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CYCLIC HYDROXAMIC ACIDS OF THE INDOLE SERIES

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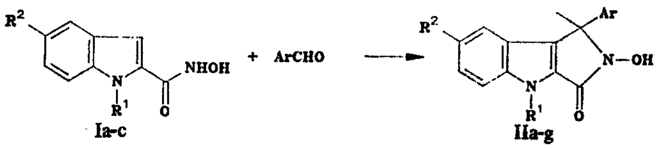
UDC 547.752'759'298.71

A convenient method was developed for obtaining 2-N-hydroxy-3-keto-1-phenyl-1,3-dihydropyrrolo[3,4-b]indoles by reaction of indole-2-hydroxamic acid with substituted benzaldehydes. Complex compounds of trivalent iron salts with cyclic hydroxamic acids were isolated.

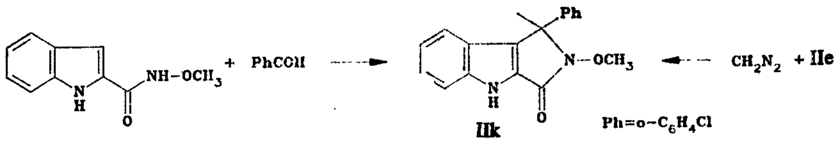
Using a principle for building tricyclic indoles [2,3] previously suggested by us we obtained cyclic hydroxamic acids of the indole series by the method



The process keeps mixtures of reagents in alcohol, saturated with HCl, at room temperature. After a short period of standing the solvent was distilled off to dryness, and the colorless crystalline residue was purified by crystallization from alcohol or acetonitrile. The yields were from 45 to 70%. The elementary composition of the compounds obtained indicates the addition of one molecule of aldehyde to one molecule of indole with loss of water. The compounds have the properties of weak acids, i.e, they dissolve in basic solutions and are isolated unchanged on acidification with acetic acid, which indicates the retention of the >CONOH hydroxamic acid fragment in the molecule formed.

Acetylation of compounds (IIa, e) with boiling acetic anhydride leads to the formation of 2-acetoxy derivatives (IIh, i) not soluble in bases and having lower melting points.

Cyclic hydroxamic acids (IIa, e) are readily alkylated by diazomethane giving 2-methoxy derivatives (IIj,k). For the purpose of establishing the direction of methylation we obtained the methylated derivative (IIk) by an alternate synthesis from the methyl ester of indole-2-hydroxamic acid:



The absence of a melting point depression and the agreements of the Rf and the spectra of the compounds obtained by both methods testifies to their identity and unequivocally shows the direction of methylation.

Leningrad Institute of Pharmaceutical Chemistry, Leningrad 197022. Khimiya Geterotsiklicheskikh Soedinenii, No. 2, pp. 227-229, February, 1985. Original article submitted March 27, 1984.

0009-3122/85/2102-0188$09.50

The IR spectra of compounds (IIa,b) contain carbonyl absorption bands in the 1680 cm^{-1} range, the same frequency that the carbonyl has in the (IIg) N^4-methyl derivative, which indicates the absence of intramolecular hydrogen bonds between the NH of the pyrrole group and the carbonyl, characteristic of dihydropyrrolo[3,4-b]-3-indoles [2]. The UV spectrum of compound (IIa), its acetyl derivative (IIh), and its O-methyl derivative (IIj) are quite similar to each other and at the same time close to that of indole-2-hydroxamic acid. Thus, for compounds (IIa,h,j), $\lambda_{max} = 300 \pm 2$ nm (log ε = 4.12-4.22), but for indole-2-hydroxamic acid λ_{max} = 296 nm (log ε = 4.15).

Because of the fact that the 2-N-hydroxy-3-keto-1-phenyl-1,3-dihydropyrrolo[3,4-b]indole (II) synthesized is a cyclic hydroxamic acid, we studied its ability to form complex compounds with salts of trivalent iron. By stirring and subsequent distillation of the acidified alcoholic solutions of the ligand of (IIa) and $FeCl_3$ in 0.1 N concentration a dark-red residue was formed of composition $Fe[Li{-}H]_3$. On adding water to this same solution a precipitate was formed of composition $FeOH[Li{-}H]_2 \cdot C_2H_5OH$. The structures of these complexes are evidently the same as those of the complexes with noncyclic hydroxamic acids, in which one metal bond with the ligand is produced by replacing a hydrogen atom of the hydroxyl group and the second as a result of the positioning of the electrons on the acid carbonyl with respect to the d orbitals of the iron atom [4]. The cyclic structures of the hydroxamic acids obtained preclude formation of other possible bonds with metals.

A qualitative comparison of the stabilities of Fe(III) complexes with cyclic hydroxamic acids (compound IIa) and the noncyclic ones (compound Ia) showed that the former are less stable, inasmuch as they break up (are decolorized) on dilution with alcoholic solutions.

The ability to form complexes is characteristic of all cyclic hydroxamic acids with unsubstituted $>$NOH groups including the N^4-methylated compounds (IIg) but completely absent in O-acetyl (IIh,e) and O-methyl (IIj,k) derivatives.

EXPERIMENTAL

The IR spectra were taken on a UR-22 apparatus in mineral oil mulls; the UV spectra, on an SF-16 apparatus in ethyl alcohol. The iron contents of the complex compounds were determined by an emission spectroscopy method. The purity of all compounds obtained was determined chromatographically on Silufol using a 3:5 (by volume) hexane—ethyl acetate system.

Characteristics of the compounds synthesized are shown in Table 1.

5-Methoxyindole-2-hydroxamic Acid (Ib). This acid was synthesized analogously to indole-2-hydroxamic acid [5] by treating 2.1 g (10 mmoles) of the ethyl ester of the 5-methoxyindole-2-carboxylic acid with hydroxylamine base obtained from 1.4 g of hydroxylamine hydrochloride in 20 ml methanol at room temperature. After standing 24 h the solvent was distilled off to dryness in a vacuum at a temperature not above 50°C. The dry residue was crystallized from 10 ml 20% acetic acid, heating the solution not above 60°C. There was obtained 1.1 g of compound (Ib) (55%), mp 165-168°C (decomp.). Found: C 62.0; H 5.6; N 7.2%. $C_{10}H_{12}N_2O_3$. Calculated: C 62.0; H 5.2; N 7.3%.

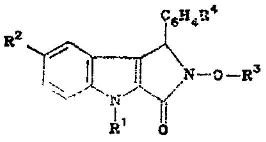
1-Methylindole-2-hydroxamic Acid (Ic). A solution of 6.1 g (30 mmoles) of the ethyl ester of 1-methylindole-2-carboxylic acid in 20 ml of methanol was poured into a solution obtained by adding 5.1 g (90 mmoles) of KOH in 20 ml of methanol to 4.2 g (60 mmoles) of hydroxylamine hydrochloride in 20 ml methanol, the KCl filtered off, and after standing 2 h at room temperature the solvent was distilled off to dryness in a vacuum; the residue was crystallized from 20% acetic acid. There was obtained 4.0 g (65%) of acid (Ic), mp 157-158°C (decomp.). Found: N 14.3%. $C_{10}H_{12}N_2O_2$. Calculated: N 14.5%.

1-p-Methoxyphenyl-2-hydroxy-3-keto-1,3-dihydropyrrolo[3,4-b]indole (IIc). To a mixture of 1.76 g (10 mmoles) of indole-2-hydroxamic acid and 1.6 g (12 mmoles) of p-methoxybenzaldehyde 20 ml of alcohol was added, saturated with HCl, stirred and the mixture was left standing 2 h at room temperature. The solvent was distilled off to dryness in a vacuum, and the residue was washed with ethyl alcohol and crystallized from 10 ml acetonitrile. There was obtained 1.35 g (45%) of compound (IIc).

Compounds (IIa-g) were obtained in an analogous manner. As in obtaining compound (IIb) they precipitated spontaneously from the reaction mass.

1-Phenyl-2-acetozy-3-keto-1,3-dihydropyrrolo[3,4-b]indole (IIh). Compound (IIa) (0.27 g, 1 mmole) was boiled for 5 min in 3 ml of acetic anhydride and cooled; crystals of (IIh) were separated from the solvent by filtration.

TABLE 1. 2-Hydroxy-3-keto-1-phenyl-1,3-dihydropyrrolo[3,4-b]indoles (IIa-k)



Compound	R^1	R^2	R^3	R^1	mp, deg C	Found, %			Empirical formula	Calculated, %			Yield, %
						C	H	N		C	H	N	
IIa	H	H	H	H	260—263	72,3	4,5	10,2	$C_{16}H_{12}N_2O_2$	72,7	4,5	10,6	70
IIb	H	OCH_3	H	H	255—256	68,7	4,4	9,2	$C_{17}H_{14}N_2O_3$	69,4	4,8	9,5	65
IIc	H	H	H	*n*-OCH_3	215—216	69,0	4,6	9,2	$C_{17}H_{14}N_2O_3$	69,4	4,8	9,5	45
IId	H	OCH_3	H	*o*-Cl	260—262	61,8	4,2	8,1	$C_{17}H_{13}ClN_2O_3$	62,2	4,0	8,1	70
IIe	H	H	H	*o*-Cl	245—247	65,2	3,9	9,2	$C_{16}H_{11}ClN_2O_2$	64,4	3,7	9,4	60
IIf	H	H	H	*o*-OH	360—365	67,9	4,2	10,1	$C_{16}H_{12}N_2O_3$	68,5	4,3	10,0	40
IIg	CH_3	H	H	H	235—236	72,6	5,0	9,7	$C_{17}H_{14}N_2O_2$	73,4	5,0	10,1	70
IIh	H	H	CH_3CO	H	215—217	71,2	4,3	9,1	$C_{18}H_{14}N_2O_3$	70,6	4,6	9,1	80
IIi	H	H	CH_3CO	*o*-Cl	225—227	63,1	3,9	8,0	$C_{18}H_{13}ClN_2O_3$	63,5	3,8	8,2	75
IIj	H	H	CH_3	H	190—193	73,9	4,7	9,6	$C_{17}H_{14}N_2O_2$	73,4	5,0	10,1	65
IIk	H	H	CH_3	*o*-Cl	210—212	64,7	4,3	8,8	$C_{17}H_{13}ClN_2O_2$	65,2	4,1	8,9	60

2-Methoxy-3-keto-1-o-chlorophenyl-1,3-dihydropyrrolo[3,4-b]indole (IIk). A. An ether solution of diazomethane obtained from 0.4 g nitrosomethylurea was added to a suspension of 0.4 g (1.3 mmoles) of compound (IIe) in 15 ml of ether. After stirring at room temperature for 4 h to complete dissolution, the solvent was distilled off to dryness in a vacuum; the residue was crystallized from alcohol. There was obtained 0.24 g (60%) of indole (IIk), R_f

B. Into a suspension of 0.35 g (0.2 mmole) of indole-2-hydroxamic acid in ether was poured an ether solution of diazomethane obtained from 0.3 g of nitrosomethylurea. After stirring 10 h to complete dissolution, the ether was distilled off, and to the oily residue consisting mainly of the methyl ester of indole-2-hydroxamic acid was added 0.3 g (0.22 mmole) of o-chlorobenzaldehyde and 5 ml of ether, the solution saturated with HCl. After standing 10 h the ether was distilled off. The residue was washed with a small amount of ether, the compound was dissolved in alcohol, base was added to pH 9-10 for separating it from the starting hydroxamic acid, and compound (IIh) was precipitated out by means of water. It was purified by chromatography on silica gel, R_f 0.45, obtaining 0.07 g (20%) of indole (IIk). There was no mixed mp depression with the sample obtained according to method A.

Compound IIj was synthesized according to method A.

Obtaining Complex Compounds (IIIa,b). To a solution of 0.17 g (0.64 mmole) of compound (IIa) in 25 ml alcohol containing 0.1 ml of conc. HCl was added 6.4 ml of a 0.1 N alcoholic solution of $FeCl_3$. After evaporating in a vacuum to a volume of 5 ml a dark-brown precipitate of the complex compound (IIIa) of composition $Fe[Li—H]_3$ separated out. Found: C 65.3; H 4.1; Fe 7.4; N 10.34. $C_{48}H_{33}FeN_6O_6$. Calculated: C 68.0; H 3.9; Fe 6.6; N 9.9%. The compound does not melt up to 380°C.

The solution of the complex compound obtained as above was diluted with a threefold amount of water, by which means a red-brown precipitate of compound (IIIb) came out of composition $FeOH[Li—H]_2 \cdot C_2H_5OH$. Found: C 61.4; H 4.6; Fe 9.8; N 9.8%. $C_{34}H_{29}FeN_4O_6$. Calculated: C 63.5%; H 4.3; Fe 8.7; N 8.7%.

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