4. A. Albert and E. Serjeant, Ionization Constants of Acids and Bases, Methuen (1962).
5. J. Shvo and H. Shanon-Atidy, J. Am. Chem. Soc., 91, 6689 (1969).
6. L. A. Ignatova, P. L. Ovechkin, M. Z. Branzburg, A. E. Gekhman, and B. V. Unkovskii, Khim., Geterotsikl. Soedin., No. 8, 1037 (1972).
7. L. A. Ignatova, A. E. Gekhman, P. L. Ovechkin, and B. V. Unkovskii, Khim. Geterotsikl. Soedin., No. 3, 354 (1974).
8. P. L. Ovechkin, L. A. Ignatova, A. E. Gekhman, and B. V. Unkovskii, Khim., Geterotsikl. Soedin., No. 357 (1974).
9. K. Weygand, Experimental Methods in Organic Chemistry [Russian translation], Inostr. Lit., Moscow (1950), p. 149.

REARRANGEMENT OF THE SEMIDINE TYPE IN THE INDOLE SERIES. SYNTHESIS OF 2-ARYLAMINO-3-ACETAMIDOINDOLES

G. N. Kurilo, N. I. Rostova,
A. A. Cherkasova, and A. N. Grinev

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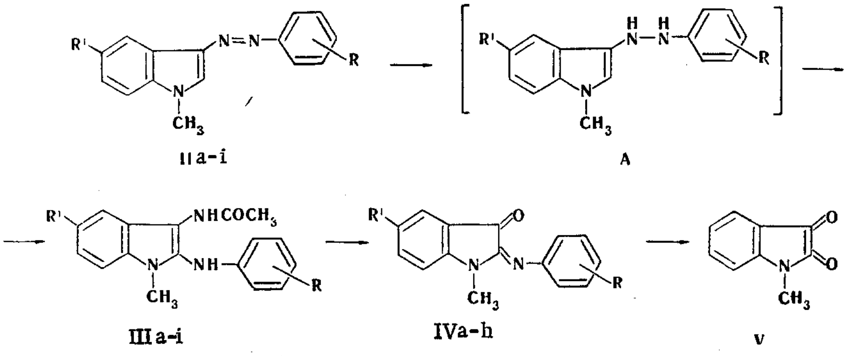
A previously unknown (in the indole series) rearrangement of the semidine type leading leading to the formation of 1-methyl-2-arylamino-3-acetamidoindoles, the oxidation of which gives 1-methylisatin α-anils, occurs when 1-methyl-3-arylazoindoles are treated with zinc in acetic acid in the presence of acetic anhydride and sodium acetate. Data from the UV, IR, and PMR spectra are presented.

We have found that 3-arylazoindoles (I) without a substituent attached to the nitrogen atom of the indole ring form indolo[1,2-c]quinazolines when they are reduced with zinc in acetic acid in the presence of acetic anhydride and sodium acetate [1]. The intermediates in this reaction are hydrazo derivatives, which undergo a rearrangement of the benzidine type during the reaction. In the present research we have established that compounds III, with a methyl group attached to the nitrogen atom of the indole ring of the 3-arylazoindoles, evidently also initially form hydrazo derivatives A; however, this is followed by a previously unknown (in the indole series) rearrangement of the semidine type to give 1-methyl-2-arylamino-3-acetamidoindoles (IIIa-i). The structures of IIIa-i were proved by their IR, UV, and PMR spectra and by oxidation to 1-methylisatin α-anils (IVa-h), of which IVa is identical to the known 1-methylisatin α-anil [2]. In addition, IVa was converted to the known 1-methylisatin (V) [3] by acid hydrolysis.

Rearrangements of the benzidine and semidine type have been previously observed in the case of the action of zinc in acetic acid on arylazo derivatives of imidazole [4].



S. Ordzhonikidze All-Union Scientific-Research Pharmaceutical-Chemistry Institute, Moscow 119021. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 3, pp. 353-356, March, 1977. Original article submitted February 16, 1976.

TABLE 1. 3-Arylazoindoles (Ia-c)

Compound	R	mp, °C (from methanol)	Found, %			Empirical formula	Calc., %			Yield, %
			C	H	N		C	H	N	
Ia	*o*-OCH_3	167—168	71,6	5,2	16,7	$C_{15}H_{13}N_3O$	71,7	5,2	16,7	29
Ib	*m*-OCH_3	133—134	71,3	5,2	16,7	$C_{15}H_{13}N_3O$	71,7	5,2	16,7	38
Ic	*p*-$COOC_2H_5$	188—189	69,9	4,8	14,3	$C_{17}H_{15}N_3O_2$	69,6	5,1	14,3	62

*This is the yield after recrystallization.

TABLE 2. 1-Methyl-3-arylazoindoles (IIIa-i)

Compound	R	R′	mp, °C (from methanol)	Found, %			Empirical formula	Calc., %			Yield, %
				C	H	N		C	H	N	
IIa	H	H	100,5—101,5	76,6	5,7	18,2	$C_{15}H_{13}N_3$	76,6	5,6	17,9	97
IIb	H	CH_3	144,5—145,5	77,0	6,1	16,9	$C_{16}H_{15}N_3$	77,1	6,1	16,9	64
IIc	*o*-CH_3	H	128—129	77,0	6,1	17,0	$C_{16}H_{15}N_3$	77,1	6,1	16,9	99
IId	*o*-OCH_3	H	153—154	72,2	5,8	15,9	$C_{16}H_{15}N_3O$	72,4	5,7	15,8	99
IIe	*m*-OCH_3	H	155—156	72,6	5,7	15,8	$C_{16}H_{15}N_3O$	72,4	5,7	15,8	98
IIf	*p*-CH_3	H	123—124	77,3	5,9	17,1	$C_{16}H_{15}N_3$	77,1	6,1	16,9	96
IIg	*p*-CH_3	CH_3	117—118	77,8	6,5	15,9	$C_{17}H_{17}N_3$	77,5	6,5	16,0	42
IIh	*p*-Cl	H	132—133	66,4	4,6	15,4	$C_{15}H_{12}N_3Cl$*	66,8	4,5	15,6	96
IIi	*o*-$COOC_2H_5$	H	176—177	70,2	5,6	14,0	$C_{18}H_{17}N_3O_2$	70,3	5,6	13,7	85

*Found: Cl 13.0%. Calculated: Cl 13.1%.

EXPERIMENTAL

The IR spectra of mineral oil suspensions of the compounds were recorded with a UR-10 spectrometer. The UV spectra of alcohol solutions of the compounds were recorded with an EPS-3-spectrophotometer. The PMR spectra of a CCl_4 solution of IVa and of a mixture of IIIa with deuterodimethyl sulfoxide were recorded with a JNM-4H-100 spectrometer. Hexamethyldisiloxane was used as the standard. Monitoring of the individuality of the substances and the course of the reaction was accomplished by chromatography on a Silufol UV-254 plate in a benzene—methanol system (9:1).

3-Arylazoindoles (Ia-c).* A diazonium salt obtained by the usual method from 0.5 mole of appropriate arylamine, 150 ml of concentrated HCl, and 0.5 mole of sodium nitrite was added at 0° and pH 8-9 to a solution of 0.5 mole of indole in 500 ml of methanol. The pH of the reaction mixture was held constant by the simultaneous addition of a saturated sodium carbonate solution. At the end of the addition, the mixture was maintained at 0° for 2 h. The resulting precipitate was removed by filtration, washed with water, and dried. Data on Ia-c are presented in Table 1.

1-Methyl-3-arylazoindoles (IIa,c-f,h,i). A saturated solution of 0.5 mole of sodium hydroxide in water was added all at once to a solution of 0.1 mole of 3-aryalazoindole in 150 ml of acetone, after which the mixture was stirred for 2-3 min. Dimethyl sulfate (0.2 mole) was then added dropwise, after which the mixture was stirred for another 45 min. It was then poured into water, and the precipitate was removed by filtration, washed with water, and dried. Data on IIa,c-f,h,i are presented in Table 2. UV spectrum of IIa λ_{max} (log ε): 280 (4.05) and 374 nm (4.40).

1-Methyl-3-arylazoindoles (IIb,g). A neutralized (with sodium acetate) to pH 6 solution of a diazonium salt, obtained by the usual method from 0.1 mole of the appropriate arylamine, 30 ml of concentrated HCl, and 0.1 mole of sodium nitrite, was added gradually at 0° to a solution of 0.1 mole of 1,5-dimethylindole in 400 ml of methanol. At the end of the addition, the mixture was maintained at 0° for 1 h. The resulting precipitate was removed by filtration, washed with water, and dried. Data on IIb,g are presented in Table 2.

1-Methyl-2-arylamino-3-acetamidoindoles (IIIa-i). A 0.03-mole sample of acetic anhydride, 0.014 mole of fused sodium acetate, and, in portions, 0.06 mole of zinc dust were added successively to a solution of 0.01 mole of IIa-i in 20 ml of glacial acetic acid while maintaining the temperature at 50-60°. The mixture was then stirred for 30 min as the temperature was reduced to room temperature. The resulting precipitate was removed by filtration

TABLE 3. 1-Methyl-2-arylamino-3-acetamidoindoles (IIIa-i)

Compound		R	R′	mp, °C	Found, %				Empirical formula	Calc., %				Yield, %
					C	H	Cl	N		C	H	Cl	N	
IIIa	Base	H	H	203—204,5^a (dec.)	73,1	6,4		15,1	$C_{17}H_{17}N_3O$	73,1	6,1		15,0	60
	Hydrochloride			214—216^b (dec.)			11,0		$C_{17}H_{17}N_3O \cdot HCl$			11,2		
IIIb	Base	H	CH_3	226,5—228^a (dec.)	73,6	6,5		14,5	$C_{18}H_{19}N_3O$	73,7	6,5		14,3	85
	Hydrochloride			213—215^b (dec.)			10,8		$C_{18}H_{19}N_3O \cdot HCl$			10,8		
IIIc	Base	*o*-CH_3	H	207,5—209^a (dec.)	73,6	6,6		14,4	$C_{18}H_{19}N_3O$	73,7	6,5		14,3	41
	Hydrochloride			>220^b (dec.)			10,8		$C_{18}H_{19}N_3O \cdot HCl$			10,8		
IIId	Base	*o*-OCH_3	H	203,5—204,5^a	69,9	6,2		13,8	$C_{18}H_{19}N_3O_2$	69,9	6,2		13,6	60
	Hydrochloride			208—210^b (dec.)			10,2		$C_{18}H_{19}N_3O_2 \cdot HCl$			10,3		
IIIe	Base	*m*-OCH_3	H	179—180^a	69,8	6,1		13,4	$C_{18}H_{19}N_3O_2$	69,9	6,2		13,6	44
IIIf	Base	*p*-CH_3	H	192—193^a	73,3	6,4		14,2	$C_{18}H_{19}N_3O$	73,7	6,5		14,3	40
	Hydrochloride			220,5—222,5^b (dec.)			10,8		$C_{18}H_{19}N_3O \cdot HCl$			10,8		
IIIg	Base	*p*-CH_3	CH_3	198—199^a (dec.)	73,8	6,9		13,3	$C_{19}H_{21}N_3O$	74,2	6,9	10,3	13,7	66
	Hydrochloride			217—219^b (dec.)			10,3		$C_{19}H_{21}N_3O \cdot HCl$					
IIIh	Base	*p*-Cl	H	204—205^a	65,2	5,2	11,5	13,5	$C_{17}H_{16}N_3ClO$	65,1	5,1	11,3	13,4	40
IIIi	Base	*p*-$COOC_2H_5$	H	200—201^a	68,4	6,1		12,3	$C_{20}H_{21}N_3O_3$	68,4	6,0		12,0	37

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[a] From methanol. [b] From acetone—methanol—ether (1:1:1).

TABLE 4. 1-Methylisatin α-Anils (IVa-h)

Compound	R	R'	mp, °C (from methanol)	Found, %			Empirical formula	Calc., %			O_2 bubbling time, h	Yield, %
				C	H	N		C	H	N		
IVa	H	H	131—131,5[a]	76,3	5,2	12,0	$C_{15}H_{12}N_2O$	76,3	5,1	11,9	8	55
IVb	H	CH_3	125—125,5	76,9	5,7	11,1	$C_{16}H_{14}N_2O$	76,8	5,6	11,2	8	52
IVc	o-CH_3	H	109,5—110,5	76,7	5,8	11,1	$C_{16}H_{14}N_2O$	76,8	5,5	11,2	15	46
IVd	o-OCH_3	H	121—122	72,4	5,3	10,7	$C_{16}H_{14}N_2O_2$	72,2	5,3	10,5	11	31
IVe	p-CH_3	H	118—119	76,4	5,6	11,2	$C_{16}H_{14}N_2O$	76,8	5,6	11,2	4	74
IVf	p-CH_3	CH_3	141,5—142,5	77,3	6,4	10,3	$C_{17}H_{16}N_2O$	77,3	6,1	10,6	4	61
IVg	p-Cl	H	133—134	66,6	4,1	10,4	$C_{15}H_{11}N_2ClO$[b]	66,6	4,1	10,4	5	57
IVh	p-$COOC_2H_5$	H	159,5—161,5	70,6	5,3	9,1	$C_{18}H_{16}HN_2O_3$	70,1	5,2	9,1	3	55

[a] According to the data in [3], this compound has mp 132°C.
[b] Found: Cl 13.0%. Calculated: Cl 13.1%.

and washed with glacial acetic acid,* and the mother liquor was cooled and diluted with water. The resulting precipitate was removed by filtration, washed with methanol, and dried. The hydrochlorides of IIIa-d,f,g were isolated by the usual method from chloroform solutions of the bases.

Data on IIIa-i and their hydrochlorides are presented in Table 3. IR spectrum: 3250 and 3310 (NH); 1630-1640 cm^{-1} (amide C=O). UV spectrum of IIIa, λ_{max} (log ε): 240 shoulder (4.37) and 296 nm (4.16). PMR spectrum of IIIa (δ, ppm): 1.92 (s, $COCH_3$), 3.30 (s, NCH_3), 9.37 (s, NH), and 6.50-7.43 (m, nine aromatic protons).

1-Methylisatin α-Anils (IVa-h). A 0.1-g sample of copper acetate dehydrate was added to a solution of 0.02 mole of IIIa-d,f-i in 60 ml of DMF containing 4 ml of water, after which a stream of oxygen was bubbled in at 50° (see Table 4 for the gas bubbling times). The mixture was then allowed to stand overnight, after which it was diluted with an equal volume of water, and the precipitate was removed by filtration, washed with cold methanol, and dried. Data on IVa-h are presented in Table 4. Bands of stretching vibrations of NH groups are absent in the IR spectra of these compounds. UV spectrum of IVa, λ_{max} (log ε): 230 (4.28), 263 (4.53), and 500 nm (3.25). PMR spectrum of IVa (δ, ppm): 3.22 (s, NCH_3) and 6.66-7.41 ppm (m, nine aromatic protons).

1-Methylisatin (V). Concentrated HCl (1 ml) was added to a solution of 0.24 g (0.001 mole) of (IVa in 3 ml of dioxane, and the mixture was refluxed for 30 min. It was then poured into water, and the aqueous mixture was made alkaline with concentrated ammonium hydroxide and extracted with ether. The ether extract was dried, the ether was removed by distillation, and the residue was washed with methanol. Workup gave 0.1 g (62.5%) of V with mp 133-134° (from alcohol) (mp 132-134° [6]). No melting-point depression was observed for a mixture of this product with 1-methylisatin obtained by the method in [6].

LITERATURE CITED

1. V. I. Shvedov, G. N. Kurilo, A. A. Cherkasova, and A. N. Grinev, Khim. Geterotsikl. Soedin., No. 8, 1096 (1975).
2. R. Pummerer, Ber., 44, 338 (1911).
3. J. Harley-Mason and R. F. J. Ingleby, J. Chem. Soc., No. 10, 3640 (1958).
4. R. G. Fargher and F. L. Pyman, J. Chem. Soc., 115, 217 (1919).
5. V. G. Avramenko, G. N. Pershin, V. D. Nazina, T. N. Zykova, and N. N. Suvorov, Khim.-farm. Zh., 6, 15 (1970).

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*Compounds IIIc,d,h precipitated and were separated from the unchanged zinc by heating with dimethylformamide.