SYNTHESIS OF 2-AMINOINDOLES FROM N-ACYLAMINO DERIVATIVES OF TETRAHYDROQUINOLINE

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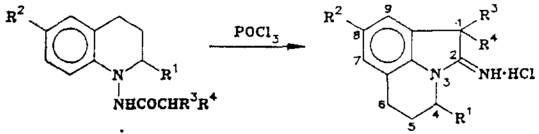
Previously unknown tricyclic derivatives of the 2-aminoindole series were obtained by heterocyclization of 1-acylaminotetrahydroquinolines.

The Kost reaction is a general and fairly universal method for the synthesis of 2-aminoindole derivatives, consisting in the rearrangement of acid aryl hydrazides by the action of electrophilic agents [1]. In the present work, we used N-acylamino-1,2,3,4-tetrahydroquinolines Ia-j [2] as the starting materials. These are derivatives of aryl-cycloalkylhydrazines, the transformations of which by the action of phosphorus oxychloride lead to the previously unknown derivatives of the 2-aminoindole IIa-g series:



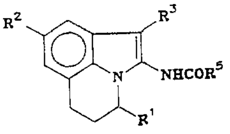
Ia-j

IIa-g

I, II a $R^1=R^2=R^4=H$, $R^3=CH_3$; b $R^1=R^4=H$, $R^2=R^3=CH_3$; c $R^2=R^4=H$, $R^1=R^3=CH_3$; d $R^1=R^4=H$, $R^2=OCH_3$, $R^3=CH_3$; e $R^1=R^4=H$, $R^2=CH_3$, $R^3=C_6H_5$; f $R^1=CH_3$, $R^2=H$, $R^3-R^4=(CH_2)_5$; g $R^1=H$, $R^2=Cl$, $R^3-R^4=(CH_2)_5$; h $R^1=R^2=R^4=H$, $R^3=C_6H_5$; i $R^1=R^4=H$, $R^2=OCH_3$, $R^3=C_6H_5$; j $R^1=R^4=H$, $R^2=Cl$, $R^3=C_6H_5$

Using compounds IIf, g as examples, the possibility was shown of obtaining spiro compounds from cyclohexanoylamino derivatives of the tetrahydroquinoline series. By varying the reaction conditions, it was found that the optimal solvent is dioxane and the optimal reaction time is 1 to 1.5 h.

Hydrochlorides of compounds IIh-j were found to be hygroscopic, and therefore the corresponding 2-aminoindoles were isolated and identified in the form of acyl derivatives IIIa-d:



IIIa-d

III a $R^1=R^2=H$, $R^3=C_6H_5$, $R^5=CH_2C_6H_5$; b $R^1=H$, $R^2=OCH_3$, $R^3=C_6H_5$, $R^5=CH_2C_6H_5$; c $R^1=H$, $R^2=Cl$, $R^3=C_6H_5$, $R^5=CH_3$; d $R^1=H$, $R^2=R^3=CH_3$, $R^5=CH_2C_6H_5$

The structure of the compounds obtained was confirmed by IR and PMR spectral data (see Table 1), which correspond to the data previously obtained for other 2-aminoindole derivatives [3].

EXPERIMENTAL

The IR spectra were run on a UR-20 spectrophotometer in mineral oil and hexachlorobutadiene, the ^1H and ^{13}C NMR spectra – on Tesla BS-467 A (60 MHz) and JEOL-FX-100

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TABLE 1. 2-Amino-4,5-dihydro(6H)pyrrolo[1,2,3-i,j]quinolines II and III

Compound	Empirical formula	mp, °C	IR spectrum, cm^{-1}		Solvent	PMR spectrum, ppm (J, Hz)			R^5	Yield, %
			C=N, C=O*	NH		R^3, R^4	R^1, 4H—6H	R^2, Ar, NH		
IIa	$C_{12}H_{14}N_2 \cdot HCl$	236...237	1700	2920	CF_3COOH	1,7 (d, J=8, 3H, $1\text{-}CH_3$); 4,5 (m, 1H, 1-H)	4,2 (m, 2H, 4-H); 2,3 (m, 2H, 5-H); 3,0 (m, 2H, 6-H)	7,4 (br.s, 3H, 7—9-H); 7,95 (br.d, 2H, NH)	—	42
IIb	$C_{13}H_{16}N_2 \cdot HCl$	237...238	1700	2930	CD_3OD	1,7 (s 1-CH_3)	4,0 (t, J=7,0, 2H, 4-H); 2,2 (m, 2H, 5-H); 2,8 (t, 2H, 6-H)	2,4 (s 8-CH_3); 7,15...7,25 (m, 2H, 7-H, 9-H)	—	91
IIc	$C_{13}H_{16}N_2 \cdot HCl$	233...234	1695	2920	CD_3OD	1,6 (s, 1-CH_3)	1,45 (d J=7,0, 4-CH_3); 4,8 (m, 2H, 4-H); 2,15 (m, 2H, 5-H); 2,95 (m, 2H, 6-H)	7,3 (m, 3H, 7—9-H)	—	40
IId	$C_{13}H_{16}N_2O \cdot HCl$	229...231	1695	2930	CD_3OD	1,6 (s. 1-CH_3)	4,0 (t, J=7,0, 2H, 4-H); 2,15 (m, 2H, 5-H); 2,75 (t, 2H, 6-H)	3,75 (s 3H, 8-OCH_3); 6,6...7,1 (m, 2H, 7-H, 9-H)	—	58
IIe	$C_{18}H_{18}N_2 \cdot HCl$	225...226	1700	2940	CD_3OD	7,7 (m, 1-C_6H_5)	4,07 (t J=7,0, 2H, 4-H); 2,0 (m 2H, 5-H); 3,0 (t 2H, 6-H)	2,0 (s 8-CH_3); 7,25...7,50 (m, 2H, 7-H, 9-H)	—	67
IIf	$C_{17}H_{22}N_2 \cdot HCl$	255...256	1700	2930	CD_3OD	1,5...2,15 (m, C_6H_{10})	1,3 (d J=7,0, 4-CH_3); 4,6 (m 1H, 4-H); 2,2 (m 2H, 5-H); 2,8 (m, 2H, 6-H)	7,25...7,80 (m 3H, 7—9-H)	—	44
IIg	$C_{16}H_{19}ClN_2 \cdot HCl$	244...245	1700	2930	CD_3OD	1,6...2,2 (m, C_6H_{10})	4,05 (t, J=7,0, 2H, 4-H); 2,2 (m 2H, 5-H); 2,95 (t 2H, 6-H)	7,35 (s 7-H); 7,61 (s 9-H)	—	58
IIIa	$C_{25}H_{22}N_2O$	213...214	1670	3220	DMSO-D_6	7,2...7,7 (m 1-C_6H_5)	2,06 (m 2H, 5-H); 2,92 (m, 2H, 6-H); 3,85 (m, 2H, 4-H)	6,9...7,15 (m 3H, 7,8,9-H); 10,20 (s NH)	3,69 (s, 2H, CH_2)	31
IIIb	$C_{26}H_{24}N_2O_2$	173...174	1670	3200	$CDCl_3$	6,8...7,6 (m, 1-C_6H_5)	3,95 (m 2H, 4-H); 1,95 (m, 2H, 5-H); 2,8 (m 2H, 6-H)	6,5...6,8 (m, 2H, 7-H, 9-H); 3,8 (br.s, 8-OCH_3)	3,6 (br.s, CH_2)	32
IIIc	$C_{19}H_{17}ClN_2O$	148...150	1675	3225	$CDCl_3$+ +DMSO-D_6	7,0...7,6 (m 1-C_6H_5)	3,95 (m 2H, 4-H); 2,25 (m, 2H, 5-H); 2,9 (m, 2H, 6-H)	6,8 (br.s, 2H, 7-H, 9-H); 9,5 (s NH)	2,08 (s); 2,12 (s) (3H, CH_3)	24
IIId	$C_{21}H_{22}N_2O$	195...196	1680	3270	DMSO-D_6	2,03 (s, 3H, 1-CH_3)	2,03 (m., 2H, 5-H); 2,81 (m, 2H, 6-H); 3,73 (m, 2H, 4-H)	6,60 (s, 1H, 7-H); 7,00 (s 1H, 9-H); 7,35 (m, Ph); 2,33 (s 3H, 8-CH_3); 9,91 (s, NH)	3,69 (s, 2H, CH_2)	30

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*For compounds IIa-g – the C=N group, for IIIa-d – the C=O group.

spectrometer using TMS as internal standard. The course of the reaction was monitored by TLC on Silufol UV-254 plates in a benzene-acetone (5:1) system.

The elemental analysis data for compounds II, III correspond to the calculated values.

The starting N-acylaminotetrahydroquinolines were obtained by the method previously described in [2].

2-Amino-4,5-dihydro(6H)pyrrolo[1,2,3-i,j]quinolines (II). A 2 mmole portion of freshly distilled phosphorus oxychloride was added to a solution of 1 mmole of hydrazide I in absolute dioxane and the mixture was allowed to stand for 30 min at room temperature, and then boiled for 1 to 1.5 h. The dioxane was evaporated off and the excess $POCl_3$ was removed by distillation with dry benzene. A solution of hydrogen chloride in absolute ethanol was added to the residue, and the mixture was boiled for 1 h. Alcohol was evaporated off, the residue was ground with a small amount of dry ether, and the precipitate obtained was washed on the filter with acetone, and then recrystallized from an acetone-methanol mixture.

2-Acylamino-4,5-dihydro(6H)pyrrolo[1,2,3-i,j]quinolines (III). The heterocyclization was carried out under the same conditions as for compounds II. After evaporation of dioxane and excess $POCl_3$, a solution of 4 mmoles of triethylamine (based on the initial hydrazide I) in dry benzene was added to the residue, and then a solution of 1.25 mmole of the corresponding acid chloride in dry benzene was added in portions. The reaction mixture was allowed to stand for 2 h at room temperature, the filtrate was washed twice with water, dried over sodium sulfate, and the benzene was evaporated off. The residue was purified on a column with silica gel 40/100 in a benzene-acetone (6:1) system. ^{13}C NMR spectrum ($DMSO-D_6$) IIIa: 22.13 [$C_{(5)}$]; 24.36 [$C_{(6)}$]; 41.07 [$C_{(4)}$]; 42.29 (CH_2Ph); 108.53 [$C_{(1)}$]; 135.61 [$C_{(2)}$]; 116.5; 118.78; 120.08; 121.79; 122.63; 125.48; 126.71; 127.85; 128.40; 128.56; 128.74; 129.22; 131.47; 134.49 (Ar); 171.48 ppm (CO); IIId: 8.49 ($1-CH_3$); 21.71 ($8-CH_3$); 22.51 [$C_{(5)}$]; 24.25 [$C_{(6)}$]; 41.1 [$C_{(4)}$]; 42.37 (CH_2Ph); 101.40 [$C_{(1)}$]; 136.1 [$C_{(2)}$]; 115.25; 119.55; 124.59; 126.65; 127.15; 128.05; 128.45; 129.1; 129.38; 129.68; 129.82; 135.5 (Ar); 170.54 ppm (CO).

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