REARRANGEMENT OF ORGANOMETALLIC COMPOUNDS OF 1-BENZYLINDAZOLES

B. A. Tertov, P. P. Onishchenko,
and V. V. Bessonov

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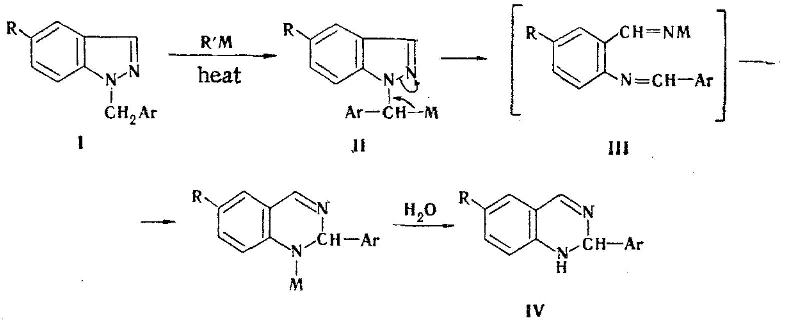
On reaction with organolithium and organomagnesium compounds 1-benzylindazoles are metallated and are then converted to 2-aryl-1,2-dihydroquinazolines. The rearrangement also takes place under the influence of lithium aluminum hydride, but the resulting dihydroquinazoline then undergoes reduction at the C=N bond.

Labile 3-sodio-1-aralkylindazoles, which are converted to N-aralkylanthranilic acid nitriles and then to 4-quinazolones, are formed by the action of sodium amide on 1-aralkylindazoles [1, 2].

We have found that active organometallic compounds react with 1-benzylindazoles in a different manner. In this case, the CH_2 group of the N-substituent rather than the 3 position of the heterocyclic ring undergoes metallation. Under the reaction conditions, the resulting organometallic compounds are rearranged to N-metallo derivatives of 2-aryl-1,2-dihydroquinazolines, the hydrolysis of which leads to the free bases.* 2-Aryl-1,2-dihydroquinazolines are formed in highest yields when phenylmagnesium bromide in ether is used with 1,2-dimethoxyethane.



I-IV a $R=H$, $Ar=C_6H_5$; b $R=CH_3$, $Ar=C_6H_5$; c $R=H$, $Ar=p\text{-}ClC_6H_4$; $R'M=C_4H_9Li$·C_6H_5MgBr, $(C_4H_9)_2Mg$

The conversion of 1-benzylindazoles to II was proved by carboxylation of the latter as described in [5]. If it is assumed that the next step in the reaction is the formation of III, aralkylidene-2-formylarylamine imines (V), their polymers, and 2-aryl-1,2-dihydroquinazolines (IV) might be considered to be the probable final products.

Inasmuch as only one $\nu_{C=N}$ band, respectively, at 1637 and 1640 cm^{-1}, is observed in the IR spectra of the products of transformations of 1-benzylindazoles Ia and Ib, monomeric aldimine structures V are excluded. The determination by a cryoscopic method

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*A paper [4] in which a similar reaction of 3-amino-1-benzylindazole with sodium hydride to give 4-amino-2-phenylquinazoline was described was published at the same time as our brief communication [3].

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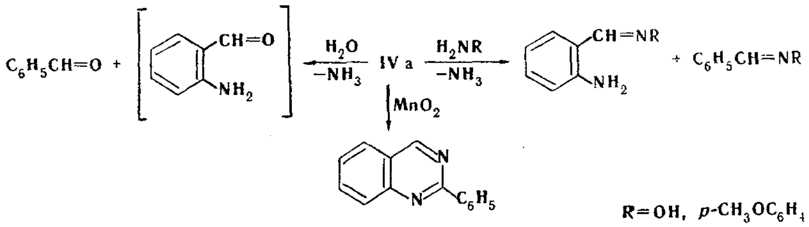
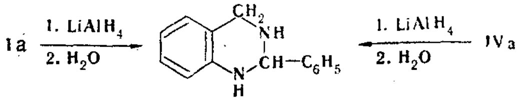
of the molecular weight of the compound obtained from indazole Ia showed that it is a monomer. Thus the IR spectral data and the cryoscopic results constitute evidence in favor of cyclic structures IV.

The individual properties of 2-aryl-1,2-dihydroquinazolines, which confirm this structure, were studied in the case of 2-phenyl-1,2-dihydroquinazoline (IVa).



It should be noted that 1-benzylindazoles are also capable of undergoing metallation by lithium aluminum hydride. The rearrangement described above occurs initially in the reaction of this compound with indazole Ia, after which the product undergoes reduction to 2-phenyl-1,2,3,4-tetrahydroquinazolines (VI), the structure of which was proved by alternative synthesis.



VI

Although 1-methylindazole can undergo metallation by butyllithium at the methyl group [5], we were unable to isolate 1,2-dihydroquinazoline from the reaction mixture.

EXPERIMENTAL

1-Benzyl-, 1-benzyl-5-methyl-, and 1-(p-chlorobenzyl)indazoles were obtained by the method in [1]. Dibutylmagnesium was obtained by the action of 1,2-dimethoxyethane on an ether solution of butylmagnesium bromide [5].

2-Phenyl-1,2-dihydroquinazoline (IVa). A total of 10 ml of 1,2-dimethoxyethane and a solution of 3 g (14.4 mmole) of 1-benzylindazole in 10 ml of toluene were added to phenylmagnesium bromide [from 1.06 g (43.6 mg-atom) of magnesium and 6.8 g (43.3 mmole) of bromobenzene in 15 ml of ether] under nitrogen, and the mixture was refluxed with stirring for 2.5 h. It was then cooled and treated with 20 ml of 25% ammonium chloride solution. The organic layer was separated and washed with water, and a large portion of the solvents was removed by distillation at 150-200 mm. 2-Phenyl-1,2-dihydroquinazoline (IVa) was precipitated from the residue with 30 ml of petroleum ether to give 1.9 g (63%) of a product with mp 131-132° (from benzene—petroleum ether). Found: C 80.5; H 5.5; N 13.2%; M 210. $C_{14}H_{12}N_2$. Calculated: C 80.7; H 5.8; N 13.4%; M 208. IR spectrum (mineral oil): 705, 751, 763 (mono- and O-disubstituted benzene rings), 1486, 1578 (aromatic C = C bonds), 1637 (C = N), 3230 (NH) cm^{-1}. The vibrations of the C = N group in the spectrum of the model compounds — benzylidenebenzylamine — appear at 1649 cm^{-1}.

When dibutylmagnesium or butyllithium are used as the metallating agents, the yields of IVa are 26 and 11%, respectively.

A 1-g sample of IVa was dissolved in 20 ml of 5% hydrochloric acid, and the solution was refluxed for 1 h. The benzaldehyde that formed was removed by steam distillation and extracted from the distillate with ether. A total of 0.7 g (51%) of benzaldehyde 2,4-dinitrophenylhydrazone with mp 236-237° (from alcohol) was obtained. The product was identical to an authentic sample.

Reaction of 2-Phenyl-1,2-dihydroquinazoline (IVa) with Hydroxylamine. A solution of 1 g (4.8 mmole) of IVa, 1 g (14.4 mmole) of hydroxylamine hydrochloride, and 1.2 g (15.2 mmole) of pyridine in 20 ml of alcohol was refluxed for 1.5 h. The alcohol was removed by distillation, and the mixture was diluted with 20 ml of water. The reaction product was then extracted with ether. The ether was removed by distillation, and the residue was dissolved by heating in the minimum amount of benzene. Cooling of the benzene solution precipitated 0.37 g (56%) of o-aminobenzaldehyde oxime with mp 134-135° [6]. No melting-point depression was observed for a mixture of this product with an authentic sample of o-aminobenzaldehyde oxime. The presence of benzaldehyde oxime in the reaction product was proved by thin-layer chromatography (TLC) on aluminum oxide (with benzene as the solvent).

Reaction of 2-Phenyl-1,2-dihydroquinazoline (IVa) with p-Anisidine. A solution of 1 g (4.8 mmole) of IVa and 1.23 g (10 mmole) of p-anisidine in 20 ml of alcohol was refluxed for 2 h, after which 10 ml of alcohol was removed by distillation. The solution was then cooled, and the resulting crystals of o-aminobenzylidene-p-anisidine were removed by filtration to give 0.57 g (52%) of a product with mp 118-119° (mp 121-122° [7]). The alcohol was removed from the mother liquor by distillation, and the residue was recrystallized twice from alcohol. The yield of benzylidene-p-anisidine with mp 61-62° [8] was 0.1 g (10%). No melting-point depressions were observed for mixtures of the resulting azomethines with authentic samples.

Oxidation of 2-Phenyl-1,2-dihydroquinazoline (IVa). A solution of 1 g (4.8 mmole) of IVa and 4.35 g (50 mmole) of active manganese dioxide in 30 ml of benzene was refluxed for 2 h. The mixture was then filtered, the benzene was removed by distillation, and the residue was recrystallized from alcohol. The yield of 2-phenylquinazoline with mp 100-101° [6] was 0.41 g (41%). Found: C 81.7; H 4.9; N 13.5%. $C_{14}H_{10}N_2$. Calculated: C 81.5; H 4.9; N 13.6%. The absorption band of an NH group was absent in the IR spectrum.

6-Methyl-2-phenyl-1,2-dihydroquinazoline (IVb). A 2-g (9 mmole) sample of 1-benzyl-5-methylindazole, phenylmagnesium bromide [from 0.7 g (28.7 mg-atom) of magnesium and 4.4 g (28 mmole) of bromobenzene in 10 ml of ether], and 7 ml of 1,2-dimethoxyethane were subjected to reaction. At the end of the reaction, the mixture was treated with 15 ml of 25% ammonium chloride solution, the organic layer was separated, and the base was extracted with 20 ml of 5% hydrochloric acid. Compound IVb was precipitated from the hydrochloric acid extract with 10% ammonium hydroxide to give 0.64 g (32%) of a product with mp 127-128° (from benzene-petroleum ether). Found: C 80.8; H 6.2; N 12.3%. $C_{15}H_{14}N_2$. Calculated: C 81.0; H 6.4; N 12.6%. IR spectrum (mineral oil): 702, 765, 828, 891 (mono- and trisubstituted benzene rings), 1502, 1589 (aromatic C=C bonds), 1640 (C=N), 3240 (NH) cm^{-1}.

2-(p-Chlorophenyl)-1,2-dihydroquinazoline (IVc). As in the preceding experiment, 3 g of 1-(p-chlorobenzyl)indazole gave 1.44 g (48%) of IVc with mp 147-148° (from alcohol). Found: C 68.9; H 4.7; N 11.9%. $C_{14}H_{11}ClN_2$. Calculated: C 69.3; H 4.6; N 11.5%.

2-Phenyl-1,2,3,4-tetrahydroquinazoline (VI). A) A 1.5-g (39.5 mmole) sample of lithium aluminum hydride was added to a solution of 2 g (9.6 mmole) of 1-benzylindazole in 25 ml of tetrahydrofuran (THF), and the mixture was refluxed for 3 h. It was then cooled, 30 ml of water was added, and the mixture was treated several times with ether (40 ml). Removal of the solvents by distillation gave 1.8 g (89%) of VI with mp 98-99° (from heptane). Found: C 80.0; H 7.0; N 13.5%. $C_{14}H_{14}N_2$. Calculated: C 80.0; H 6.7; N 13.3%.

B) A solution of 1 g (4.8 mmole) of IVa in 10 ml of THF and 0.57 g (15 mmole) of lithium aluminum hydride was refluxed for 1 h. After workup as described in the preceding experiment, 0.99 g (98%) of VI with mp 98-99° (from heptane) was obtained. The IR spectra of the two samples were identical.

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