gave, from benzene, colorless crystals, soluble in benzene, dioxane, ethanol, slightly soluble in CCl_4, insoluble in cyclohexane, ether, and water, mp 179-180°. Found: Hg 41.22; N 2.52%. Calculated for $C_{17}H_{13}HgNO_3$: Hg 41.74; N 2.92%.

Heating stoichiometric amounts of the reactant in glacial acetic acid or alcohols under similar temperature conditions gave diminished yields of VI. Use of more drastic temperature conditions (e.g., boiling isobutanol) gave an oily product which was difficult to purify.

Hydrolysis of IV, Va, VI-VIII. 0.2 g mercury-substituted oxazole was dissolved in 8 ml dioxane, and 0.4 ml conc HCl added with heating. The solution was allowed to stand for about 24 hr, then by adding water 0.06-0.1 g crystalline material precipitated. Mixed mp with the corresponding starting oxazole undepressed. Yellow mercuric oxide (~ 0.08 g) was obtained when the aqueous mother liquor was made alkaline.

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