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SOME TRANSFORMATIONS OF 2,3-DIAMINOINDOLE DERIVATIVES. SYNTHESIS OF INDOLO[2,3-b]QUINOXALINES

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1-Methyl-3-methoxy- and 1-methyl-3-piperidino-3-acetamidooxindole anils, respectively, were obtained by oxidation of 1-methyl-2-arylamino-3-acetamidoindoles with oxygen in the presence of copper acetate in methanol and in a mixture of dimethylformamide and piperidine. When the oxindole anils are heated, they undergo cyclization to indolo[2,3-b]quinoxalines. Indolo[2,3-b]quinoxaline N-oxides were obtained from the latter by the usual method.

We have found that 1-methyl-2-arylamino-3-acetamidoindoles form 1-methyl-3-methoxy-3-acetamidooxindole anils (Ia-f) when they are oxidized with oxygen in the presence of copper acetate in methanol. If the oxidation is carried out in dimethylformamide (DMF) in the presence of piperidine, 1-methyl-3-piperidino-3-acetamidooxindole anils (Ig,h) are formed. The formation of the known [1] 1-methylisatin α-anils as side products is observed in all cases. The PMR spectrum of Ic contains singlets at 1.67 (CH_3Ar), 2.25 ($COCH_3$), 3.01 (OCH_3), 3.15 (NCH_3), and 8.48 ppm (NH), as well as a multiplet signal at 6.63-7.40 ppm (eight aromatic protons). One absorption band at 3250 cm^{-1} (NH) is observed in the IR spectra of derivatives Ia-h.

The reaction probably proceeds through a step involving substituted 1-methylisatin diimine, after which methanol or piperidine add to the C=N bond in the 3 position of the latter to give Ia-h (See scheme on following page).

Compounds Ia,c,e,f,h were cyclized to indolo[2,3-b]quinoxalines (IIa-d) by heating to 200-210°C. The formation of indolo[2,3-b]quinoxalines evidently also proceeds through a

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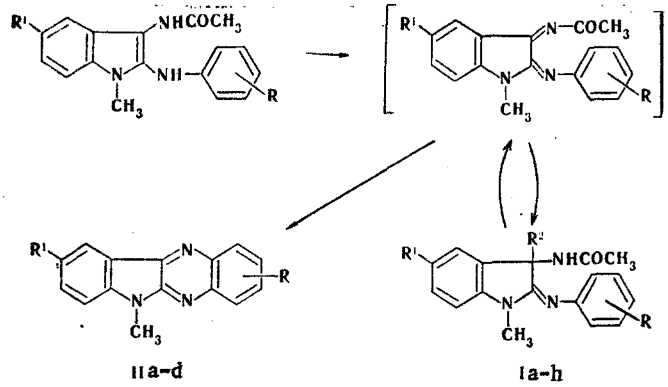

step involving substituted 1-methylisatin diimine with subsequent splitting out of acetaldehyde. Indolo[2,3-b]quinoxalines IIIa,b were obtained from IIc,d by the usual method.

EXPERIMENTAL

The IR spectra of mineral oil suspensions of the compounds were recorded with a UR-10 spectrometer. The PMR spectrum of a deuteropyridine solution of Ic was recorded with a JNM-4H-100 spectrometer with hexamethyldisiloxane as the internal standard. The mass spectra were recorded with an MKh-1303 mass spectrometer with direct introduction of the samples into the ion source at an ionizing-electron energy of 30 eV.

1-Methyl-3-methoxy-3-acetamidooxindole Anils (Ia-f). A 0.15-g sample of copper acetate dihydrate was added to a solution of 0.03 mole of the appropriate 2-arylamino-3-acetamidoindole [1] in 150 ml of methanol, and a stream of oxygen was bubbled into the mixture at 50°C for 3-5 h.* The mixture was then cooled. In the case of Ia,c,e the precipitate that formed immediately was removed by filtration, whereas in the case of Ib,d,f the mixture was evaporated to two-thirds of its original volume, and the resulting precipitate was removed by filtration and washed with hexane. Data on Ia-f are presented in Table 1.

1-Methyl-3-piperidino-3-acetamidooxindole Anils (Ig,h). A 0.05-g sample of copper acetate dihydrate and 0.02 mole of piperidine were added to a solution of 0.01 mole of the appropriate 2-arylamino-3-acetamidoindole in 30 ml of distilled DMF, and a stream of oxygen was passed through the mixture at 50°C for 4 h. The mixture was then cooled and diluted with an equal volume of water, and the resulting precipitate was removed by filtration, dried, and washed with hexane—ethyl acetate (1:1). Data on Ig,h are presented in Table 1.

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*The end of the reaction was determined chromatographically from the absence of a spot of the starting compound on a Silufol UV-254 plate in a benzene—methanol system (9:1) (for Ia-d) and in an ethyl acetate—hexane system (7:3) (for Ie,f). The precipitate of Ih was isolated immediately during cooling.

TABLE 1. 1-Methyl-3-methoxy- and 1-Methyl-3-piperidino-3-acetamidooxindole Anils (Ia-h)

Compound	R	R¹	R²	mp, °C	Found, %			Empirical formula	Calc., %			Yield, %
					C	H	N		C	H	N	
Ia	H	H	OCH_3	180—181[a]	69,9	6,3	13,4	$C_{18}H_{19}N_3O_2$	69,9	6,2	13,6	50
Ib	H	CH_3	OCH_3	185,5—186,5[b]	70,1	6,5	13,3	$C_{19}H_{21}N_3O_2$	70,6	6,6	13,0	40
Ic	o-CH_3	H	OCH_3	183—184[b]	70,6	6,7	13,2	$C_{19}H_{21}N_3O_2$[c]	70,6	6,6	13,0	52
Id	p-CH_3	CH_3	OCH_3	179,5—180,5[d]	70,9	6,9	12,3	$C_{20}H_{23}N_3O_2$	71,2	6,9	12,5	64
Ie	p-Cl	H	OCH_3	189—190[b]	63,3	5,2	12,3	$C_{18}H_{18}ClN_3O_2$[e]	62,9	5,3	12,2	57
If	p-$COOC_2H_5$	H	OCH_3	187—188[b]	66,6	6,1	11,2	$C_{21}H_{23}N_3O_4$	66,1	6,1	11,0	55
Ig	H	H	Piperidino	179—181[a]	73,0	7,3	15,6	$C_{22}H_{26}N_4O$	72,9	7,2	15,5	48
Ih	p-Cl	H	Piperidino	192—195[b] (dec.)	66,2	6,4	14,3	$C_{22}H_{25}ClN_4O$[f]	66,6	6,4	14,1	51

a) From hexane—ethyl acetate (1:1). b) From methanol. c) M^+ 323. d) From benzene—hexane (1:2). e) Found: Cl 10.3%. Calculated: Cl 10.3%. f) Found: Cl 9.0%. Calculated: Cl 8.9%.

TABLE 2. Indolo[2,3,-b]quinoxalines (IIa-d)

Compound	R	mp, °C	Found, %			Empirical formula	Calc., %			Yield, %
			C	H	N		C	H	N	
IIa	H	150—151[a]	77,3	4,6	18,1	$C_{15}H_{11}N_3$	77,2	4,8	18,0	33
IIb	4-CH_3	182,5—183,5[b]	77,7	5,3	16,9	$C_{16}H_{13}N_3$[c]	77,7	5,3	17,0	15
IIc	2-Cl	209—209,5[d]	67,3	3,8	15,6	$C_{15}H_{10}ClN_3$[e]	67,3	3,8	15,7	27
IId	2-$COOC_2H_5$	208—209,5[b]	70,9	4,8	13,5	$C_{18}H_{15}N_3O_2$	70,8	5,0	13,8	27

a) From ethanol. b) From methanol. c) M^+ 247. d) From methanol—dimethylformamide (1:1). e) Found: Cl 13.7%. Calculated: Cl 13.2%.

Indolo[2,3-b]quinoxalines (IIa-d). A 0.01-mole sample of Ia,c,e,f was heated at 200-210°C for 5 min, after which it was cooled and triturated with methanol. The resulting solid was removed by filtration and dried. Data on IIa-d are presented in Table 2. Compound IIc was obtained under similar conditions also from Ih. The structures of IIa-d were confirmed in the case of IIa, obtained by this method, by the absence of a melting-point depression for a mixture of a sample of this product with a sample of 6-methylindolo[2,3-b]-quinoxaline obtained by the method described in [2]. The UV spectra of these compounds were also identical.

2-Chloro-6-methylindolo[2,3-b]quinoxaline N-Oxide (IIIa). A 17.5-ml sample of 30% hydrogen peroxide was added to a solution of 2.32 g (8.7 mmole) of IIc in 175 ml of glacial acetic acid, and the mixture was stirred at 50°C for 5 h. Another 17.5 ml of hydrogen peroxide was added to the mixture, and heating was continued for another 5 h. The mixture was then cooled, and the precipitate was removed by filtration, washed with water, and dried to give 2.1 g (87%) of IIIa with mp 272-272.5°C (from DMF). Found, %: C 63.4; H 3.7; Cl 12.6; N 14.8. $C_{15}H_{10}ClN_3O$. Calculated, %: C 63.5; H 3.6; Cl 12.5; N 14.8.

2-Carbethoxy-6-methylindolo[2,3-b]quinoxaline N-Oxide (IIIb). This compound was obtained from IId under the conditions of the synthesis of IIIa. Compound IIIb, with mp 242-244° (from DMF) and M^+ 321, was obtained in 61% yield. Found, %: C 67.6; H 4.7; N 13.6. $C_{18}H_{15}N_3O_3$. Calculated, %: C 67.3; H 4.7; N 13.1.

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