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RESEARCHES ON INDAZOLE DERIVATIVES

IV. Mechanism of Indazole Pyrazole Ring Enlargement by Sodamide*

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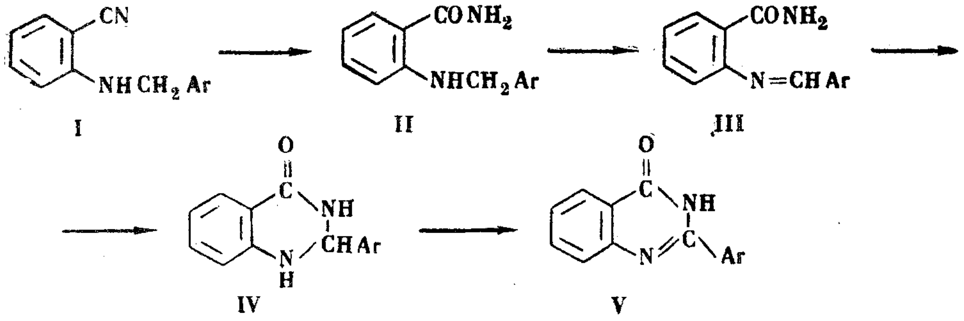
The action of sodamide on 1-aralkylindazoles gives a 2-arylquinazolone-4 structure through cyclization of the amide or amidine of an N-aralkyl-substituted anthranilic acid.

It was previously shown [1, 2] that heating certain 1-aralkylindazoles (1-benzyl- and 1-o-xylylindazoles) with sodamide in boiling xylene gives quinazolone-4 derivatives, along with products arising from scission of the N—N bond of the pyrazole ring. The experiments showed that ring enlargement was a secondary reaction.

The first product of the action of sodamide on 1-benzylindazole is N-benzylanthranilonitrile (I) [3]. Its formation proceeds particularly smoothly when, for example, the reaction is run in liquid ammonia. Further, in the reaction the nitrile is converted to 2-phenyl-quinazolone-4 (V), via formation of the amide (II) or possibly the amidine [2] of the N-substituted anthranilic acid, as can readily be shown by heating the compound isolated from the reaction products, with sodamide in xylene. The quinazolone is accompanied by N-benzylanthranilamide, and the latter under such conditions also gives the quinazolone (V).

It can be assumed that transformation of amide II (or, correspondingly, of amidine) to quinazolone proceeds through an anil of o-aminobenzamide III (or of o-aminobenzamidine) whose sodio derivative is converted to 2-aryl-quinazolone-4 (V) by successive cyclization and aromatization of the dihydroquinazoline ring (in IV)



I—V Ar = C_6H_5

In support of this view experiments can be performed [4] where it is shown that o-arylideneaminobenzamides are easily converted to 2-aryl-1, 2-dihydroquinazolones-4 and the latter oxidized to 2-arylquinazolones-4.

Experimental

Reaction of 1-benzylindazole with potassimide in liquid ammonia. 30 ml liquid ammonia was introduced into a 100 ml three-necked flask, and 0.39 g (0.01 g. at.) potassium metal dissolved in it. Stirring and cooling were continued until the initially blue solution became pale yellow. Then 1.04 g (0.005 mole) 1-benzylindazole was introduced into the reaction mixture, and the coolant removed. The solution turned an intense red, and was stirred until all the ammonia had evaporated (1.5 hr). The dry residue was decomposed with a small amount of alcohol, then 10 ml water added. The precipitate was filtered off and washed with water. It was N-benzylanthranilonitrile mp 117-118° (from alcohol). Yield. 0.7 g (67%). 1-Phenylquinazolone-4 was isolated from the alkaline mother liquor mp 235-236°, yield 0.06 g (5%).

Reaction of N-benzylanthranilonitrile with sodamide. A mixture of 0.7 g N-benzylanthranilonitrile, 0.3 g sodamide, and 10 ml xylene was refluxed for 6 hr. Considerable tar formation was observed. After cooling 10 ml water was added, and the water layer separated off and neutralized with 10% hydrochloric acid. The precipitate formed was filtered off and washed with water. Yield 0.15 g (21%) material which, recrystallized from alcohol, formed small needles mp 235-236°, mixed mp with authentic 2-phenylquinazolone-4 undepressed.

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*For Part III see [2].

Using hydrochloric acid, 0.35 g material was isolated from the xylene solution. When recrystallized from alcohol, it formed colorless prisms mp 174-175°, identical with N-benzylanthranilamide.

Reaction of N-benzylanthranilamide with sodamide. A mixture of 0.7 g N-benzylanthranilamide, 0.3 g sodamide, and 15 ml o-xylene was refluxed for 6 hr. Partial tar formation was observed. After cooling 10 ml water was added, the aqueous layer separated off, and neutralized with 10% hydrochloric acid. The precipitate formed was filtered off and washed with water. Yield 0.25 g (36%). After recrystallizing from alcohol, the compound had mp 235-236°, and was identical with 2-phenylquinazolone-4.

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