

REARRANGEMENT OF THE BENZIDINE TYPE
 IN THE INDOLE SERIES
 SYNTHESIS OF INDOLO[1,2-c]QUINAZOLINES

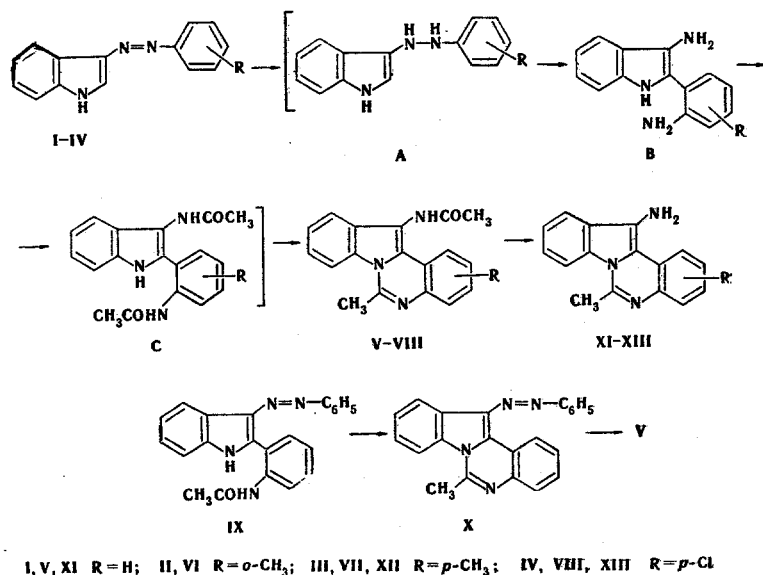
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12-Acetamidoindolo[1,2-c]quinazolines were obtained by treatment of 3-arylazaindoles with zinc in acetic acid in the presence of acetic anhydride and sodium acetate. The products were converted to the corresponding amines by hydrolysis.

In a study of the reduction of 3-arylazaindoles (I-IV) with zinc in acetic acid in the presence of acetic anhydride and sodium acetate we found that the reaction gives 12-acetamidoindolo[1,2-c]quinazolines (V-VIII). The IR spectra of derivatives V-VIII contain absorption bands at 3260 (NH) and 1640-1645 cm^{-1} (amide C = O). Singlets at 2.25 (COCH_3) and 3.15 ppm (CH_3) and a multiplet at 7.85-8.35 ppm (eight aromatic protons) are observed in the PMR spectrum of V. In addition, diazo coupling of 2-(o-acetamidophenyl) indole [1] with benzenediazonium chloride gave 2-(o-acetamidophenyl)-3-phenylazaindole (IX). The latter gives 6-methyl-12-phenylazaindolo[1,2-c]quinazoline (X) in high yield. Reduction of X with zinc in acetic acid in the presence of acetic anhydride and sodium acetate gives 6-methyl-12-acetamidoindolo[1,2-c]quinazoline (V), which was identical to a sample of V obtained by reduction of 3-phenylazaindole (I).

The reduction of 3-arylazaindoles apparently proceeds through a step involving the formation of 3-arylhydrazaindoles (A), which undergo a rearrangement of the benzidine type that was previously unknown in the indole series.



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TABLE 1. 12-Acetamidoindolo[1,2-c]quinazolines (V-VIII)

Com- pound	R	mp, °C (dec.,* from DMF)	Empirical formula	Found, %			Calc., %			Yield, %
				C	H	N	C	H	N	
V	H	305—306	C ₁₈ H ₁₅ N ₃ O	74.5	5.4	14.7	74.7	5.2	14.5	52
VI	<i>o</i> -CH ₃	299—300	C ₁₉ H ₁₇ N ₃ O	75.2	5.7	14.0	75.2	5.7	13.9	10.3
VII	<i>p</i> -CH ₃	316—318	C ₁₉ H ₁₇ N ₃ O	75.2	5.7	14.0	75.2	5.7	13.9	32
VIII	<i>p</i> -Cl	330—332	C ₁₈ H ₁₄ N ₃ OCl*	66.7	4.4	12.9	66.8	4.4	13.0	10.6

*Found: Cl 11.2%. Calculated: Cl 11.0%.

The 2-(*o*-aminoaryl)-3-aminoindoles (B) formed as a result of the rearrangement are converted under the reaction conditions to 2-(*o*-acetamidoaryl)-3-acetamidoindoles (C), which then undergo cyclization to indolo[1,2-c]quinazolines (V-VIII).

12-Acetamido[1,2-c]quinazoline derivatives V-VIII are readily hydrolyzed with hydrochloric acid to 12-aminoindolo[1,2-c]quinazolines (XI-XIII).

Derivatives XI and XII react with benzaldehyde to give Schiff bases (XIV, XV) in high yields. The absence in the IR spectra of XIV and XV of absorption bands associated with the stretching vibrations of an amino group, which are observed in the spectra of starting XI and XII, confirms that the reaction proceeds at the NH₂ group rather than at the CH₃ group. The starting 3-arylazindoles (I-IV) were obtained by diazo coupling of indole with arenediazonium salts; 3-phenylazindole (I) and 3-(*p*-chlorophenylazo)indole (IV) were previously synthesized [2, 3].

EXPERIMENTAL METHOD

The IR spectra of mineral oil suspensions of the compounds were recorded with Perkin-Elmer and UR-10 spectrometers. The UV spectra of dioxane solutions of the compounds were recorded with an EPS-3 spectrophotometer. The PMR spectra of trifluoroacetic acid solutions were recorded with a INM-4H-100 spectrometer with tetramethylsilane as the standard.

3-(*o*-Methylphenylazo)indole (II). A diazonium salt obtained in the usual way from 53.3 g (0.5 mole) of *o*-toluidine, 150 ml of concentrated HCl, and 34.5 g (0.5 mole) of sodium nitrite was added gradually to a solution of 58.5 g (0.5 mole) of indole in 500 ml of methanol at 0° while maintaining the pH of the medium at 8-9 by the simultaneous addition of a saturated solution of sodium carbonate. At the end of the addition, the reaction mixture was allowed to stand at 0° for 2 h. The resulting precipitate was removed by filtration, washed with water, and dried. The yield of II, with mp 116-117°, after recrystallization from methanol was 58.5 g (50%). Found: C 76.6; H 5.6; N 17.9%. C₁₅H₁₃N₃. Calculated: C 76.6; H 5.6; N 17.9%.

3-(*p*-Methylphenylazo)indole (III). This compound, with mp 176-177°, was obtained in 45% yield (from methanol) under the conditions of the synthesis of II. Found: C 76.6; H 5.5; N 17.9%. C₁₅H₁₃N₃. Calculated: C 76.6; H 5.6; N 17.9%.

12-Acetamidoindolo[1,2-c]quinazolines (V-VIII). A 0.42-mole sample of acetic anhydride and 0.24 mole of fused sodium acetate were added to a solution of 0.16 mole of I-IV in 300 ml of glacial acetic acid, after which 0.92 mole of zinc powder was added in portions while maintaining the temperature of the mixture at 50-60°. At the end of the addition of the zinc dust, the mixture was refluxed for 1 h. It was then cooled, and the resulting precipitate was removed by filtration, washed with water, and refluxed in dimethylformamide (DMF). The insoluble material was removed by filtration, and the mother liquor was cooled and diluted with water. The resulting precipitate was removed by filtration, washed with methanol, and dried. Data on V-VIII are presented in Table 1.

2-(*o*-Acetamidophenyl)-3-phenylazindole (IX). This compound was obtained under the conditions of the synthesis of II. The yield of washed (with methanol) azoindole IX, with mp 220-221° (dec., from methanol), was 76.8%. Found: C 74.4; H 5.1; N 16.0%; C₂₂H₁₈N₄O. Calculated: C 74.6; H 5.1; N 15.8%.

6-Methyl-12-phenylazindolo[1,2-c]quinazoline (X). Ether (5 ml) saturated with hydrogen chloride was added to a solution of 0.5 g (0.0014 mole) of IX in 500 ml of ether, and the mixture was allowed to stand at room temperature overnight. The resulting precipitate was removed by filtration, washed with ether, and dried. It was then dissolved in a mixture of methanol and dioxane (200 ml), and the solution was cooled and made alkaline with ammonium hydroxide. It was then diluted with water, and the resulting

TABLE 2. 12-Aminoindolo[1,2-c]quinazolines (XI-XIII)

Com- pound	R	mp, °C (from meth- anol)	Empirical formula	Found, %			Calc., %			Yield, %
				C	H	N	C	H	N	
XI	H	202,5—204 (dec.)	C ₁₆ H ₁₃ N ₃	77,6	5,3	16,9	77,7	5,3	17,0	92
XII	<i>p</i> -CH ₃	217—218	C ₁₇ H ₁₅ N ₃	78,2	5,9	16,1	78,1	5,8	16,1	99
XIII	<i>p</i> -Cl	244—245	C ₁₆ H ₁₂ N ₃ Cl*	68,0	4,1	14,9	68,2	4,3	14,9	99

* Found: Cl 12.3%. Calculated: 12.6%.

precipitate was removed by filtration, washed with water, and dried to give 0.45 g (95.7%) of X with mp 231–232° (from methanol). Found: C 78.5; H 5.0; N 16.7%; C₂₂H₁₆N₄. Calculated: C 78.6; H 4.8; N 16.7%.

6-Methyl-12-acetamidindolo[1,2-c]quinazoline (V). This compound was obtained from X under the conditions of the synthesis of V–VIII. The yield of quinazoline V, with mp 305–306° (dec., from DMF), was 61%. No melting-point depression was observed for a mixture of this product with a sample of V obtained from azoindole I by rearrangement.

12-Aminoindolo[1,2-c]quinazolines (XI–XIII). A 0.01-mole sample of V, VII, or VIII was refluxed in 100 ml of concentrated hydrochloric acid for 5 h in a flask equipped with a reflux condenser fitted with a Bunsen valve. The mixture was then cooled, and the resulting precipitate was removed by filtration. The precipitate was dissolved by heating in 250 ml of distilled water, and the solution was made alkaline with 25% ammonium hydroxide. The resulting precipitate was removed by filtration, washed with water, and dried. IR spectra: 3390–3400, 3300, and 3200 cm⁻¹ (NH). Data on XI–XIII are presented in Table 2.

6-Methyl-12-benzylideneaminoindolo [1,2-c]quinazoline (XIV). A 0.42-g (0.004 mole) sample of benzaldehyde was added to a suspension of 0.99 g (0.004 mole) of XI in 50 ml of alcohol, and the mixture was refluxed for 1 h. It was then cooled, and the resulting precipitate was removed by filtration, washed with methanol, and dried. The yield of Schiff base XIV with mp 213–5–214,5° (from DMF) was 1.2 g (90%). Found: C 82.5; H 5.0; N 12.5%. C₂₃H₁₇N₃. Calculated: C 82.4; H 5.1; N 12.5%.

2-6-Dimethyl-12-benzylideneaminoindolo[1,2-c]quinazoline (XV). This compound was obtained from XII under the conditions of the synthesis of XIV. The yield of XV, with mp 226.5–227,5° (from DMF), was 93%. Found: C 82.8; H 5.5; N 12.1%. C₂₄H₁₉N₃. Calculated: C 82.5; H 5.5; N 12.0%.

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