5. L. Bellamy, Infrared Spectra of Complex Molecules, Methuen, London (1958).
6. V. P. Mamaev and O. A. Zagulyaeva, Khim. Geterotsikl. Soedin., Collection 1, 354 (1967).
7. V. V. Lapachev, O. A. Zagulyaeva, and V. P. Mamaev, Izv. Akad. Nauk SSR, Ser. Khim., No. 11, 2633 (1977).
8. V. V. Lapachev, O. A. Zagulyaeva, and V. P. Mamaev, Dokl. Akad. Nauk SSSR, 236, 113 (1977).
9. E. A. Oostveen and H. C. van der Plas, Rec. Trav. Chim., 93, 233 (1974).
10. R. Elderfield (ed.), Heterocyclic Compounds, Vol. 2, Wiley.
11. L. Bellamy, The Infrared Spectra of Complex Molecules, 3rd ed., Halsted Press (1975).
12. A. R. Katritzky and J. M. Lagowsky, Chemistry of the Heterocyclic N-Oxides, London — New York (1971), p. 287.
13. F. Bellamy and J. Streith, Heterocycles, Vol. 4 (1976), p. 1391.
14. J. H. Chesterfield, J. F. W. McOmie, and M. S. Tute, J. Chem. Soc., 4590 (1960).
15. E. A. Oostveen and H. C. van der Plas, Rec. Trav. Chim., 96, 64 (1977).
16. J. P. Freeman, E. G. Duthie, M. J. O'Hare, and J. F. Hansen, J. Org. Chem., 37, 2756 (1972).
17. V. F. Sedova, A. S. Lisitsyn, and V. P. Mamaev, Khim. Geterotsikl. Soedin., No. 10, 1392 (1978).
18. H. Yamanaka, S. Nittsuma, T. Sakamoto, and M. Mizugaki, Heterocycles, 5, 255 (1976).

SYNTHESIS OF SUBSTITUTED INDOLO[1,2-c]QUINAZOLINES

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It was established that N-acetylindoxyl arylhydrazones are converted to 12-acetamidoindolo[1,2-c]quinazolines in acetic acid in the presence of acetic anhydride, evidently through a step involving the formation of arylhydrazoindole derivatives. A new method for the synthesis of 12-acetamidoindolo[1,2-c]quinazolines from N,O-diacetylindoxyls and arylhydrazines is proposed.

We have shown that indolo[1,2-c]quinazolines are formed in the reduction of N-acetyl-3-arylazoindoles with zinc dust in acetic acid in the presence of acetic anhydride and sodium acetate [1]. We assumed that the indicated reaction proceeds through an intermediate step involving the formation of N-acetyl-3-arylhydrazoindoles, which in acidic media undergo a rearrangement of the o-benzidine type and are then converted to indolo[1,2-c]quinazolines [1]. In this connection, in the present research we carried out the synthesis and studied the behavior in acidic media of N-acetylindoxyl arylhydrazones, which in the tautomeric form can be regarded as N-acetyl-3-arylhydrazoindoles. The phenylhydrazone (Ia), p-chlorophenylhydrazone (Ib), and p-nitrophenylhydrazone (Ic) of N-acetylindoxyl were obtained from N-acetylindoxyl [2] and the corresponding arylhydrazines (Ia was previously described in [3]). The presence in the PMR spectra of these compounds of singlet signals at δ 4.75 ppm with an intensity of two proton units, which are due to the methylene protons of the indoxyl molecule, confirms the structure of Ia-c. When Ia-c are heated in acetic acid in the presence of acetic anhydride, they undergo a rearrangement similar to the o-benzidine rearrangement, probably through a step involving the formation of the tautomeric hydrazine form (A), after which, as a result of cyclocondensation of the rearrangement product (B), they form 12-aminoindolo[1,2-c]quinazolines (IIa-c), which are acetylated during the reaction and are converted to 12-acetamidoindolo[1,2-c]quinazolines (IIIa-c).

We also studied the reaction of N,O-diacetylindoxyls with a twofold excess of the arylhydrazines in alcohol and found that the reaction proceeds in different directions, depending on the character of the substituents in the phenyl ring of the arylhydrazine and the benzene ring of the indoxy molecule. Thus N-acetylindoxyl arylhydrazones Ib and Ic, which are iden-

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TABLE 1. N-Acetylindoxyl Arylhydrazones (Ia-c)

Compound	mp, deg C[a]	IR spectrum, cm^{-1}		PMR spectrum, δ, ppm	Found, %			Empirical formula	Calculated, %			Reaction time, h		Yield, %	
		NH	C=O		C	H	N		C	H	N	1	2	1	2
Ia	170—171	3290	1650	2,2 (s, $COCH_3$), 4,75 (s, CH_2), 6,75—8,2 (aromatic ring protons)	72,2	6,1	15,9	$C_{16}H_{15}N_3O$	72,4	5,7	15,8	0,5	—	66	—
Ib	183—184	3260	1650	2,2 (s, $COCH_3$), 4,75 (s, CH_2), 7,05—8,2 (aromatic ring protons) 8,77 (s, NH)	64,0	4,7	14,2	$C_{16}H_{14}ClN_3O$[b]	64,1	4,7	14,0	4	3	50	52
Ic	233 (dec.)	3310	1670	2,2 (s, $COCH_3$), 4,75 (s, CH_2), 7,18—8,83 (aromatic ring protons) 9,93 (s, NH)	61,8	4,2	18,0	$C_{16}H_{14}N_4O_3$	61,9	4,6	18,1	4	10	55	53

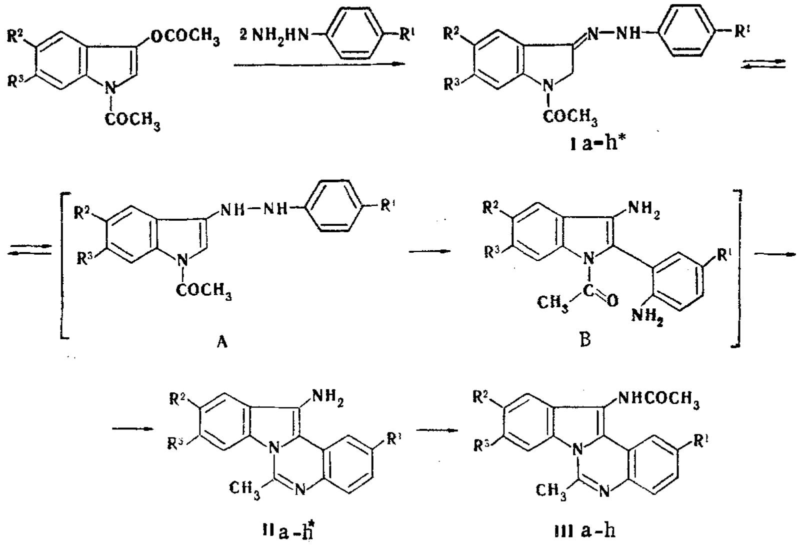
[a] The compounds were recrystallized: Ia from dioxane, Ib from DMF—methanol (1:1), and Ic from DMF. [b] Found: Cl 11.7%. Calculated: Cl 11.8%.

TABLE 2. 12-Aminoindolo[1,2-c]quinazolines (IIa, d, e)

Compound	mp, deg C[a]	IR spectrum, cm^{-1} (NH_2)	UV spectrum λ_{max}, nm (log ε)	Found, %				Empirical formula	Calc., %				Reaction time, h	Yield, %
				C	H	Br	N		C	H	Br	N		
IIa	210—212	3400, 3310, 3220	245 sh (4,22) 282 (4,71) 370 (4,11)	77,8	5,3	—	17,0	$C_{16}H_{13}N_3$[b]	77,7	5,3	—	17,0	10	56,5
IId	237—238	3390, 3290, 3200	220 (4,22), 255 (4,24) 287 (4,44), 380 (4,58)	58,6	3,8	24,9	12,8	$C_{16}H_{12}BrN_3$	58,9	3,7	24,5	12,9	3,5	53
IIe	263	3370, 3220	225 (4,46), 260 (4,35), 290 (4,79), 386 (4,11)	53,1	3,0	22,1	11,8	$C_{16}H_{11}BrClN_3$[c]	53,3	3,1	22,2	11,7	3,5	42

[a] The compounds were recrystallized: IIa from DMF—methanol (1:1), IId from DMF—methanol (2:1), and IIe from DMF. [b] M^+ 247. [c] Found: Cl 9.8%. Calculated: Cl 9.8%.

tical to Ib, c obtained from N-acetylindoxyl and the corresponding arylhydrazines, are formed in the reaction of N,O-diacetylindoxyl with p-chlorophenyl- and p-nitrophenylhydrazines; in this case 1 mole of the arylhydrazine is evidently consumed in the hydrazinolysis of the N,O-diacetylindoxyl, and the resulting N-acetylindoxyl reacts with a second mole of arylhydrazine to give the N-acetylindoxyl arylhydrazone. The corresponding 12-aminoindolo[1,2-c]quinazolines (IIa, d, e) were obtained in the reaction of N,O-diacetylindoxyl with phenylhydrazine and in the reaction of 5-bromo-N,O-diacetylindoxyl [5] with phenyl- and p-chlorophenylhydrazines without isolation of the N-acetylindoxyl arylhydrazones (Ia, d, e).



I, II, III a $R^1=R^2=R^3=H$; b $R^1=Cl$, $R^2=R^3=H$; c $R^1=NO_2$, $R^2=R^3=H$; d $R^1=R^3=H$, $R^2=Br$; e $R^1=Cl$, $R^2=Br$, $R^3=H$; f $R^1=R^2=H$, $R^3=NO_2$; g $R^1=Cl$, $R^2=H$, $R^3=NO_2$; h $R^1=NO_2$, $R^2=H$, $R^3=NO_2$

The structure of IIa, d, e was confirmed in the case of IIa from the absence of a depression of the melting point of a mixture of the product with a sample with a known structure [1, 4] and by the identical character of the IR and UV spectra of these compounds. The structure of IIIa-c was similarly confirmed in the case of IIIa, b from the absence of a depression of the melting point of mixtures of these products with samples previously obtained in [1, 4] and by the identical character of their IR and UV spectra.

If the reaction of N,O-diacetylindoxyls with a twofold excess of the arylhydrazine is carried out in acetic acid rather than in alcohol with the subsequent addition of acetic anhydride, in all cases, regardless of the substituents in the phenyl ring of the arylhydrazine and in the benzene ring of the indoxyl molecule, the process does not stop at the step involving the formation of the arylhydrazones (Ia-h) of 12-aminoindolo[1,2-c]quinazolines (IIa-h) but leads to 12-acetamidoindolo[1,2-c]quinazolines (IIIa-h). Thus IIIa-c and IIIf-h were obtained in the reaction of N,O-diacetylindoxyl and 6-nitro-N,O-diacetylindoxyl [6] with phenyl-, p-chlorophenyl-, and p-nitrophenylhydrazines, while IIId, e were obtained in the reaction of 5-bromo-N,O-diacetylindoxyl with phenyl- and p-chlorophenylhydrazines.

EXPERIMENTAL

The PMR spectra of solutions of the Ia-c in d_6-DMF were recorded with a JNM-4H-100 spectrometer with hexamethyldisiloxane as the internal standard, and the PMR spectrum of IIIe in d_6-DMSO was recorded with a WH-90 spectrometer with tetramethylsilane as the internal standard. The IR spectra of mineral oil suspensions were recorded with a UR-10 spectrometer. The UV spectra of solutions of IId, e and IIIa in dioxane and of a solution of IIa in alcohol were recorded with an EPS-3 spectrophotometer. The mass spectra of IIa, IIIc, and IIIf-h were recorded with a Varian MAT-112 spectrometer (70 eV). The course of the reaction and the individuality of the compounds were monitored on Silufol UV-254 plates in a benzene—methanol system (9:2).

N-Acetylindoxyl Arylhydrazones (Ia-c). Method 1. A mixture of 0.02 mole of N-acetylindoxyl and 0.02 mole of the arylhydrazine was refluxed in 30 ml of alcohol, and the result-

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*Compounds Id-h, IIb, c, and IIf-h were not isolated.

TABLE 3. 12-Acetamidoindolo[1,2-c]quinazolines (IIIa-h)

Compound	mp, °C (DMF)	IR spectrum, cm-1		Found, %				Empirical formula (M, by mass spectrometry)	Calculated, %				Yield, %	
		ν_{NH}	$\nu_{C=O}$	C	H	Cl	N		C	H	Cl	N	1	2
IIIa[a]	308—310	3260	1640	74,6	5,1	—	14,2	$C_{18}H_{15}N_3O$	74,7	5,2	—	14,5	41	70
III b	332	3260	1640	66,7	4,5	10,9	13,0	$C_{18}H_{14}ClN_3O$	66,8	4,4	11,0	13,0	38	75
III c	365	3260	1660	64,6	4,1	—	16,8	$C_{18}H_{14}N_4O_3$ (334)	64,7	4,2	—	16,8	7	6,3
III d	340—342	3270	1650	58,5	3,6	—	11,3	$C_{18}H_{14}BrN_3O$[b]	58,7	3,8	—	11,4	76	—
III e[c]	359	3280	1650	53,6	3,1	8,7	10,6	$C_{18}H_{13}BrClN_3O$[d]	53,7	3,3	8,8	10,4	34	—
III f	362	3260	1650	65,0	4,6	—	16,4	$C_{18}H_{14}N_4O_3$ (334)	64,7	4,2	—	16,8	52	—
III g	>420	3270	1650	58,6	3,8	9,6	15,0	$C_{18}H_{13}ClN_4O_3$ (368)	58,6	3,7	9,6	15,2	55	—
III h	375	3220	1650	56,8	3,5	—	18,2	$C_{18}H_{13}N_5O_5$ (379)	57,0	3,5	—	18,5	5,5	—

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[a] UV spectrum of IIIa, λ_{max} (log ε): 247 (4.51), 273 (4.74), 283 (4.98), 292 sh (4.17), 346 (4.20), 360 nm sh (4.16).
[b] Found: Br 22.1%. Calculated: Br 21.7%. [c] PMR spectrum of IIIe, δ, ppm: 2.26 (s, $COCH_3$), 3.08 (s, CH_3), 7.25-8.36 (aromatic ring protons), and 10.0 (s, NH). [d] Found: Br 19.6%. Calculated: Br 19.9%.

ing precipitate was removed by filtration, washed with alcohol, and dried. The reaction times and data on Ia-c are presented in Table 1.

Method 2. Compounds Ib, c were also obtained by refluxing 0.01 mole of N,O-diacetylindoxyl and 0.02 mole of the arylhydrazine in 20 ml of alcohol. The reaction times and yields of Ib, c for this method are presented in Table 1.

12-Aminoindolo[1,2-c]quinazolines (IIa, d, e). A mixture of 0.015 mole of N,O-diacetylindoxyl and 0.03 mole of the arylhydrazine was refluxed in 30 ml of alcohol, after which the mixture was cooled, and the resulting precipitate was removed by filtration, washed with alcohol, and dried. The reaction times and data on IIa, d, e are presented in Table 2.

12-Acetamidoindolo[1,2-c]quinazolines (IIIa-h). Method 1. A 10-mmole sample of the arylhydrazine was added to a solution of 5 mmole of N,O-diacetylindoxyl in 10 ml of acetic acid, and the mixture was refluxed for 30 min. A 1.4-ml (15 mmole) sample of acetic anhydride was then added, and the mixture was refluxed for another 10 min. It was then cooled, and the precipitate was removed by filtration and washed with methanol. Data on IIIa-h are presented in Table 3.

Method 2. A mixture of 5 mmole of N-acetylindoxyl arylhydrazone (Ia-c), 10 ml of acetic acid, and 0.015 mole of acetic anhydride was stirred at 60-70°C for 10 min, after which it was cooled, and the precipitate was removed by filtration, washed with methanol, and dried. The yields of IIIa-c obtained by this method are presented in Table 3. (In the preparation of IIIc 6 mmole of fused sodium acetate was added to the mixture of starting compounds, and the mixture was refluxed for 1 h).

LITERATURE CITED

1. V. I. Shvedov, G. N. Kurilo, A. A. Cherkasova, and A. N. Grinev, Khim. Geterotsikl. Soedin., No. 3, 377 (1977).
2. G. I. Zhungietu, V. A. Budylin, and A. N. Kost, The Preparative Chemistry of Indole [in Russian], Shtiintsa, Kishinev (1975), p. 63.
3. W. Madelung, Ber., 57, 251 (1924).
4. V. I. Shvedov, G. N. Kurilo, A. A. Cherkasova, and A. N. Grinev, Khim. Geterotsikl. Soedin., No. 8, 1096 (1975).
5. G. I. Zhungietu, V. A. Budylin, and A. N. Kost, The Preparative Chemistry of Indole [in Russian], Shtiintsa, Kishinev (1975), p. 64.
6. J. Schwarz, Monatsh. Chem., 26, 1259 (1905).