SYNTHESIS OF 10-PHTHALIMIDOALKYLTETRAHYDROPYRIMIDO[1,2-a]-INDOLES

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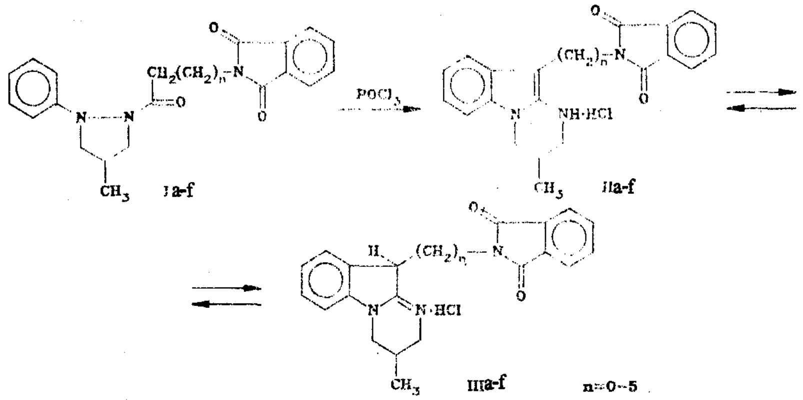
10-Phthalimidoalkyltetrahydropyrimido [1,2-a] indoles were obtained by rearrangement of cyclic hydrazides of N-phthalyl-ω-amino acids, viz., 1-phenyl-2-acyl-pyrazolidines, under the influence of phosphorus oxychloride.

We have previously shown that N-phthalyl-ω-amino acid phenylhydrazides undergo rearrangement via the Kost reaction [1] to 3-(ω-aminoalkyl)-2-aminoindole derivatives [2] upon reaction with phosphorus oxychloride. In order to develop a method for the synthesis of pyrimidoindoles with an ω-aminoalkyl group in the 10 position, in the present research we studied the rearrangement of cyclic hydrazides of N-phthalyl-ω-amino acids, viz., 1-phenyl-2-acylpyrazolidines I.



We have established that acylpyrazolidines Ib-f quite readily undergo conversion to the corresponding tetrahydropyrimido[1,2-a]indoles; a shorter reaction time is required for their complete conversion than in the indolization of N-phthalyl-ω-amino acid N-methyl-N-phenylhydrazides (under comparable conditions). This is in agreement with previously obtained data that indicate that the presence of substituents attached to both nitrogen atoms facilitates the rearrangement of phenylhydrazides significantly [3]. It should be noted that 2-phthalimidoacetylpyrazolidine (Ia, n = 0) undergoes rearrangement to pyrimidoindole II with greater difficulty than the other 2-acylpyrazolidines (for which n ≥ 1); this is evidently due to the steric effect of the phthalimido group.

The structure of pyrimidoindoles IIa-f was confirmed by data from the IR and UV spectra. Thus the UV spectra of hydrochlorides II contain absorption bands at λ_{max} 217-229 and 270-275 nm (log ε 4.65-4.70 and 3.41-3.88), which are characteristic for pyrimidoindoles [3]. Broad absorption bands at 2300-2750 cm^{-1} (stretching vibrations of the ammonium group) and intense absorption at 1665-1680 cm^{-1} (C=N vibrations) are observed in the IR spectra (Table 2); this indicates that pyrimidoindole salts II, like aminoindoles, exist in indoline form

TABLE 1. 2-Acyl-1-phenylpyrazolidines Ia-c

Compound	n	mp, deg C	IR spectrum, cm^{-1}	Found, %		Empirical formula	Calculated, %		Yield, %
				C	H		C	H	
Ia	0	146—149	1775, 1725, 1680	68,3	5,0	$C_{20}H_{19}N_3O_3$	68,7	5,5	65
Ib	1	135—137	1770, 1720, 1650	69,0	5,8	$C_{21}H_{21}N_3O_3$	69,4	5,8	67
Ic	2	143—145	1770, 1710, 1660	70,1	6,3	$C_{22}H_{23}N_3O_3$	70,1	6,1	74

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TABLE 2. Characteristics of 1,2,3,4-Tetrahydropyrimido[1,2-a]indole Hydrochlorides IIa-f

Compound	n	Reaction time at 80 deg C, h	mp, deg C (from ethanol)	UV spectrum, λ_{max}, nm (log ϵ) (in alcohol)	IR spectrum, cm^{-1} (mineral oil)			Found, %		Empirical formula	Calculated, %		Yield, %
					$\nu_{\overset{+}{N}H}$	$\nu_{C=O}$	$\nu_{C=N}$	C	H		C	H	
IIa	0	90	144—145	219 (4,69), 285 (3,41)		1730, 1780	1680	64,8	4,9	$C_{20}H_{17}N_3O_2 \cdot HCl$	65,3	4,9	52
IIb	1	12	155 (dec.)	219 (4,68), 275 (3,68)	2400—2740, 3200—3500	1720, 1775	1680	65,8	5,6	$C_{21}H_{19}N_3O_2 \cdot HCl$	66,0	5,3	85
IIc	2	13	170—172	217 (4,65), 274 (3,83)	2300—2700, 3400—3470	1715, 1770	1670	66,4	6,0	$C_{22}H_{21}N_3O_2 \cdot HCl$	66,7	5,6	61
IId	3	10	187—190	219 (4,69), 270 (3,79)	2500—2750	1710, 1770	1680	67,0	5,6	$C_{23}H_{23}N_3O_2 \cdot HCl$	67,4	5,9	58
IIe	4	12	184—185	219 (4,71), 273 (3,93)	2350—2740	1710, 1775	1670	67,8	6,5	$C_{24}H_{25}N_3O_2 \cdot HCl$	68,0	6,2	63
IIf	5	12	180—182	220 (4,70), 272 (3,88)	2400—2760	1710, 1770	1665	68,3	6,7	$C_{25}H_{27}N_3O_2 \cdot HCl$	68,6	6,4	51

III. In addition, absorption bands of carbonyl groups of the phthalimide ring at 1770-1775 and 1710-1720 cm^{-1} are present. It is interesting to note also that an additional broad absorption band of an ammonium group at 3200-3500 cm^{-1}, which is absent in the spectra of IId-f with longer aminoalkyl chains (n = 3-5), is observed in the IR spectra of pyrimidoindoles Ib-c (for which n = 1-2). However, the absorption of an ammonium group is completely absent in the case of IIa (n = 0); this is evidently associated with the formation of a rather strong intramolecular hydrogen bond between the NH group and the phthalimide carbonyl group.

EXPERIMENTAL

The UV spectra of solutions of the compounds in alcohol were recorded with a Perkin—Elmer 402 spectrophotometer. The IR spectra of mineral oil suspensions of the compounds were obtained with a Perkin—Elmer 577 spectrometer. The course of the reactions was monitored by chromatography on Al_2O_3 [benzene—methanol (10:1)].

The characteristics of Ia-c and IIa-f are presented in Tables 1 and 2.

1-Phenyl-2-acylpyrazolidines Ia-f. A 0.1-mole sample of the corresponding N-phthalyl-ω-amino acid chloride was added slowly with cooling and stirring to a mixture of 0.1 mole of 4-methyl-1-phenylpyrazolidine [4] and 0.1 mole of triethylamine in absolute benzene, after which the mixture was refluxed for 1 h. It was then cooled and treated with 150 ml of water, and the aqueous mixture was transferred to a separatory funnel and washed thoroughly with water. The benzene layer was dried with magnesium sulfate, and the benzene was removed by distillation. Dry ether was added to the residue, and the resulting crystals were removed by filtration and recrystallized from alcohol.

1-Phenyl-2-acylpyrazolidines Id-e were obtained in the form of uncrystallizable oils and were then subjected to reaction with phosphorus oxychloride without prior purification.

Tetrahydropyrimido[1,2-a]indole Hydrochlorides IIa-f. A mixture of 0.01 mole of 2-acyl-4-methyl-1-phenylpyrazolidine I and 0.02 mole of phosphorus oxychloride in 50 ml of absolute benzene was refluxed until the reaction was complete (monitoring by TLC), after which the benzene and excess phosphorus oxychloride were removed by vacuum distillation. Absolute ethanol was added to the residue, and the mixture was cooled. The resulting precipitate was removed by filtration and recrystallized from ethanol with the addition of activated charcoal.

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