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RESEARCHES ON INDAZOLE DERIVATIVES
III. Reaction of 1-Alkyl- and 1-Arylindazoles with Sodamide*

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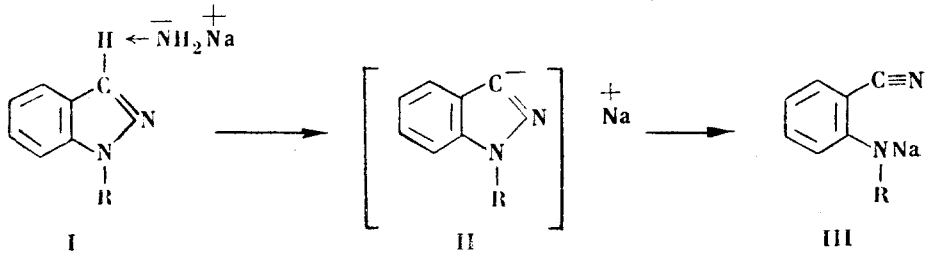
It is shown that treatment of 1-alkyl- and 1-arylindazoles with sodamide leads to rupture of the N-N link in the pyrazole ring and formation of derivatives (nitriles, amides, and amidines) of N-alkyl- and N-arylanthranilic acids. The mechanism of the changes observed is discussed. It was previously shown that treatment of 1-arylkyl substituted indazoles with sodamide gives products (nitriles, amides [1], amidines [2]) formed by opening of the pyrazole ring, and by ring enlargement (quinazolone derivatives [1]). The present paper describes the action of sodamide on 1-alkyl-(see also [3]) and 1-arylindazoles, and considers the mechanism of the transformation.

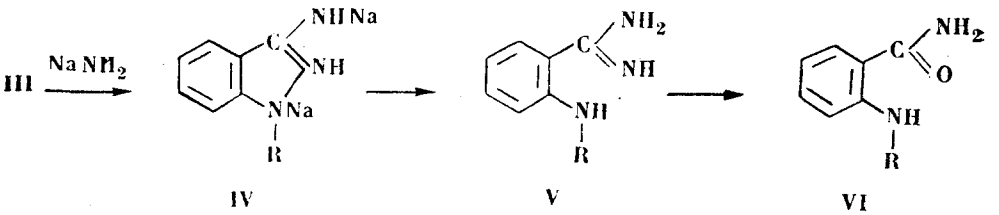
Amides of N-alkylanthranilic acids are formed by heating 1-alkylindazoles (where alkyl is methyl, ethyl, propyl, isopropyl, and n-butyl) with sodamide, or sodamide and sodium hydroxide, in boiling xylene. 1-Butylindazole also gives N-n-butylanthranilonitrile. Under those conditions the pyrazole ring of 1-aryl-substituted indazoles is opened to form various acid derivatives whose nature depends on the structure of the aryl group. 1-Phenylindazole forms an amide, 1-p-methoxyphenylindazole a nitrile, while 1-o-methoxyphenylindazole gives the amidine of the corresponding N-aryl-substituted anthranilic acid.

Apparently the mechanism involved in the opening of the pyrazole ring of 1-substituted indazoles by sodamide or potassimide is as follows. First of all there is direct nucleophilic attack by the sodamide on the hydrogen at position 3 in the pyrazole ring. This gives rise to splitting off of a proton, separation of ammonia,** and formation of a sodio derivative II. Immediately after, or simultaneously, there is redistribution of electron density in the ring, leading first to weakening of the N—N bond, then to rupture and formation of a nitrile III. Thus the first stage in the process, and one where the transformation stops in a number of cases, is rearrangement of the 1-substituted indazole to a nitrile of a N-substituted anthranilic acid.



I-III R = alkyl or aryl

Probably the other transformation products, amidines and amides, are formed thus. The nitrile III formed adds sodamide [4-6] at the CN group, changing into the sodio derivative of amidine IV, which further changes into amidine V or amide VI [7].



Regarding indazoles as cyclic hydrazones, it is easy to see what the rearrangement described has in common with N—N bond scission in the pyrazole ring [8], and with analogous transformations with hydrazones [9], pyrazolines [10, 11], isoxazoles [12], etc. One of the prerequisites for the reaction to proceed is the presence of a hydrogen atom at the carbon-nitrogen double bond (position 3 in the pyrazoline or pyrazole ring unsubstituted.) So the present experiments indicate that indazoles which are substituted at position 3 (1-benzyl-3-bromoindazole, 1-methyl-3-bromoindazole, etc)

* For Part II see [3].

** One mole of ammonia separates per mole of compound.

do not react with sodamide.

The present results make it possible to regard the rearrangement of 1-substituted indazoles as a special case of the general ability of hydrazones to undergo splitting with N—N bond breaking, a transformation first observed by Arbuzov in 1910 [13]. It should be noted that under the Arbuzov reaction conditions (220°, CuCl), 1-substituted indazoles do not undergo rearrangement, apparently because of the high aromaticity of the indazole ring. 2-Substituted indazoles, which do not show a similarity to hydrazones, do not react with sodamide.

Experimental

N-methylanthranilamide. This compound was prepared by treating 1-methylindazole with sodamide in boiling xylene. Yield 50%, plates, mp 159.5-160.5° (from alcohol); the literature gives [14] mp 159-160°. Treatment with mixed sodamide-sodium hydroxide, or with sodamide, in boiling benzene, proceeds similarly. Hydrolysis of the reaction product with alcoholic potassium hydroxide gave N-methylanthranilic acid, plates mp 178-179°; the literature gives [15] mp 178°.

N-ethylanthranilamide, mp 128-129° [16], was formed under the same conditions from 1-ethylindazole.

N-propylanthranilamide. A mixture of 3.2 g (0.02 mole) 1-propyl-indazole, 1.6 g (0.04 mole) sodamide, 1.2 g (0.03 mole) sodium hydroxide was heated in 30 ml xylene, the temperature being slowly raised. Reaction started at 100°, and heating was stopped. The xylene began to boil, and boiling continued for an hour, a copious precipitate being formed, accompanied by evolution of ammonia. After boiling had slackened, the mixture was refluxed for 3 hr, the products cooled, 2 ml water added, the precipitate filtered off and washed with petrol ether, yield 1.1 g; a further 0.5 g amide separated from the xylene solution, total yield 45%. Long prisms mp 112-113° (from aqueous alcohol), readily soluble in alcohol and benzene. Found: C 67.31, 67.32; H 8.05, 8.05%. Calculated for $C_{10}H_{14}N_2O$: C 67.39; H 7.92%.

N-isopropylanthranilamide. This experiment was carried out like the preceding one. 15 ml water was added to the cooled reaction products, when the precipitate dissolved. The aqueous layer was separated off, and the xylene one washed, first with a small quantity of water, and then with 20% hydrochloric acid. The hydrochloric acid extract was neutralized with ammonia, the oil which separated extracted with ether, the ether distilled off, and the residue vacuum distilled, when 1-isopropylindazole (37%) distilled over at 110-130° (10 mm). The residue in the flask was dissolved in dilute hydrochloric acid, and bulked with the previously obtained water solutions. The slightly acid solution was boiled with active charcoal, and N-isopropylanthranilamide isolated by adding an equal volume of 40% sodium hydroxide solution. Yield 51%. Long prisms, mp 88.5-89.5° (from benzene-petrol ether), soluble in alcohol, acetone, ether, and water, insoluble in petrol ether. Found: C 67.25, 67.29; H 8.03, 8.02%. Calculated for $C_{10}H_{14}N_2O$: C 67.39; H 7.92%.

N-n-butylanthranilamide and N-n-butylanthranilonitrile. 1-Butylindazole was reacted with sodamide under the conditions previously described. The precipitate obtained was filtered off, and washed with petrol ether, then decomposed with water. The oily product formed was extracted with ether, the ether extract washed with water, and dried over sodium sulfate. The ether was distilled off, and the residue vacuum distilled, two cuts being collected. N-n-butylanthranilonitrile distilled over at 177-180° (6 mm), yield 34%. Repeated distillation under reduced pressure gave a light yellow oil readily soluble in the usual organic solvents, n_D^{20} 1.561. The UV spectrum of this compound was similar to that of N-benzylanthranilonitrile [1]: λ_{max} 255, 340 mμ. lg ε 4.018, 3.679. Found: N 16.16, 16.20%. Calculated for $C_{11}H_{14}N_2$: N 16.08%.

The second cut distilled over at 185-190° (6 mm); it was N-butylanthranilamide, and crystallized on standing, yield 28%. Needles (from alcohol), mp 94-95°, readily soluble in chloroform and acetone, less soluble in benzene. Found: C 68.70, 68.76; H 8.45, 8.49%. Calculated for $C_{11}H_{16}N_2O$: C 68.72; H 8.39%.

N-phenylanthranilamide. A mixture of 2 g (0.01 mole) 1-phenylindazole [17], 0.8 g (0.02 mole) sodamide, and 15 ml xylene was refluxed for 5 hr. There was evolution of ammonia, formation of a precipitate, and marked resinification of the reaction mixture. After cooling, the reaction products were treated with water, the xylene layer separated off, boiled with activated charcoal, and dried over sodium sulfate. On standing for a long time, a precipitate of N-phenylanthranilamide separated, yield 0.5 g (23%), colorless crystals mp 129-129.5° (from aqueous alcohol), readily soluble in organic solvents, insoluble in water. Found: C 73.51; H 5.66; N 12.16%. Calculated for $C_{13}H_{12}N_2O$: C 73.56; H 5.70; N 13.20%. When the reaction was run in benzene, the starting 1-phenylimidazole was obtained. Hydrolysis of the amide gave N-phenylanthranilic acid mp 183-184° (from aqueous alcohol); the literature gives [18] mp 183-184°.

N-(p-methoxyphenyl) anthranilonitrile. This compound was obtained by reacting 1-(p-methoxyphenyl) indazole with sodamide in the presence of sodium hydroxide, in xylene. Extensive resinification was observed. Addition of petrol ether to the xylene layer after washing with water and drying, precipitated coarse crystals of N-(p-methoxyphenyl) anthranilonitrile, yield 25%, hexahedral plates, mp 122-122.5° (from alcohol), readily soluble in benzene, acetone, sparingly soluble in ether and hot water, insoluble in dilute hydrochloric acid and petrol ether. Found:

C 75.10, 75.05; H 5.48, 5.47%. Calculated for $C_{14}H_{12}N_2O$: C 74.98; H 5.39%.

Hydrolysis of the nitrile gave the previously described [19] N-(p-methoxyphenyl) anthranilic acid.

N-(o-methoxyphenyl) anthranilamidine. This compound was obtained by treating 1-(o-methoxyphenyl) indazole with sodamide in boiling benzene. Dilution of the benzene solution with petrol ether precipitated N-(o-methoxyphenyl) anthranilamidine, yield 50%, plates mp 109-110° (from aqueous alcohol), readily soluble in benzene, ether, chloroform, and dilute hydrochloric acid, insoluble in petrol ether and water. The compound gives a positive amidine reaction [20]. Found: C 69.67, 69.69; H 6.32, 6.32; N 17.31, 17.26%. Calculated for $C_{14}H_{15}N_3O$: C 69.69; H 6.27; N 17.41%.

Picrate. Yellow needles mp 237-238° (from alcohol). Found: N 17.66%. Calculated for $C_{14}H_{15}N_3O \cdot (NO_2)_3C_6H_2OH$: N 17.87%.

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