

SYNTHESIS AND STRUCTURE OF SUBSTITUTED

2-AMINO-3-ARYLINDOLES

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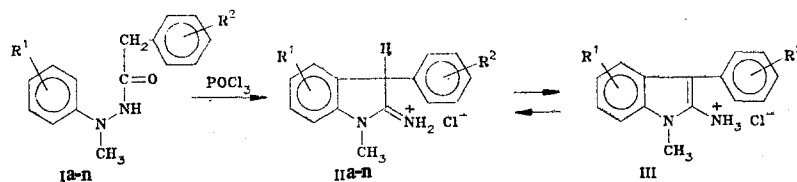
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The corresponding 2-amino-3-arylindole hydrochlorides were obtained by the reaction of substituted arylacetic acid arylhydrazides with phosphorus oxychloride (the Kost reaction). The effect of substituents in the aryl rings on the rearrangement was examined qualitatively. The IR, PMR, and UV spectra of the compounds obtained are discussed in relationship with the peculiarities of their structure.

Electronic factors play a substantial role in the indolization of arylhydrazones of carbonyl compounds, particularly under the conditions of a process involving heterogeneous catalysis [1]. No information regarding this effect in the synthesis of 2-amino-indoles via the Kost reaction is available in the literature. In the present research the subjects of investigation are substituted phenylacetic acid β -methyl- β -arylhydrazines Ia-n. The selection of these models was due to the fact that, first, the effect of substitution in the phenyl ring of an arylhydrazone on the rearrangement has not been studied and, second, due to the possibility that by selection of the substituents in the phenyl ring of arylacetic acids one can change the labilities of the hydrogen atoms attached to the α -carbon atom of the acyl residue, since, according to the data in [2], the character of the environment of this atom has a substantial effect on the rate of rearrangement.

Unfortunately, the physicochemical properties of the starting hydrazides, the intermediate reaction masses, and the resulting 2-aminoindole hydrochlorides do not make it possible to use known methods for obtaining accurate kinetic principles. The evaluation of the effect of substituents was therefore made only qualitatively with respect to the time during which the reaction occurs "up to its completion" [up to the point of complete disappearance of the starting hydrazide according to thin-layer chromatography (TLC)].

The rearrangement of hydrazides Ia-m was carried out in benzene at 80°C at a hydrazide: POCl₃ molar ratio of 1:3. 2-Amino-3-arylindole hydrochlorides IIa-m are formed in good yields under these conditions (Table 1).



In addition, let us note that the formation of 2-amino-indoles II is accompanied by their phosphorylation and that the resulting salts are difficult to separate. Compounds II were therefore subjected to two to four crystallizations for analytical purposes and spectral investigations. However, even this was not always successful (IIa).

Two absorption bands that are characteristic for 2-amino-indole salts at 2700-3200 cm⁻¹ (a salified amino group) and 1680-1695 cm⁻¹ (C=N bond) are observed in the IR spectra of IIa-m. The UV spectra (in alcohol) of hydrochlorides IIa-m contain two absorption maxima at 210-255 nm (log ϵ 4.4-4.6) and 260-270 nm (log ϵ 3.9-4.1) and are similar to the spectra of 2-amino-3-alkyl-indole salts [3, 4]. The presence of substituents in the 3-aryl ring leads to a slight change in the position and extinction of the long-wave band. The extinction

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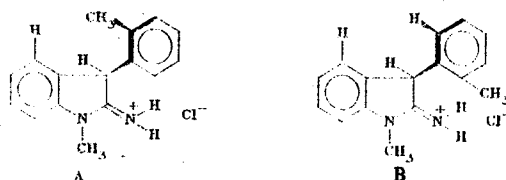
of the short-wave band also changes slightly as a function of the character of the substituent; however, a pronounced (up to 20 nm) bathochromic shift is observed for III, n, which have bromo and nitro groups in the para position.

In the case of 2-amino-3-phenylindoles that have substituents in the benzene part of the indole molecule the position and extinction of the long-wave band depend on the location of the substituent. Thus a rather pronounced decrease in the extinction of the band at 260 nm is observed in the UV spectrum of indole IIc; this constitutes evidence for steric interaction of the 7-CH₃ and N-CH₃ groups, as a result of which conjugation of the nitrogen atom with the phenyl ring is evidently weakened. This decrease in the extinction as a result of ortho interaction is also observed for the starting o-substituted β-methyl-β-phenylhydrazides [5] and is characteristic for o-substituted dialkylanilines [6].

It is known that 3-alkyl-2-aminoindole salts have 2-aminoindoline structures [3, 4]. The introduction of an aryl substituent, particularly one that has an acceptor substituent, into the 3 position could promote stabilization of the indole structure. However, a singlet of a β proton (5.17 ppm) and a broad signal of an NH₂ group at 7.53-8.00 ppm are observed in addition to signals of an N-CH₃ group (3.53 ppm) and a multiplet of aromatic protons centered at 7.13 ppm in the PMR spectrum (in CF₃COOH) of IIIm; this constitutes evidence that this compound, as well as the other II, exists in the 2-iminoindoline form. The character of the PMR spectra of II in water does not change, whereas in D₂O the signals of the β proton and the protons attached to the nitrogen atom vanish because of rapid deuterium exchange due to the existence in solutions of an equilibrium between forms II and III, although it is apparently shifted markedly to favor the II form.

The introduction of a substituent into the ortho position of the 3-phenyl ring leads to retarded rotation of the aryl substituent about the C(3)-Ar bond, which is readily observed in the PMR spectra. Thus two, rather than one, signals of the o-methyl group at 1.53 and 2.57 ppm with a signal ratio of 1:1, as well as two signals of a β proton at 5.25 and 5.58 ppm with the same ratio, are observed in the PMR spectrum of 2-amino-1-methyl-3-(o-tolyl)indole hydrochloride (IIIi) in CF₃COOH. When the temperature is raised to 70°C, the signals of the β proton merge to give one broad signal centered at 5.41 ppm. The signals of the o-methyl groups also become broader simultaneously; this constitutes evidence for retarded rotation of the 3-(o-tolyl) substituent. The PMR spectrum of IIg also has a similar form. However, if the ortho substituent in the 3-phenyl ring is a bromine atom (IIk), in addition to two signals of the β proton with a ratio of 1:1, a quartet of the ortho proton (0.5H; 6.60 ppm) appears at stronger field in its PMR spectrum. The second part of the signal of this proton cannot be isolated from the spectrum because of superimposition of the signals of the other protons of the aromatic rings.

It follows from an examination of Dreiding three-dimensional models of IIg, i, k that the most likely reason for retarded rotation is steric hindrance created by the 4-H proton and the >C=NH₂⁺ grouping. In this case there are two possible orientations of the 3-aryl ring, in one of which (form A) the ortho substituent (or the ortho proton of the 3-aryl ring) is under the shielding influence of the indole system (a shift to strong field), whereas in the other (form B) it is under a deshielding influence (a shift to weak field).



Thus under normal conditions o-substituted 3-aryl-2-amino-indoles II exist in the form of two rotational isomers A and B.

The previously proposed mechanism of the rearrangement of arylhydrazides [3, 4] includes several steps (for example, the formation of an enehydrazine, etc.) that are similar to those for the Fischer synthesis of indoles, for which a step involving the formation of an enehydrazine has been proved [7] and for which it has been established kinetically that this is the slowest step in the process [8, 9]. We made only a qualitative evaluation of the effect of substituents R and R¹ on the course of the reaction, and we will examine their effect on the course of the process from the point of view of the formation of an intermediate

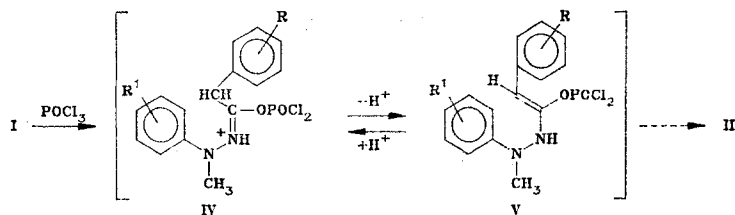
TABLE 1. 2-Amino-3-aryl-1-methylindole Hydrochlorides IIa-m

Compound	R ¹	R ²	mp, deg C	Reaction time, h	pK _a of hydrate II	Found, %		Calculated, %		Yield, %
						C	H	C	H	
IIa	5-OCH ₃	H	229-232	2	-0.8	65.2	6.5	66.5	5.9	51
IIb	5-CH ₃	H	239-241	2.5	-1.3	68.1	6.3	70.4	6.2	60
IIc	7-CH ₃	H	214-216	2.5	-	68.5	6.3	70.4	6.2	53
IIe	5-Br	H	273-275*	6	-2.0					88
IIe	5-Br	H	209-212	7	-2.6	53.1	4.6	53.3	4.1	82
IIe	H	3,4-(OCH ₃) ₂	180-182	20	-2.0	63.6	6.4	64.0	6.0	72
IIg	H	2,4-(CH ₃) ₂	185-188	15	-2.0	70.1	6.7	71.1	6.6	63
IIh	H	4-OCH ₃	172-173	16	-2.0	66.5	5.8	66.5	5.9	52
IIi	H	2-CH ₃	260-263	5	-2.0	70.4	6.3	70.4	6.2	73
IIj	H	4-CH ₃	200-202	7	-2.0	69.8	6.8	70.4	6.2	54
IIk	H	2-Br	244-247	2	-2.0	53.6	4.2	53.3	4.1	90
IIl	H	3-Br	200-202	2	-2.0	53.1	4.4	53.3	4.1	85
IIm	H	4-Br	210-212	2.5	-2.0	53.5	4.7	53.3	4.1	85
IInt	H	4-NO ₂	223-227	12	-2.0					62

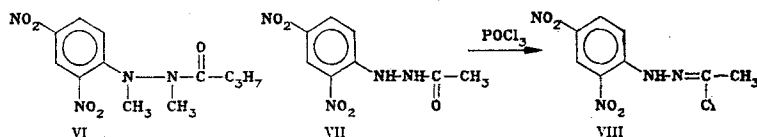
*According to the data in [3], this compound had mp 278-280°C and was obtained in 77% yield.

†The melting point and yield of a crude sample are presented for II m. The benzoyl derivative had mp 244-245°C [from ethyl acetate-hexane (1:1)]. Found: C 71.2; H 5.2%. C₂₂H₁₇N₃O₂. Calculated: C 71.2; H 4.9%.

enehydrazine as the rate-determining step. Intermediate protonated isohydrazide structure IV is formed initially in the reaction of hydrazides I with POCl_3 . The isolation in some cases of chlorohydrazone by the action of the complex of POCl_3 with pyridine on β -dialkylhydrazides constitutes indirect evidence for the existence of such structures [10].



Structure IV is stabilized by electron-donor substituents R^1 of the β -aryl ring as in the protonation of hydrazides II, and the difference may be only in the degree of transmission of the effect of substituent R^1 . As demonstrated in a study of the mass-spectral behavior of β -arylhydrazides of the I type [12], the intensity of the arylhydrazinium cation in their mass spectra increases as the electron-donor character of the substituent increases, which constitutes evidence for their participation in stabilization of the cation. Consequently, donor substituents R^1 should favor the formation of isohydrazide structure IV and thereby increase the probability of its conversion to enehydrazine V, which also should lead to acceleration of the rearrangement. As seen from Table 1, this effect is actually observed: hydrazide Ia (pK_a 0.8) undergoes rearrangement three times faster than hydrazide Id (pK_a 2.0). However, in the case of arylhydrazides with a nitro group in the β -phenyl ring we could not detect the formation of the corresponding 2-aminoindoles by chromatography. Thus, after prolonged heating in benzene, hydrazide VI is recovered unchanged from the reaction mixture, whereas acetyldinitrophenylhydrazine VII gives chlorohydrazone VIII under similar conditions.



The molecular mass of this compound determined by mass spectrometry coincides with the calculated value. The UV spectrum differs only slightly from that of the starting compound. The IR spectrum contains a characteristic band of stretching vibrations of an NH group at 3290 cm^{-1} (two bands of stretching vibrations of NH groups appear in the spectrum of the starting compound). In addition to a singlet or a methyl group, individual signals of three protons of the aromatic ring that are characteristic for 2,4-dinitroaniline are observed in the PMR spectrum.

It is to be expected that chlorohydrazone VIII could be formed only from a structure of the IV type. Consequently, the impossibility of indolization in the case of VI and VII is probably due to the fact that, because of the high degree of electron-acceptor character of the $\text{NO}_2\text{-C}_6\text{H}_4$ grouping, the $\text{IV} \rightleftharpoons \text{V}$ equilibrium is shifted completely to favor isohydrazide IV, and the enehydrazine structure is not realized. On the other hand, it should also be assumed that groups with a high degree of electron-acceptor properties deactivate the aryl ring to further attack of the resulting enehydrazine both via a scheme involving electrophilic reaction and via a scheme involving a [3, 3]-sigmatropic shift, although in the latter case the effect of electronic factors should not play such a decisive role [9].

The lability of the hydrogen atom attached to the α -carbon atom of the acyl residue is another important factor that determines the state of the $\text{V} \rightleftharpoons \text{IV}$ equilibrium. It has been previously noted [2] that the rearrangement of 1-methyl-1-phenyl-2-acetylhydrazine proceeds more slowly by a factor of 10 than the rearrangement of the corresponding propionylhydrazide under identical conditions. This is due to lower capacity of the methyl group to undergo enolization under acidic-catalysis conditions than the methylene group [13]. The introduction of electron-donor and electron-acceptor substituents into the phenyl ring of the phenacyl residue therefore should affect the lability of the hydrogen atoms attached to the α -carbon atom of the acyl residue and have a corresponding effect on the rate of rearrangement

TABLE 2. Characteristics of Arylacetic Acid β -Methyl- β -phenylhydrazides If-n

Com- pound	R	mp, deg C	IR spectrum cm ⁻¹		Found, %		Empirical for- mula	Calc., %		Yield, %
			NH	CO	C	H		C	H	
If	3,4-(OCH ₃) ₂	105-106	3250	1660	67,7	6,7	C ₁₇ H ₂₀ N ₂ O ₃	67,9	6,7	46
Ig	2,4-(CH ₃) ₂	139-140	3220	1660	75,7	7,6	C ₁₇ H ₂₀ N ₂ O	76,1	7,5	51
Ih	4-OCH ₃	160-161	3220	1660	71,3	7,0	C ₁₆ H ₁₈ N ₂ O ₂	71,1	6,8	48
Ii	2-CH ₃	105-106	3200	1660	75,4	7,2	C ₁₆ H ₁₈ N ₂ O	75,6	7,1	36
Ij	4-CH ₃	124-125	3200	1660	75,4	7,0	C ₁₆ H ₁₈ N ₂ O	75,6	7,1	44
Ik	2-Br	148-149	3250	1660	56,5	4,8	C ₁₅ H ₁₅ BrN ₂ O	56,4	4,7	17
Il	3-Br	108-109	3150	1650	56,6	4,8	C ₁₅ H ₁₅ BrN ₂ O	56,4	4,7	24
Im	4-Br	109-110	3200	1660	56,4	4,7	C ₁₅ H ₁₅ BrN ₂ O	56,4	4,7	41
In	4-NO ₂	169-170	3200	1665	62,9	5,0	C ₁₅ H ₁₅ N ₃ O ₃	63,1	5,2	40

of hydrazides I; donor substituents should decrease the lability of the α -hydrogen atoms of the methylene group and thereby hinder realization of enehydrazine form V. Acceptor substituents in the phenyl ring of the acyl residue act in the opposite direction. In fact, as seen from Table 1, a completely definite dependence of the reaction time on the character of the substituent in the phenyl ring is observed: the higher the degree of its electron-donor properties, the slower the process. The anomaly in the case of hydrazide In is evidently most likely associated with the subsequent steps in the rearrangement rather than with the step involving the formation of enehydrazine V.

EXPERIMENTAL

The IR spectra of mineral oil suspensions of the compounds were obtained with a UR-20 spectrometer. The PMR spectra were recorded with a Varian T-60 spectrometer with hexamethyl-disiloxane as the external standard. The UV spectra of solutions in alcohol were recorded with a Specord spectrophotometer. The end of the reaction was determined by thin-layer chromatography (TLC) on activity II Al₂O₃ in a benzene-methanol system (10:1) with respect to disappearance of the spot of the starting hydrazide with R_f 0.3-0.5. Starting hydrazides Ia-e were described in [5].

The characteristics of I are presented in Table 2, and the characteristics of II are given in Table 1.

Arylacetic Acid β -Methyl- β -phenylhydrazides If-m. An equimolar amount of the crude chloride of the corresponding aryl-acetic acid was added with vigorous stirring to a benzene solution of equimolar amounts of α -methyl- α -phenylhydrazine and triethylamine while preventing the mixture from heating up markedly. After all of the acid chloride had been added, the mixture was stirred at 70°C for another 1-2 h. The precipitated substance was removed by filtration, washed thoroughly with water, dried, and crystallized from ethyl acetate. The benzene solution was washed with water and a solution of potassium carbonate, dried over Na₂SO₄, and evaporated to give an additional amount of hydrazides I.

p-Nitrophenylacetic Acid β -Methyl- β -phenylhydrazide (In). A mixture of 18 g (0.1 mole) of p-nitrophenylacetic acid and 12 g (0.1 mole) of α -methylphenylhydrazine in 100 ml of toluene was refluxed for 15 h with a Dean-Stark trap, after which it was cooled, and the precipitate was removed by filtration and recrystallized from ethyl acetate-benzene (1:1).

2-Amino-1-methylindole Hydrochlorides IIa-n. General Method. A mixture of 5 mmole of the corresponding Ia-n and 15 mmole of freshly distilled phosphorus oxychloride in 45 ml of absolute benzene was refluxed until the reaction was complete. The precipitate that formed after evaporation of the excess POCl₃ and the solvent (if no precipitate formed, absolute ether was added) was washed with absolute ether and recrystallized from absolute n-propanol.

For analytical purposes and spectral studies hydrochlorides II were crystallized two to three times from n-propanol. All of the compounds melted with decomposition.

Acetyl Chloride 2,4-Dinitrophenylhydrazone (VIII). A 0.3-g (1.2 mmole) sample of 2,4-dinitrophenylacetylhydrazine was refluxed with 1 ml of POCl₃ in 10 ml of benzene, after which the benzene and excess oxychloride were evaporated *in vacuo*, and the residue was crystallized from alcohol to give 0.05 g (26%) of chlorohydrazone VIII with mp 141-142°C (with sublimation. Found: C 37.0; H 2.7; Cl 13.3%; M⁺ 258. C₆H₇ClN₄O₄. Calculated:

C 37.2; H 2.7; Cl 13.7%; M⁺ 258. PMR spectrum (in CH₂Cl₂): 2.96 (3H, s, CH₃), 8.23 (1H, d, ³J₅₆ = 10 Hz, 6-H), 8.62 (1H, dd, ⁴J₅₃ = 10 Hz, ⁴J₃₅ = 3 Hz, 5-H), and 9.51 ppm (1H, d, ⁴J₃₅ = 3 Hz, 3-H).

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