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RESEARCHES ON INDAZOLE DERIVATIVES

II. Preparation of Amidines by the Action of Sodamide on 1-Aralkylindazoles*

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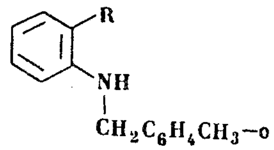
Heating some aralkylindazoles with sodamide in xylene is found to lead to breaking of the N—N bond in the pyrazole ring and formation of amidines of N-substituted anthranilic acids as the main reaction product.

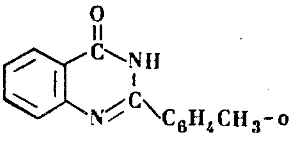
Continuing a study of the changes occuring when indazole derivatives are treated with sodamide [1, 2], 1-(o-oxylyl)-and 1-(p-anisyl) indazole have been caused to react with the latter. The compounds in question were prepared by reacting indazole with the appropriate aralkyl halides. Comparison of their electronic absorption spectra with those of 1- and 2-benzylindazoles made it possible to assign them 1-substituted structures.

It was previously shown [1] that treatment of 1-benzylindazole with sodamide and sodium hydroxide in boiling xylene gives products (nitrile and amide derived from N-benzylanthranilic acid) formed by opening of the pyrazole ring and by ring enlargement (2-phenylquinazolone-4). Under the same conditions 1-(o-xylyl) indazole (IA) gives compounds of similar structure, the nitrile (IIa) and amide (IIb) from N-(o-xylyl) anthranilic acid and 2 o-tolylquinazolone-4(III), though the yields were much lower (3.6% and 6% respectively). But here the main reaction product (44% yield) is a substance of strongly basic character, giving the color reaction for amidines with the bisulfite compound of glyoxal [3], and hydrolyzed by aqueous alcoholic alkali to o-xylylanthranilic acid, so that it is the amidine of that acid (IVa). Heating 1-(p-anisyl) indazole (Ib) with sodamide and sodium hydroxide gives only one reaction product N-p-anisylanthranilamidine (IVb).

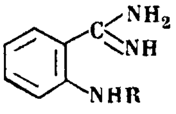
Ia $R=o\text{-}CH_3C_6H_4CH_2$,
b $R=p\text{-}CH_3OC_6H_4CH_2$



IIa $R=CN$,
b $R=CONH_2$



III



IVa $R=o\text{-}CH_3C_6H_4CH_2$
b $R=p\text{-}CH_3OC_6H_4CH$
c $R=o\text{-}ClC_6H_4CH_2$.

Evidently formation of amidines by reaction of 1-aralkylindazoles with sodamide depends on adding of the sodamide to nitriles [4, 5], which latter arise through opening of the indazole pyrazole ring. 1-Aralkylindazoles give rather good yields of amidines, and hence the reaction can be of preparative interest. In the case of preparation of N-(o-chlorobenzyl) anthranilamidine (IVc) (isolated as the hydrochloride), it has now been shown that a mixture of 1- and 2-substituted indazoles** can be submitted to reaction, such a mixture being formed by N-substitution, and difficult to separate in a number of cases.

Experimental

1-(o-Xylyl) indazole (Ia). A mixture of 11.8 g (0.1 mole) indazole and 21 g (0.15 mole) o-xylylchloride (50% excess) was heated for 4 hr on an oil bath at 190°, and then for about 1 hr at 200-205° till hydrogen chloride evolution ceased. After cooling, the reaction products were dissolved in chloroform, the solution washed with water, and then dried with calcium chloride. The chloroform was distilled off, and the residue distilled under reduced pressure. Repeated distillation gave a cut boiling at 187° (5 mm), which distilled as a colorless oil, readily soluble in the usual organic solvents. Yield 12.7 g (57%); n_D^{20} 1.6210. Found: C 80.93, 81.02; H 6.54, 6.44%. Calculated for $C_{15}H_{14}N_2$: C 81.05; H 6.38%.

UV spectrum λ_{max} 256, 264, 292, 304 mμ; lg ε 3.54, 3.56, 3.69, 3.65.***

1-(p-Anisyl) indazole (Ib). Heating indazole with p-anisylchloride at 190° results in extensive resinification. Hence the reaction was carried out in ethanol solution, in the presence of sodium ethoxide. A solution of sodium

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[*] For Part I see [1].

[**] 2-Substituted indazoles do not react with sodamide.

[***] The spectra of all the compounds were measured with a SF-4 instrument, in methanol solution, $c = 10^{-5}$.

ethoxide (from 3.5 g sodium), 11.8 g (0.1 mole) indazole, and 31.3 g (0.2 mole) p-methoxybenzylchloride in ethanol was refluxed for 3 hr. The sodium chloride formed was filtered off, the filtrate diluted with water, and the oil which separated extracted with chloroform. The chloroform extract was dried with calcium chloride, the chloroform distilled off, and the residue vacuum distilled, (5 mm). p-Methoxybenzylchloride distilled up to 108°, and 1-anisylindazole at 200-202°, as an oil which crystallized on standing. Yield 12 g (50%). Rhombic crystals mp 63-64° (from petrol ether, readily soluble in the ordinary organic solvents. Found: C 75.66, 75.44; H 5.92, 5.87; N 11.59%. Calculated for $C_{15}H_{14}N_2O$: C 75.61; H 5.92; N 11.76%.

UV spectrum: λ_{max} 256, 264, 284, 292, 304 mμ; lg ε 3.66, 3.69, 3.76, 3.76, 3.62.

Picrate, plates mp 146-147° (from alcohol).

1- and 2-(o-Chlorobenzyl)indazoles. A mixture of these compounds was formed when indazole was heated with o-chlorobenzylbromide in alcohol solution in the presence of sodium ethoxide. After diluting with water, the solution was extracted with benzene. The extract was distilled, and a 200-230° (16 mm) cut taken. Investigation of fractionally precipitated picrates of this, showed that it contained about equal amounts of isomeric 1-(o-chlorobenzyl) indazoles [6].

Reaction of 1-(o-xylyl) indazole with sodamide. A mixture of 4.4 g (0.02 mole) 1-(o-xylyl) indazole, 2.34 g (0.06 mole) sodamide (which had been powdered under xylene in a mortar), 0.9 g (0.023 mole) sodium hydroxide, and 25 ml dry xylene was placed in a round bottomed flask fitted with mechanical stirrer and reflux condenser. Reaction began when the reactants had been heated to 100-110°, and proceeded exothermically, so that the xylene boiled. Evolution of ammonia was observed, ceasing 30-40 min after heating started, and a copious precipitate was formed. The mixture was refluxed for 3 hr, cooled, treated with water, the water layer separated, and the xylene layer carefully washed with water.

The aqueous layer and wash waters were bulked, and neutralized with dilute hydrochloric acid. A flocculent precipitate of 2-(o-tolyl)-quinazolone-4 (III) was formed (0.15 g), small needles mp 234-235° (from benzene), readily soluble in alcohol, acetone, dilute alkalies and acids. The literature [7] gives mp 236°.

On standing the xylene solution deposited a white precipitate, which was filtered off, and washed with 10 ml petrol ether. Yield 2.1 g, mp 112-113°. This compound was N-(o-xylyl) anthranilamidine.

The filtrate was diluted with petrol ether. After standing overnight N-(o-xylyl) anthranilamide separated as coarse crystals, yield 0.3 g.

Solvent was distilled off from the mother liquor, and the residue vacuum distilled, a 190-205° (7 mm) cut being taken. Recrystallization from alcohol gave 0.3 g N-(o-xylyl)-anthranilonitrile.

N-(o-xylyl) anthranilamidine (IVa). The substance isolated from the xylene solution was recrystallized first from benzene, then from alcohol, using decolorizing charcoal. Colorless plates mp 113-113.5°, readily soluble in chloroform and ether. The compound is alkaline to litmus. Found: C 74.96, 75.18; H 7.16, 7.26; N 17.56%. Calculated for $C_{15}H_{17}N_3$: C 75.28; H 7.16; N 17.56%.

UV spectrum: λ_{max} 217, 335 mμ; log ε 4.31, 3.46.

The hydrochloride mp 182°, was prepared by passing hydrogen chloride into an ether solution of the base.

N-(o-xylyl) anthranilic acid. A solution of 0.3 g (0.013 mole) IVa amidine and 0.5 g potassium hydroxide in 3 ml alcohol and 1 ml water was refluxed for 24 hr on a water bath, ammonia being evolved. On neutralization colorless crystals (0.25 g) formed, soluble in sodium bicarbonate solution, prisms mp 182° (from alcohol). An alcohol solution of the compound fluoresced azure blue. Found: N 5.76, 5.67%. Calculated for $C_{15}H_{15}NO_2$: N 5.80%. The same compound was obtained by hydrolysis of nitrile IIa.

UV spectrum: λ_{max} 218, 258, 342 mμ; lg ε 4.43, 4.08, 3.73.

N-(o-xylyl) anthranilamide (IIb). Prisms mp 146-147.5° (from aqueous alcohol), readily soluble in alcohol and benzene, insoluble in water. An alcohol solution fluoresced an azure blue. Found: C 75.04; H 6.89; N 11.58%. Calculated for $C_{15}H_{16}N_2O$: C 74.97; H 6.71; N 11.66%.

UV spectrum: λ_{max} 218, 260, 346 mμ; lg ε 4.41, 4.08, 3.72.

N-(o-xylyl) anthranilonitrile (IIa). This compound was purified by successive recrystallization from alcohol, benzene, alcohol. Pyramidal crystals mp 121.5-123°, sparingly soluble in ether, readily soluble in acetone and chloroform. Found: C 80.98, 81.19; H 6.30, 6.29; N 12.46%. Calculated for $C_{15}H_{14}N_2$: C 81.05; H 6.35; N 12.60%.

UV spectrum: λ_{max} 220, 254, 335 mμ; lg ε 4.44, 4.11, 3.77.

Reaction of 1-(p-anisyl) indazole and sodamide. A mixture of 3.3 g (0.014 mole) 1-(p-anisyl) indazole, 1.5 g (~ 0.04 mole) sodamide, and 1.5 g sodium hydroxide was heated at 120-130° in 15 ml xylene for 5 hr, with stirring. Evolution of ammonia was observed, the reaction mixture turned yellow, then turned lighter. After cooling, the mixture was decomposed with 10 ml water, heat was evolved, and the precipitate dissolved. On standing a copious crystalline precipitate of N-(p-anisyl) anthranilamide was formed, and this was filtered off, washed with water, and then with petrol ether. Yield 2.4 g.

N-(p-anisyl) anthranilamidine (IVb) formed tetragonal plates, mp 111-112° (from benzene), readily soluble in alcohol, dioxane, dilute hydrochloric acid, insoluble in cold water, and aqueous alkalies, An aqueous alcoholic solution was alkaline to litmus. With the bisulfite compound of glyoxal it gives the qualitative reaction for amidines. Found: C 70.79, 70.71; H 6.78, 6.73; N 16.33%. Calculated for $C_{15}H_{17}N_3O$: C 70.56; H 6.71; N 16.46%.

Picrate. Yellow needles mp 159-160° (from alcohol). Found: N 17.31%. Calculated for $C_{15}H_{17}N_3O \cdot C_6H_3(NO_2)_3OH$: N 17.36%.

Hydrochloride. When a solution of the amidine in 20% hydrochloric acid was allowed to stand and then cooled, a coarsely crystalline precipitate of amidine monohydrochloride formed. Snow-white needles mp 263-264° (from alcohol), readily soluble in water and alcohol. Found: N 14.20%. Calculated for $C_{15}H_{17}N_3O \cdot HCl$: N 14.40%.

N-(p-anisyl) anthranilamidine benzoate was obtained in quantitative yield on mixing chloroform solutions of equimolecular amounts of the amidine and benzoic acid. Hexahedral prisms mp 209° (from dioxane), soluble in alcohol, dioxane, and water. Found: C 69.98, 70.16; H 6.16, 6.07; N 11.27%. Calculated for $C_{15}H_{17}N_3O \cdot C_6H_5COOH$.

N-(p-anisyl) anthranilic acid. A solution of 0.2 g (~ 0.8 mmole) amidine IVb and 0.4 g potassium hydroxide in 4 ml 70% alcohol was refluxed for 20 hr, diluted with water, and neutralized with hydrochloric acid. The precipitate was filtered off and washed with water. Yield 0.2 g. Rhombic crystals mp 159-160° (from alcohol). Found: N 5.23, 5.26%. Calculated for $C_{15}H_{15}NO_3$: N 5.44%.

Reaction of a mixture of 1- and 2-(o-chlorobenzyl) indazoles with sodamide. 4.8 g (0.185 mole) mixed o-chlorobenzylindazoles, 1.56 g (0.04 mole) sodamide, 1 g sodium hydroxide, and 15 ml xylene were refluxed for 3 hr 30 min. The very hygroscopic precipitate was rapidly filtered off and washed with petrol ether, then dissolved in concentrated hydrochloric acid, diluted with an equal volume of water, and boiled with active charcoal. The filtrate was neutralized with ammonia, and the precipitate formed (1.77 g) recrystallized from aqueous alcohol and then from alcohol-benzene, to give colorless crystals mp 218°, soluble in hot chloroform and hot water. The compound contained ionizable chlorine, gave the qualitative reaction for aromatic amidines, and was N-(o-chlorobenzyl) anthranilamidine hydrochloride (IVc) · HCl. Found: N 14.21, 14.44%. Calculated for $C_{14}H_{15}N_3Cl \cdot HCl$: N 14.20%.

UV spectrum: λ_{max} 219, 332 mμ; lg ε 4.31, 3.42.

Hydrolysis of the compound with alcoholic potassium hydroxide (18 hr) gave N-(o-chlorobenzyl) anthranilic acid, prisms mp 185-185.5°. Found: N 5.16%. Calculated for $C_{14}H_{12}ClNO_2$: N 5.35%.

UV spectrum: λ_{max} 218, 254, 338 mμ; lg ε 4.44, 4.03, 3.72.

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