N-ANIONS OF HETEROAROMATIC AMINES

VII.* AUTOOXIDATION OF N-ANIONS OF 3-AMINOINDAZOLES

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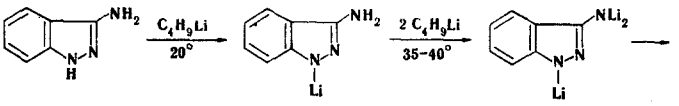
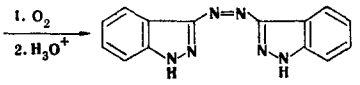
The N-anions of 3-aminoindazole and its 1-substituted derivatives are oxidized by air oxygen to give 3,3'-azo- and in some cases 3,3'-azoxyindazoles.

A few years ago one of us and co-workers observed the ability of poly-N-anions of 2-aminobenzimidazoles to undergo autoxidation under unusually mild conditions (in liquid ammonia) to give 2,2'-azo- and, of particular interest, 2-nitrobenzimidazoles [2]. In the present research we attempted to extend this reaction to 3-aminoindazoles, which are isomers of 2-aminobenzimidazoles.

One equivalent of butane is evolved in the reaction of 3-aminoindazole (I) with excess n-butyllithium in ether at room temperature; this constitutes evidence for the formation of a monolithium salt (II). The latter, like the monolithium salt of 2-aminobenzimidazole [3], is oxidized extremely slowly in air. Another two equivalents of butane are evolved when the temperature is raised to 35-40°C, i.e., salt III is converted to trilithium salt III. An intense crimson coloration, which is associated with the formation of the dianion of 3,3'-azoindazole, develops almost instantaneously under the influence of pure oxygen or air oxygen. The yield of yellow azo compound IV is almost quantitative.



I II III



IV

Primarily the dianion is evidently formed in the reaction of amine I with potassium amide (3 moles) in liquid ammonia [4]. Autooxidation of the dianion also leads to IV in 88% yield. Close results are obtained in the case of the action of sodium metal on 1-benzyl-3-aminoindazole (Va) in liquified ammonia. These results make it possible to assume that the crimson coloration that appears when an alkaline solution of 3-aminoindazole is heated [5] is also due to autooxidation of the N-anions, which are formed in small amounts and exist in equilibrium. However, we were unable to isolate IV after treatment of I with aqueous alkali.

The oxidation of the anions of 1-methyl-3-aminoindazole (Vb) proceeds in a more peculiar manner. Two substances – a yellow substance with 262-263° and a lemon-yellow substance with mp 219-220° (in 32 and 25% yields, respectively) – are formed by the action of 2 moles of KNH_2 in liquid ammonia on amine Vb and subsequent autooxidation of anions VI (possibly a mixture of the mono- and dianion). The first of these compounds is also formed by oxidation of amine Vb with sodium hypochlorite in alkaline media and by methylation of the dianion of 3,3'-azoindazole. On the basis of this it can be concluded that the compound is

* See [1] for communication VI.

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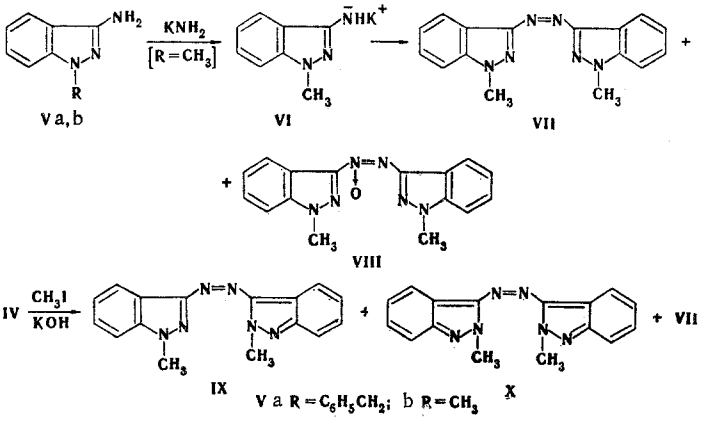
1,1'-dimethyl-3,3'-azoindazole (VII). Judging from the results of elementary analysis, the color (λ_{max} 395 nm), and the IR spectrum (from the absence of ν_{NH} and ν_{NO_2} bands), the second compound is 1,1'-dimethyl-3,3'-azoxyindazole (VIII). A characteristic difference between the azoxy compound and the azo compound is the absence in the UV spectrum of the former of the band at 261 nm (log ε 4.0) that is characteristic for VII.

Methylation of IV in alkaline media gives all three possible isomers: 1,1'-dimethyl- (VII), 1,2'-dimethyl- (IX), and 2,2'-dimethyl-3,3'-azoindazole (X) in 25, 36, and 34% yields, respectively. These isomers are easily distinguished by means of their colors and UV spectra. Isomers VII and IX absorb at λ_{max} 398 and 430 nm, respectively. It is known [6, 7] that the long-wave bands in the spectra of 2-substituted indazoles, which have a quinoid structure, are found, as a rule, in the longer-wave region than those of the 1-substituted compounds.



Va,b VI VII VIII IX X

V a R = $C_6H_5CH_2$; b R = CH_3

Thus our study showed that the N-anions of 3-aminoindazoles, like the N-anions of 2-aminobenzimidazoles, readily undergo autooxidation. However, in contrast to the latter, they do not form nitro compounds and in some cases are converted to azoxy compounds, the formation of which has not been observed in the 2-aminobenzimidazole series.

EXPERIMENTAL

The IR spectra of mineral oil suspensions and chloroform solutions of the compounds were measured with a UR-20 spectrometer. The UV spectra of methanol solutions were recorded with an SF-4A spectrophotometer. The PMR spectra of solutions of the compounds (0.4 mole/liter) were obtained with a Tesla spectrometer (80 MHz) with hexamethyldisiloxane as the internal standard.

1-Methyl-3-aminoindazole (Vb). A 5.15-g (0.03 mole) sample of 1-methylindazole-3-carboxylic acid [8] was refluxed in 50 ml of thionyl chloride for 1.5 h, after which the excess $SOCl_2$ was removed by distillation, and the residue was dissolved in 70 ml of acetone. A solution of 14 g (0.3 mole) of sodium azide in 70 ml of water was added with ice cooling to the resulting solution of the acid chloride, and the mixture was stirred for 2 h. Crushed ice was then added, and the 1-methyl-3-indazolyl azide that precipitated in the course of 1.5 h was removed by filtration, washed with water, and dried in a vacuum desiccator at room temperature to give 5.23 g (86%) of sand-colored crystals with mp 100-101° (from aqueous alcohol or octane). IR spectrum (mineral oil): ν_{NO_3} 2150 cm^{-1}. Found: C 5.40; H 3.8; N 35.0%. $C_9H_7N_5O$. Calculated: C 53.7; H 3.5; N 34.8%.

A 4.5-g (0.022 mole) sample of 1-methyl-3-indazolyl azide was refluxed in 230 ml of alcohol for 22 h, after which half of the solvent was removed by distillation without isolating the urethane, 70 ml of 30% potassium hydroxide solution was added, and the mixture was refluxed for another 20 h. The alcohol was removed by distillation, the residual oil was triturated with water, and the solid was removed by filtration and dried. It was purified by chromatography with a column filled with aluminum oxide (elution with chloroform) with collection of the fraction with R_f 0.35. The product from this fraction was crystallized from hexane to give snow-white needles with mp 97-98°. The yield was 2.6 g (81%). IR spectrum ($CHCl_3$): ν_{as} 3448, ν_s 3380, and δ_{NH_2} 1617 cm^{-1}. Found: C 65.6; H 6.3; N 28.2%. $C_8H_9N_3$. Calculated: C 65.3; H 6.2; N 28.5%.

1-Benzyl-3-aminoindazole (Va). This compound was obtained as white needles with mp 116° (from ethanol) by the method in [9].

Reaction of n-Butyllithium with 3-Aminoindazole. A 0.67-g (5 mmole) sample of 3-aminoindazole [10] was added slowly at room temperature under nitrogen to butyllithium obtained in ether from 0.45 g (0.06 g-atom) of lithium. Bubbles of butane gas began to evolve immediately and were collected under a layer of a so-

dium chloride solution. Under these conditions, 110 ml of butane was collected, whereas 230 ml were collected upon subsequent heating of the mixture on a water bath; the total volume of butane was therefore 340 ml, in agreement with the formation of a trilithium salt (the theoretical yield of butane is 336 ml). At the end of gas evolution, the ether was evaporated, and the dry residue was oxidized with air for 24 h. Water (30 ml) was then added, and the mixture was filtered to give 0.65 g (quantitative yield) of light-brown 3,3'-azoindazole. Orange crystals with mp 330-331° (dec.) were obtained by crystallization from alcohol–dimethylformamide (DMF). UV spectrum: λ_{max} 390 nm (log ε 4.11). Found: C 64.3; H 4.1; N 31.9%. $C_{14}H_{10}N_6$. Calculated: C 64.1; H 3.8; N 32.1%.

Reaction of Potassium Amide with 3-Aminoindazole. A 1.33-g (0.01 mole) sample of I was added to a suspension of 1.65 g (0.03 mole) of KNH_2 in 60 ml of liquid ammonia. The initially intensely red suspension turned brown at the end of the first hour. The mixture was stirred at −80° for 1 h and at room temperature for 1 h, after which the ammonia was evaporated, and the residual mixture was allowed to stand in air for 24 h for oxidation. The dry residue in the flask was treated with 50 ml of water, and the mixture was filtered to give 0.96 g of IV. Another 0.2 g of the same product was isolated from the neutral filtrate for an overall yield of 88%. The product had mp 330°.

Reaction of Sodium with 1-Benzyl-3-aminoindazole. A 0.38-g (0.015 g-atom) of Na was added in small portions to a suspension of 1.1 g (5 mmole) of Va in 60 ml of liquid ammonia, and the reaction was carried out under the standard conditions. The NH_3 was then evaporated, and the residue was oxidized for 20 h. Water (30 ml) was added to the dry residue, and the mixture was filtered to give 0.15 g of solid. Neutralization of the filtrate with HCl gave another 0.28 g of the same product. Crystallization from alcohol containing DMF gave orange needles (66%) that were identical to IV with respect to their melting point and the results of thin-layer chromatography (TLC). A total of 0.15 g (23%) of unsubstituted 3-aminoindazole was extracted from the neutral solutions with ethyl acetate.

1,1'-Dimethyl-3,3'-azoindazole (VII). A total of 2 ml of a dilute solution of sodium hypochlorite was added with cooling to a solution of 0.15 g (1 mmole) of Vb in 6 ml of alcohol. After 15 min, the mixture was filtered to give 0.12 g (80%) of a yellow solid with mp 262-263° (from benzene). UV spectrum: λ_{max} 398 nm (log ε 4.13). Found: C 66.3; H 5.2; N 28.7%. $C_{16}H_{14}N_6$. Calculated: C 66.2; H 4.9; N 29.0%.

Reaction of Potassium Amide with 1-Methyl-3-aminoindazole. A 0.9-g (6 mmole) sample of Vb was added to a suspension of 0.66 g (12 mmole) of KNH_2 in 90 ml of liquid ammonia, and the reaction was carried out under the standard conditions. The ammonia was evaporated, and the residue was allowed to stand for 24 h. The oxidized dry residue in the flask was treated with 30 ml of water, and the mixture was filtered to give 0.61 g of undissolved reaction product consisting of VII (R_f 0.95) and a substance with R_f 0.5, which were separated by chromatography with a column filled with Al_2O_3 (elution with chloroform) to give 32% VII and 25% of a lemon-yellow substance with mp 219-220° (from isopropyl alcohol), which was identified as VIII. UV spectrum: λ_{max} 395 nm (log ε 4.29). PMR spectrum (in $C_6H_5NO_2$): δ_{CH_3} 4.05 ppm. Found: C 62.7; H 4.6; N 27.2%. $C_{16}H_{14}N_6O$. Calculated: C 62.8; H 4.6; N 27.4%. Extraction of the neutral solution with chloroform gave 0.21 g (22%) of starting amine Vb.

Methylation of 3,3'-Azoindazole. A 0.5-g (2 mmole) sample of IV was refluxed in a mixture of 7 ml of alcoholic alkali (4 mmole) and 0.26 ml (4 mmole) of CH_3I for 10 min, after which the mixture was cooled, and the precipitate was removed by filtration and washed with alcohol to give 0.2 g (34%) of red crystals of 2,2'-dimethyl-3,3'-azoindazole (X) with mp 245-246° (from alcohol containing DMF). Found: C 65.9; H 5.0; N 28.9%. $C_{16}H_{14}N_6$. Calculated: C 66.2; H 4.9; N 29.0%. UV spectrum: λ_{max} 500 nm (log ε 4.67). The addition of water to the filtrate gave 0.35 g of a precipitate, from which 0.14 g (25%) of yellow crystals of VII (with mp 262°) was extracted with benzene in a Soxhlet apparatus. The residual orange-yellow crystals [0.21 g (36%)], with mp 187-188° (from alcohol), were identified as unsymmetrical azoindazole IX. UV spectrum: λ_{max} 430 nm (log ε 4.38). The PMR spectrum of a CCl_4 solution contains signals of two different CH_3 groups at δ 4.02 and 4.40 ppm. Found: C 66.5; H 4.7; N 28.9%. $C_{16}H_{14}N_6$. Calculated: C 66.2; H 4.9; N 29.0%.

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PYRAZOLOANTHRONE DERIVATIVES

I. REACTIVITY OF 3-AMINOPYRAZOLOANTHRONE

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Benzoylation of 3-aminopyrazoloanthrone in aqueous alkali takes place in the 1 position, whereas in organic media the amino group is benzoylated initially, followed by benzoylation of the 2 position; 1-benzoyl-3-aminopyrazoloanthrone undergoes quantitative isomerization to 3-benzamidopyrazoloanthrone. Alkylation of 3-aminopyrazoloanthrone with butyl iodide in acetone containing KOH gives initially two isomeric heteroring-substituted derivatives, and second alkyl residue becomes attached to the amino group, and a third alkyl residue becomes attached to the oxygen atom of the isomeric form of the dialkyl-substituted compounds. Sulfonation takes place in the 5 position. The effect of the character of the substituents in the 3 position of the pyrazoloanthrone on the pK'_a values was investigated, and an anomalous effect of amino and alkylamino groups that is associated with the possibility of tautomeric transformations was noted.

Whereas "anthrimide condensation" is characteristic for pyrazoloanthrone, 1-aminoanthraquinone, etc., according to the literature data [1] and our data, the condensation of 3-aminopyrazoloanthrone (I) with 3-bromobenzanthrone was unsuccessful. To ascertain the reactivity of amine I, we studied its behavior in acylation and alkylation reactions. (See display at top of next page.)

One monoacyl derivative (II, R^1 = 1-COC_6H_5, $R^2 = R^3$ = H) was isolated in the acylation of amino derivative I with benzoyl chloride in aqueous alkali, whereas pyrazoloanthrone gives a mixture of two isomers with respect to the 1 and 2 positions with predominance of the latter. The IR spectrum of II contains bands of a carbonyl group at 1682 cm^{-1} and of an amino group at 3320 and 3408 cm^{-1}, but an intramolecular hydrogen bond is absent. Thin-layer chromatography (TLC) of the reaction products on Silufol shows the presence of two compounds, but the second substance (III) decomposes to give starting I, and this makes it possible to assign it to the o-acyl derivative. Compound II undergoes isomerization when it is melted to give 3-benzamidopyrazoloanthrone (IV, $R^1 = R^3$ = H, R^2 = COC_6H_5) in a yield close to quantitative. Benzoylation of amino compound I in organic media in the presence of acid-binding substances (K_2CO_3) with 1 mole of C_6H_5COCl gave immediately 3-benzamido derivative IV. Compound IV was also obtained by condensation of 1-chloro-2-benzamidoanthraquinone (XVIII) and hydrazine hydrate in pyridine. Dibenzoyl derivative V (R^1 = 2-COC_6H_5, R^2 = COC_6H_5) is formed in the acylation of I and IV with excess reagent in organic media. Its IR spectrum contains a strongly diffuse band at 3200 cm^{-1} (associated NH), whereas the spectrum of IV contains two bands at 3350 ($NHCOC_6H_5$) and 3065 cm^{-1} (associated NH).

Alkylation of amino compound I with butyl iodide in acetone (in the presence of KOH) leads to stepwise substitution. The first alkyl residue enters the heteroring; however, whereas pyrazoloanthrone gives

* Deceased.

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