3-CHLORO-6-ALKYLISOINDOLO[2,1-*a*]QUINAZOL-5-ONES

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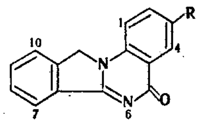
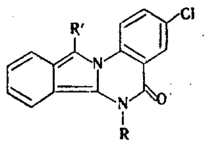
3-Chloro-11H-isoindolo[2,1-*a*]quinazol-5-one was obtained by condensation of o-chloromethylbenzonitrile with 5-chloroanthranilic acid, and its alkylation, electrophilic substitution, and addition reactions were studied.

We have previously obtained derivatives of 11H-isoindolo[2,1-*a*]quinazol-5-one (Ia) by reaction of o-chloromethylbenzonitrile with anthranilic acid esters [1]. A number of compounds with high physiological activity have recently been observed among condensed isoindoles [2, 3]. These data generated new interest in condensed isoindoles, and the present research on the synthesis of 3-chloro derivatives I is a consequence of this interest. We used 5-chloroanthranilic acid [4] as the starting compound for the preparation of Ib.



I a,b

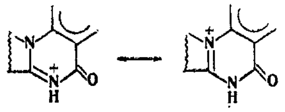


IIa,b

I a R=H; b R=Cl; II a $R=CH_3$, R′=H; b $R=C_2H_5$, R′=H

Condensation of o-chloromethylbenzonitrile with this acid occurs when the components are heated briefly in dimethylformamide (DMF). In contrast to the condensation with anthranilic acid esters [1], free base Ib, rather than a salt, is formed immediately in quantitative yield in the reaction with 5-chloroanthranilic acid under the above conditions.

Compound Ib is a weak base (it can be recrystallized unchanged from acetic acid) and gives salts only with mineral acids. The IR spectrum of Ib contains intense bands at 1670 and 1630 cm^{-1}, which we assign, respectively, to C = O and C= N. The C = O stretching vibrations for the hydrochloride from Ib are observed at 1720 cm^{-1}. This large shift in the C=O frequency makes it possible to assume that structure A corresponds to the structure of the hydrochloride in the solid state, since in this case the multiplicity of the C=O bond is higher than for structure B.



A B

Fusion of Ib with alkylating agents (dimethyl sulfate and ethyl p-toluenesulfonate) gives colorless salts, the action of alkalis or ammonia on which converts them to yellow bases – 3-chloro-6-alkylisoindolo[2,1-*a*]quinazol-5-ones (IIa,b). Exactly as in the case of the salt from Ib, the C=O absorption in the IR spectra of the salts from IIa (methylmethosulfate) and IIb (tosylate) appears at 1720 cm^{-1}. This frequency decreases to 1650 cm^{-1} on passing to the base, i.e., it decreases to the value typical for secondary amides [5].

The signal of the 11-CH_2 group present in simple salts IIa,b vanishes in the PMR spectra of bases IIa,b. A lone doublet with J = 2.5 Hz at 8.2–8.6 ppm is observed in the PMR spectra of the investigated compounds in the midst of the complex multiplet of the aromatic protons. This is the signal of the 4-H proton, which undergoes a paramagnetic shift as compared with the remaining signals of the aromatic protons due to the adjacent carbonyl group.

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TABLE 1. 3-Chloro-6-alkylisoindolo[2,1-*a*]quinazol-5-one

Compounds II	R	R′	mp, °C	Found, %		Empirical formula	Calc., %		IR spec., C=O, cm^{-1}	Charac. of PMR spectra[a]				Yield, %
				Cl	N		Cl	N		N-alkyl	R′	aromatic	4-H	
c	CH_3	$COCH_3$	225—227[b]	10,7	8,6	$C_{18}H_{13}ClN_2O_2$	10,9	8,6	1680	4,16s	2,76s	7,33—8,16m	8,33	44
d	C_2H_5	$COCH_3$	228—230	10,5	8,0	$C_{19}H_{15}ClN_2O_2$	10,4	8,3	1680	4,63q 1,55t	2,68s	7,00—7,96m	8,28	85
e	CH_3	COC_6H_5	175—176	9,4	7,3	$C_{23}H_{15}ClN_2O_2$	9,1	7,2	1680	4,16s	7,00—8,08 m		8,35	92
f	C_2H_5	COC_6H_5	220—221	9,0	6,7	$C_{24}H_{17}ClN_2O_2$	8,8	7,0	1680	4,76q 1,61t	7,06—8,02 m		8,42	93
g	CH_3	$N=NC_6H_5$	261	9,0	14,3	$C_{22}H_{15}ClN_4O$	9,2	14,5		—				52
h	CH_3	$CSNHC_6H_5$	170—171	8,7	10,1	$C_{23}H_{16}ClN_3OS$	8,5	10,0	1650	—				54
i	C_2H_5	$CSNHC_6H_5$	106—107	8,0	9,5	$C_{24}H_{18}ClN_3OS$	8,2	9,7	1650	—				79
j	CH_3	$CONHC_6H_5$	231—233	8,9	10,1	$C_{23}H_{16}ClN_3O_2$	8,8	10,4	1640[c]	—				73
k	C_2H_5	$CONHC_6H_5$	223—225	8,4	10,2	$C_{24}H_{18}ClN_3O_2$	8,5	10,1	1640[c]	—				93

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[a] The J constants of the protons of the N-ethyl group in the PMR spectra of IId,f are equal to 7.5 Hz.

[b] Compounds IIj,k were purified by recrystallization from DMF; the remaining compounds were purified by recrystallization from nitromethane.

[c] The IR spectra of IIj,k contain, in addition to a C=O band at 1640 cm^{-1}, a C=O band at 1670 cm^{-1}.

The presence of an isoindole structure in the case of IIa,b explains the ease of electrophilic substitution and addition reactions at the free 11 position of the system. Acetylation, benzoylation, diazo coupling, and reactions with phenyl iso(thio)cyanate were carried out with IIa,b, and products IIc-k were obtained. The results of elementary analysis and the spectral characteristics of the synthesized substances are presented in Table 1.

EXPERIMENTAL

The IR spectra of KBr pellets of the compounds were recorded with a UR-20 spectrometer. The PMR spectra of the compounds were measured with a ZKR-60 spectrometer with tetramethylsilane as the internal standard.

3-Chloro-11H-isoindolo[2,1-*a*]quinazol-5-one Hydrochloride. This compound was obtained as colorless needles with mp 324-325°C (from alcohol + HCl). IR spectrum: C=O 1720 cm^{-1}. PMR spectrum (in CF_3COOH): 5.90 s (2H, 11-CH_2) and 8.06-8.61 m (7H, arom.). Found: Cl 23.3; N 9.0%. $C_{15}H_{10}Cl_2NCO$. Calculated: Cl 23.2; N 9.2%.

3-Chloro-11H-isoindolo[2,1-*a*]quinazol-5-one (Ib). A mixture of 3 g of o-chloromethylbenzonitrile and 3.4 g of 5-chloroanthranilic acid in DMF was heated at 150°C for 30 min, after which the precipitated crystals were removed by filtration and washed with water and alcohol to give 3.6 g (67%) of colorless needles with mp 293-295°C (from DMF). IR spectrum: C=N 1630 and C=O 1670 cm^{-1}. Found: Cl 13.0; N 10.1%. $C_{15}H_9ClN_2O$. Calculated: Cl 13.1; N 10.4%

3-Chloro-6-methylisoindolo[2,1-*a*]quinazol-5-one Methylmethosulfate. A mixture of 5.5 g of Ib and 3 ml of dimethyl sulfate was heated at 130°C for 5 min, after which it was cooled and treated with acetone. The precipitated crystals were removed by filtration and washed with acetone and ether to give 5.2 g (73%) of colorless crystals with mp 216-217°C (from alcohol). IR spectrum: C=O 1720 cm^{-1}. PMR spectrum (in CF_3COOH): 5.91 s (2H, 11-CH_2), 3.91 s (3H, N−CH_3), 4.50 s (3H, O−CH_3), and 8.12-8.58 m (7H, arom.). Found: Cl 9.0; S 8.4%. $C_{17}H_{15}ClN_2O_5S$. Calculated: Cl 9.0; S 8.1%.

3-Chloro-6-ethylisoindolo[2,1-*a*]quinazol-5-one Tosylate. A mixture of 4 g of Ib and 8 g of ethyl p-toluenesulfonate was heated at 150-160°C for 30 min, after which it was cooled and treated with acetone. The precipitated crystals were removed by filtration and washed with acetone and ether to give 5.9 g (82%) of colorless crystals with mp 240-242°C (from alcohol). IR spectrum: C=O 1720 cm^{-1}. PMR spectrum (in CF_3COOH): 5.76 s (2H, 11-CH_2); 5.2 q (2H, NCH_2CH_3), J = 7.5 Hz; 1.76 t (3H, NCH_2CH_3), J = 7.5 Hz; 2.53 s (3H, C−CH_3); 7.10-8.45 m (7H, arom.). Found: Cl 7.4; S 6.5%. $C_{24}H_{21}ClN_3O_4S$. Calculated: Cl 7.6; S 6.8%.

3-Chloro-6-methylisoindolo[2,1-*a*]quinazol-5-one (IIa). A 1.5-g sample of 3-chloro-6-methylisoindolo-[2,1-*a*]quinazol-5-one methylmethosulfate was dissolved in 20 ml of water, and the mixture was treated with 15% KOH solution. It was then washed with water, alcohol, and ether and worked up to give 1.02 g (96%) of orange crystals with mp 216-218°C (DMF). IR spectrum: C=O 1650 cm^{-1}. Found: Cl 12.2; N 9.7%. $C_{16}H_{11}ClN_2O$. Calculated: Cl 12.5; N 9.9%.

3-Chloro-6-ethylisoindolo[2,1-*a*]quinazol-5-one (IIb). This compound was similarly obtained from 3 g of 3-chloro-6-ethylisoindolo[2,1-*a*]quinazole-5-one tosylate. Workup gave 1.8 g (95%) of orange crystals with mp 200-202°C (DMF). IR spectrum: C=O 1650 cm^{-1}. PMR spectrum (in $CDCl_3$): 1.56 t (3H, NCH_2CH_3), J = 7.5 Hz; 4.61 q (2H, NCH_2CH_3), J = 7.5 Hz; 7.09-8.43 (8H, arom.). Found: Cl 11.6; N 9.2%. $C_{17}H_{13}ClN_2O$. Calculated: Cl 11.9; N 9.4%.

3-Chloro-6-alkyl-11-acetylisoindolo[2,1-*a*]quinazol-5-ones (IIc,d). A 0.01-mole sample of IIa,b was refluxed for 5 min with 3 ml of acetic anhydride, and the precipitated crystals were removed by filtration and washed with ether. See Table 1 for data on IIc,d.

3-Chloro-6-alkyl-11-benzoylisoindolo[2,1-*a*]quinazol-5-ones (IIe,f). A 0.01-mole sample of benzoyl chloride was added to 0.01 mole of bases IIa,b in 5 ml of dry pyridine, and the mixture was heated on a water bath for 5 min. It was then diluted with water and washed with water and alcohol. See Table 1 for data on IIe,f.

3-Chloro-6-methyl-11-phenylazoisoindolo[2,1-*a*]quinazol-5-one (IIg). A solution of benzenediazonium chloride was added dropwise at 5°C to a solution of 0.28 g of IIa in 5 ml of acetic acid, after which the mixture was diluted with water and neutralized with sodium carbonate. The crystals were washed with water and alcohol. The yield was 0.2 g.

3-Chloro-6-alkyl-11-phenyl(thio)carbamoylisoindolo[2,1-*a*]quinazol-5-ones (IIh-k). Equimolar amounts of IIa,b and phenyl iso(thio)cyanate were mixed, and the resulting crystals were removed by filtration and washed with ether. The products of the reaction with phenyl isothiocyanate were yellow crystals, and their thio analogs were red crystals. See Table 1 for data on IIh-k.

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1H-THIAZOLO[3,2-b]-1,2,4-TRIAZOLIUM SALTS

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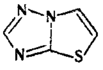
The alkylation of 4H-triazole-5-thiones with α-halo ketones takes place at the sulfur atom. 1H-Thiazolo[3,2-b]-1,2,4-triazolium – a new heteroaromatic cation – derivatives were obtained by intramolecular cyclization of the resulting β-keto sulfides.

Derivatives of the thiazolo[3,2-b]-1,2,4-triazole (I) system have been known for quite some time [1] and have been well studied [2, 3]; 1H-thiazolo[3,2-b]-1,2,4-triazolium – a new heteroaromatic cation – salts (II) were obtained by intramolecular cyclization of β-keto sulfides IV [4]. As starting compounds we used 1,2,4-triazole-5-thiones IIIa-c, which were alkylated with α-halo ketones after conversion to the corresponding anions.



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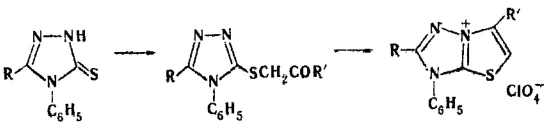

IIIa-c IV II

IIIa R = H; b R = CH_3; c R = C_6H_5

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