RING-CHAIN ISOMERIZATION OF 2-SUBSTITUTED 3-HYDROXY-3-(4-DIMETHYL-AMINOPHENYL)ISOINDOLINONES

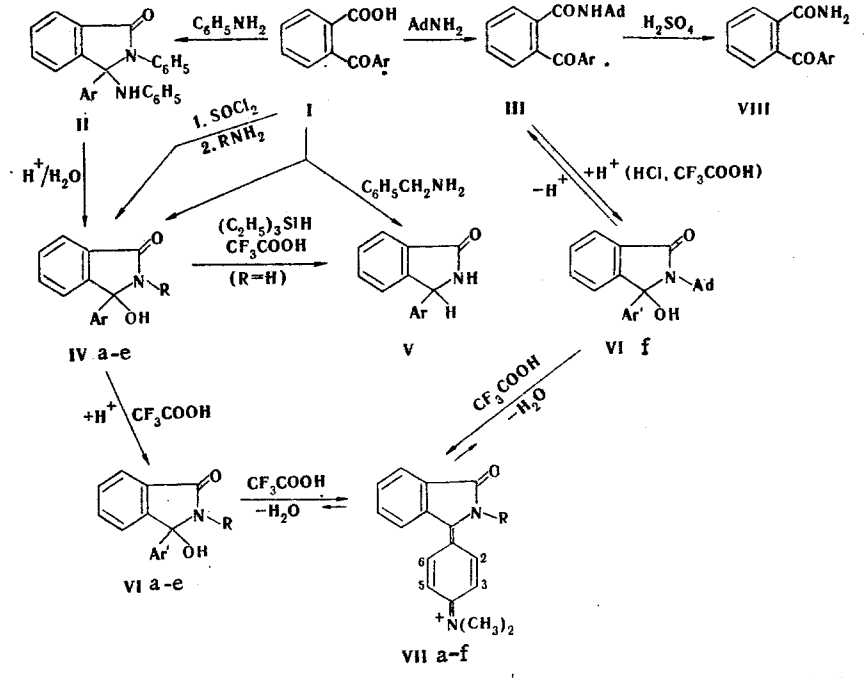
G. A. Karlivan, R. É. Valter,
R. B. Kampare, and V. P. Tsiekure

UDC 541.621:547.759.4

N-Unsubstituted and N-monosubstituted amides of 2-(4-dimethylaminobenzoyl)benzoic acid exist in the chain form of 3-hydroxyisoindolinones in the crystalline state and in solutions in dioxane, whereas the tautomeric amide ⇌ hydroxyisoindolinone equilibrium occurs (except for the methyl derivative) in more polar solvents. The analogous N-(1-adamantanyl)amide exists in the open form and does not undergo cyclization under alkaline catalysis conditions; protonation of the dimethylamino group is accompanied in all cases by splitting out of water to give compounds with a quinoid structure; an equilibrium between the protonated and quinoid forms, which is shifted markedly to favor the latter, is observed for some compounds.

Most 2-aroylbenzamides exist in the stable ring form of 3-hydroxyisoindolinones, except for those cases in which the formation of a hydroxyisoindolinone ring is impossible because of the presence of bulky substituents attached either to the nitrogen atom or to the keto group [1]. We have recently [2] shown that the introduction of electron-acceptor substituents in the aroyl ring makes it possible to obtain even N-(tert-alkyl)-2-aroylbenzamides in the ring form.

The aim of the present research was to study the structures, ring-chain transformations, and chemical properties of 2-(4-dimethylaminobenzoyl)benzoic acid amides. These com-



I—V, VIII Ar=4-$(CH_3)_2NC_6H_4$; VI Ar′=4-$(CH_3)_2\overset{+}{N}HC_6H_4$; Ad= 1-adamantanyl; IV, VI, VII a R=H, b R=CH_3, c R=C_2H_5, d R=C_6H_5, л R=$C_6H_5CH_2$; VIIf R=Ad

Riga Polytechnic Institute, Riga 226355. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 6, pp. 780-785, June, 1979. Original article submitted September 20, 1978.

 0009-3122/79/1506-0634$07.50

TABLE 1. 3-Hydroxy-3-(4-dimethylaminophenyl)isoindolinones IVa-e

Compound	R	mp, °C (from ethanol)	Found, %			Empirical formula	Calc., %			IR spectra, ν, cm^{-1}			Yield, %
			C	H	N		C	H	N	in Nujol		in d-oxane	
										C=O	O–H[a]	C=O	
IV a	H	170—171 [b]	71,4	6,0	10,4	$C_{16}H_{16}N_2O_2$	71,6	6,0	10,4	1690	3230	1715	75
IV b	CH_3	202—206 [c]	72,2	6,4	9,8	$C_{17}H_{18}N_2O_2$	72,3	6,4	9,9	1685	3200	1709	39
IV c	C_2H_5	205—208 [d]	72,3	6,8	9,6	$C_{18}H_{20}N_2O_2$	72,9	6,8	9,5	1688	3270	1707	34
IV d	C_6H_5	183—184 [e]	77,0	5,7	8,0	$C_{22}H_{20}N_2O_2$	76,7	5,9	8,1	1683	3280	1709	79
IV e	$CH_2C_6H_5$	163—165	77,3	6,2	7,8	$C_{23}H_{22}N_2O_2$	77,1	6,2	7,8	1670	3310	1695	20

[a]Broad band. [b]With decomposition, from acetone. According to the data in [3], this compound has mp 171-172°C. [c]According to the data in [3], this compound has mp 176-178°C. [d]According to the data in [3], this compound has mp 195-196°C. [e]According to the data in [3], this compound has mp 182-183°C.

pounds constitute an interesting model for the study of the influence of electronic effects of substituents attached to the keto group on the intramolecular addition to it, since the electrophilicity of the carbon atom of the keto group can be increased substantially by protonation of the dimethylamino group.

It has been established [3] that a number of 2-(4-dimethylaminobenzoyl)benzamides in the crystalline state have an open structure, although their IR spectra, which were presented in [3], do not confirm this conclusion.

We obtained the ring isomers of the amides — 3-hydroxyisoindolinones IVa-c — by the successive action of thionyl chloride and an amine on 2-(4-dimethylaminobenzoyl)benzoic acid (I). Acid I reacts with aniline to give 3-anilinoisoindolinone II, which does not undergo thermal isomerization to the corresponding anil (see [4]). The acid hydrolysis of II, which was accomplished under mild conditions [4], leads to 3-hydroxyisoindolinone IVd. Two isoindolinone derivatives (IVe and V) were isolated when acid I was heated with benzylamine. Compound V was also obtained by reduction of hydroxyisoindolinone IVa by ionic hydrogenation [5]. When acid I was heated with 1-aminoadamantane, we obtained N-(1-adamantanyl)-benzamide III, which exists in the open form both in the crystalline state and in solutions. Because of steric shielding of the nitrogen atom of the amide group by a bulky substituent, amide III does not undergo isomerization to the ring form under alkaline catalysis conditions (see [2]).

Bands of the C=O groups of a diaryl ketone, amide I, and amide II and a narrow band of an NH group are observed in the IR spectrum of amide III. The IR spectra of crystalline 3-hydroxyisoindolinones IVa-e (Table 1) contain only one band of the C=O group of the isoindolinone, which in dioxane solution is shifted 20-25 cm^{-1} to the high-frequency side. This phenomenon, as well as the broad band of associated OH groups in the spectra of the crystalline compounds, constitutes evidence for the presence of strong intermolecular hydrogen bonds (OH...O=C) in the crystalline state; this is also characteristic for other hydroxyisoindolinones [1, 2].

A comparison of the IR spectra of amide III with the spectra of the methyl-, ethyl-, and phenylamides of 2-(4-dimethylaminobenzoyl)benzoic acid makes it possible to conclude that the latter, despite the data in [3], have the ring structure of 3-hydroxy-3-(4-dimethylaminophenyl)isoindolinones (IV) in the crystalline state. The presence of broad bands of associated OH groups in the spectra of crystalline IV, which can be distinguished clearly from the narrow band of the NH group in the spectrum of amide III, provides good confirmation for this (Fig. 1).

The identification of the open or ring isomers of the 2-(4-dimethylaminobenzoyl)benzoic acid amides by means of UV spectroscopy is determined by the presence or absence of the band at ~350 nm that is characteristic [3] for the conjugated Ar—CO—Ar—$N(CH_3)_2$-p system. Thus this band appears at 356 nm in the UV spectrum of amide III in ethanol, as compared with 345 nm in dioxane. This band is absent in the UV spectra of crystalline IV recorded by the diffuse-reflection method; this is also evidence of solutions of IVa-e in dioxane, but it is observed (except in the case of IVb) for solutions in ethanol, chloroform, and acetoni-

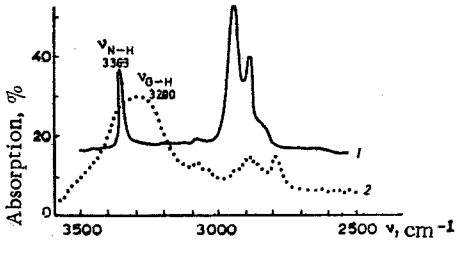


Fig. 1

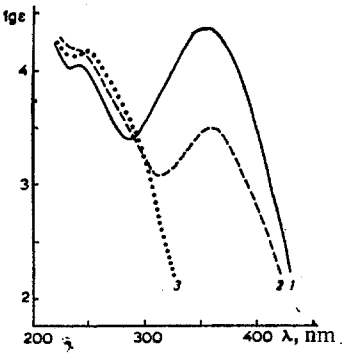


Fig. 2

Fig. 1. IR spectra in hexachlorobutadiene: 1) N-(1-adamantanyl)benzamide III; 2) 3-hydroxyisoindolinone IVd.

Fig. 2. UV spectra of N-(1-adamantanyl)benzamide III: 1) in ethanol; 2) in a 1 N solution of HCl in ethanol; 3) in a 5 N solution of HCl in ethanol.

trile; the intensity of the band in the spectra of solutions of IVa, c-e in the indicated solvents is lower than the intensity of this band in the spectra of solutions of amide III or the dimethylamide of 2-(4-dimethylaminobenzoyl)benzoic acid [3]. It follows from this that IVa, c-e in dioxane exist exclusively in the ring form, whereas in more polar solvents a tautomeric equilibrium is set up between the open amide and ring forms of the hydroxyisoindolinones (see [3]). N-Methyl derivatives IVb exist exclusively in the ring form in all of these solvents.

Tautomeric equilibrium is not observed for most of the ring isomers of N-monosubstituted 2-aroylbenzamides in solutions. Equilibrium does occur in solutions in dioxane in the presence of proton-acceptor additives that are proton carriers [2]. Equilibrium is evidently also established in this case under the influence of the basic dimethylamino group that is present in the investigated compounds.

Protonation of the dimethylamino group in amide III leads to the intramolecular cyclization III → VIf. Thus the IR spectrum of hydrochloride VIf contains the band of the C=O group of an isoindolinone and a broad band of an OH group. A considerable decrease in the intensity of the band at 356 nm (ε 3000) as compared with the spectrum of a solution in ethanol (ε 24400) is observed in the UV spectrum of amide III in 1 N HCl, whereas this band vanishes in a 5 N solution of HCl in ethanol, i.e., the III → VIf cyclization is realized completely (Fig. 2). The deprotonation of VIe is accompanied by opening of the isoindolinone ring (VIf → III).

Thus cyclization of the 2-acylbenzamide in acidic media is the first step in the case of III. The effect of a strong electron acceptor — the dimethylammonium group — which increases the electrophilicity of the carbon atom of the keto group to such an extent that intramolecular addition to the keto group of the amide group becomes possible even with such a bulky substituent as the 1-adamantanyl group attached to the nitrogen atom, is manifested in the III → VIf transformation.

When a solution of amide III is dissolved in concentrated sulfuric acid at room temperature, it undergoes dealkylation (see [6]) to give an N-unsubstituted 2-(4-dimethylaminobenzoyl)benzamide (VIII). The latter undergoes isomerization to hydroxyisoindolinone ring form IVa under the catalytic action of bases to give an equilibrium mixture (VIII ⇄ IVa) with considerable preponderance of the IVa form. Isomerization in the reverse direction (IVa → VIII) is not realizable because of thermal decomposition of IVa.

When amide III and hydroxyisoindolinones IVa-e are dissolved in trifluoroacetic acid, the solutions take on an intense red coloration. The starting compounds are isolated reversibly when the solutions are neutralized. An absorption band in the visible region at ∿500 nm appears in the spectra of the solutions. This can be explained by the fact that in trifluoroacetic acid protonation of the dimethylamino group of III and IVa-e is accompanied by intramolecular splitting out of a water molecule from the protonated form VI to give quinoid structure VII. In the case of amide III the intensity of the band at ∿500 nm increases with time: the III → VIf → VIIf transformation is realized in 24 h. Here, the step

TABLE 2. PMR Spectra of Amide III and Hydroxyisoindolinones IVa, b, d, e

Compound	In d_6-DMSO					In CF_3COOH[a]				
	δ, ppm			$J_{23}=J_{56}$, Hz	Remaining protons, δ, ppm	δ, ppm			$J_{23}=J_{56}$, Hz	Remaining protons, δ, ppm
	$N(CH_3)_2$	Protons of the dimethylaminophenyl ring				$\overset{+}{=}N(CH_3)_2$	Protons of the quinoid ring			
		and $^{3-}_{5-H}$	and $^{2-}_{6-H}$				and $^{3-}_{5-H}$	and $^{2-}_{6-H}$		
III	3,05	6,68	7,53	9,0	1,60, 1,87 adamantanyl 7,40—7,60[b]	3,62	8,41	7,30	9,7	1,80, 2,30 adamantanyl 7,70—8,20[c]
IVa	2,85	6,68	7,31	9,0	6,65 (OH), 7,30—7,60[c], 9,80 (NH)	3,64	8,44	7,32	9,8	7,90—8,20[c]
IVb	2,83	6,68	7,13	8,6	2,65 (N—CH_3), 6,76 (OH), 7,30—7,80[c]	3,57	8,38	7,38	10,3	3,81 (N—CH_3), 7,9—8,20[d]
IVd	2,80	6,58	7,20	8,0	7,10—7,70[d], 7,52 (OH)	3,51	7,95	7,04	10,3	7,30—8,30[d]
IVe	2,81	6,56	7,07	8,7	4,05, 4,51 (N—CH_2)[e], 6,90—7,70[d]	3,54	8,32	7,43	9,6	5,40 (N—CH_2), 7,0—7,4 and 7,9—8,3[d]

[a]The chemical shifts of only quinoid form VII are presented. [b]Protons of the phthaloyl ring. [c]Aromatic protons of the isoindoline ring. [d]All of the remaining aromatic protons (in addition to those specially presented). [e]Quartet of the AB type, J = 14 Hz.

that determines the rate of the conversion is evidently opening of the hydroxyisoindolinone ring, which is realized after protonation of the dimethylamino group (III → VIf). The formation of quinoid structure VII in trifluoroacetic acid solutions was also proved by PMR spectroscopy. The PMR spectra of III and IVa, b, d, e in dimethyl sulfoxide (DMSO) and trifluoroacetic acid are presented in Table 2. Two sets of signals that can be assigned to protonated form VI and quinoid form VII are observed for IVb, e in trifluoroacetic acid. The quinoid form is characterized by the appreciably larger vicinal spin—spin coupling constants (SSCC) of the quinoid protons [7]. Since two pairs of N-methyl signals from both structures — 3.05 (N—CH_3) and 3.49 ppm [$\overset{+}{N}H(CH_3)_2$] for the VIb form, and 3.81 (N—CH_3) and 3.57 ppm [$=\overset{+}{N}(CH_3)_2$] for the VIIb form — are observed in the PMR spectrum of IVb in trifluoroacetic acid, the percentage of quinoid form VIIb is 67%. Signals at 3.25 and 4.81 ppm, which can be assigned to the resonance of the $\overset{+}{N}H(CH_3)_2$ and N—CH_2 groups, respectively, are also observed for IVe in trifluoroacetic acid in the VIe form; for the VIIe form — 3.54 [$=\overset{+}{N}(CH_3)_2$] and 5.40 ppm (N—CH_2) — the percentage of quinoid form VIIe is 84%. The signals of the N-methyl groups in the spectra of protonated forms VIb, e are split because of spin—spin coupling with the $\overset{+}{N}H$ proton (J = 4 Hz). In trifluoroacetic acid IVa, d are converted completely to quinoid form VII. The VI ⇄ VII equilibrium is established immediately after dissolving of the compound. The percentage of quinoid form VIIf is 92% in a solution of amide III in trifluoroacetic acid in the equilibrium mixture VIf ⇄ VIIf, which is formed after 24 h.

The observed VI → VII transformation makes it possible to assume that the IVa → V reduction, which is carried out in trifluoroacetic acid, proceeds through a step involving the formation of quinoid structure VIIa with subsequent hydrogenation of the conjugated double bond (IVa → VIIa → V).

EXPERIMENTAL

The IR spectra of suspensions of the compounds in paraffin oil and hexachlorobutadiene and of solutions in dioxane (c $2.5 \cdot 10^{-2}$ M, l = 0.011 cm) were recorded with a Specord 751R spectrometer. The UV spectra of solutions of the compounds in ethanol, dioxane, chloroform, acetonitrile, trifluoroacetic acid, and concentrated sulfuric acid (c $5 \cdot 10^{-5}$ M, l = 0.5 and

1 cm) were recorded with a Specord UV-vis spectrophotometer. The diffuse-reflection spectra were obtained with an SFD-2 spectrometer with a PDO-1 adapter; the substances were ground with magnesium oxide. The PMR spectra were obtained with a Perkin-Elmer R-12A (60 MHz) spectrometer; the internal standard for solutions in d_6-DMSO was hexamethyldisiloxane, and the internal standard for solutions in trifluoroacetic acid was cyclohexane. The solution concentration was 10^{-1} M.

3-Hydroxy-3-(4-dimethylaminophenyl)isoindolinone (IVa, Table 1). A solution of 1.35 g (5 mmole) of 2-(4-dimethylaminobenzoyl)benzoic acid (I) [8] and 0.72 ml (10 mmole) of thionyl chloride in 10 ml of methylene chloride was maintained at room temperature for 1 h, after which it was evaporated in vacuo, and the residue was dissolved in 15 ml of methylene chloride and added with stirring to a solution of 30 ml of concentrated ammonium hydroxide. The organic layer was separated, dried with magnesium sulfate, and filtered. The filtrate was evaporated in vacuo, and the residue was recrystallized successively from ethanol and acetone.

2-Alkyl-3-hydroxy-3-(4-dimethylaminophenyl)isoindolinones (IVb, c, Table 1). A solution of 1.35 g (5 mmole) of acid I and 0.72 ml (10 mmole) of thionyl chloride in 10 ml of chloroform was refluxed for 3 h, after which it was evaporated in vacuo, and the residue was dissolved in 15 ml of chloroform and added with stirring to a solution of 10 mmole of the amine in dioxane. After 24 h, the reaction mixture was diluted with 100 ml of water, and the organic layer was separated, dried with magnesium sulfate, and filtered. The filtrate was evaporated in vacuo, and the residue was recrystallized.

2-Phenyl-3-phenylamino-3-(4-dimethylaminophenyl)isoindolinone (II). A 1.35-g (5 mmole) sample of acid I was refluxed in 5 ml of aniline for 2 h, after which the mixture was cooled and treated with 20 ml of ether. The resulting precipitate was separated to give 1.5 g (72%) of a product with mp 208-210°C (from benzene). IR spectrum in Nujol: 1693 (C=O) and 3390 cm^{-1} (N–H); in dioxane: 1703 cm^{-1} (C=O). Found: C 80.2; H 6.1; N 10.0%. $C_{28}H_{25}N_3O$. Calculated: C 80.2; H 6.0; N 10.0%.

2-Phenyl-3-hydroxy-3-(4-dimethylaminophenyl)isoindolinone (IVd, Table 1). A 0.7-g sample of II was suspended in a solution of 0.5 ml of concentrated sulfuric acid and 5 ml of acetic acid in 5 ml of water. The reaction mixture took on an intense violet coloration, but the solution became colorless after the substance dissolved. The solution was maintained at room temperature for 30 min, afterwhich it was diluted with 50 ml of water and neutralized to pH 4. The precipitate was separated, washed on the filter with water, and recrystallized.

3-(4-Dimethylaminophenyl)isoindolinone (V) and 2-Benzyl-3-hydroxy-3-(4-dimethylaminophenyl)isoindolinone (IVe, Table 1). A 1.35-g (5 mmole) sample of acid I was refluxed in 5 ml of benzylamine for 2 h, after which the mixture was cooled, and the precipitate was separated, washed with ether, and recrystallized to give 0.6 g (48%) of V with mp 237-239°C (dec., from ethanol). IR spectrum in Nujol: 1690 (C=O) and 3190 cm^{-1} (N–H); in dioxane: 1712 cm^{-1} (C=O). PMR spectrum (in d_6-DMSO): 2.77 [6H, s, $N(CH_3)_2$], 5.44 (1H, s, isoindolinone C–H), 6.56 (2H, d, J = 9 Hz, 3-H, 5-H), 6.94 (2H, d, J = 9 Hz, 2-H, 6-H), 7.20-7.70 (4H, m, aromatic protons of the isoindoline ring), and 8.73 ppm (1H, s, N–H). Found: C 77.1; H 6.4; N 11.1%. $C_{16}H_{16}N_2O$. Calculated: C 76.2; H 6.4; N 11.1%.

The filtrate after separation of isoindolinone V was diluted with a mixture of ether and hexane, and the resulting precipitate was separated and recrystallized to give IVe.

The IVa → V Reduction. A mixture of 0.27 g (1 mmole) of IVa, 0.5 ml (3 mmole) of triethylsilane, and 0.5 ml of trifluoroacetic acid was heated at 80°C for 1 h, after which it was cooled and treated successively with 5 ml of ethanol and 20 ml of ether. After 24 h, the precipitate was separated, washed with ether, and recrystallized to give 0.2 g (80%) of V; its identity was proved by a mixed-melting-point determination and the IR and PMR spectra.

N-(1-Adamantanyl)-2-(4-dimethylaminobenzoyl)benzamide (III). A mixture of 1.35 g (5 mmole) of acid I and 0.75 g (5 mmole) of 1-aminoadamantane was heated at 230°C for 2 h, after which it was cooled, and the solid material was recrystallized from benzene to give 0.85 g (42%) of a product with mp 185-186°C. IR spectrum in Nujol: 1650 (C=O), 1638 (amide I), 1525 (amide II), and 3363 cm^{-1} (N–H); in dioxane: 1655, 1635 (shoulder); 1530 cm^{-1}. UV spectrum in ethanol, λ_{max} (log ε): 241 (4.06) and 356 nm (4.39). Found: C 77.4; H 7.5; N 7.2%. $C_{26}H_{30}N_2O_2$. Calculated: C 77.6; H 7.5; N 7.0%.

2-(1-Adamantanyl)-3-hydroxy-3-(4-dimethylaminophenyl)isoindolinone Hydrochloride (VIf). A solution of 0.4 g (1 mmole) of amide III in 10 ml of dioxane was saturated with dry hydrogen chloride, after which it was treated with 30-40 ml of ether. After 24 h, the resulting precipitate was separated to give 0.4 g (92%) of a product with mp 130°C (dec.). IR spectrum in Nujol: 1684 (C=O) and 3270 cm^{-1} (broad O–H band). Found: C 71.8; H 6.8; Cl 8.7; N 6.0%. $C_{26}H_{30}N_2O_2 \cdot HCl$. Calculated: C 71.1; H 7.1; Cl 8.1; N 6.4%.

2-(4-Dimethylaminobenzoyl)benzamide (VIII). A 0.4-g (1 mmole) sample of amide III was dissolved with stirring in 5 ml of concentrated sulfuric acid, and the solution was maintained at room temperature for 1 h. It was then poured over 50 g of finely crushed ice, and the precipitate was removed by filtration to give 0.12 g of a substance that was identified as 1-hydroxyadamantane [9]. The filtrate was neutralized to pH 7-8, and the precipitate was separated, washed with water, dried, and recrystallized to give 0.2 g (75%) of a product with mp 177-179°C (from ethanol). IR spectrum in dioxane: 1688 (C=O), 1650 (amide I), and 3430 cm^{-1} (N–H, in Nujol). UV spectrum in dioxane: λ_{max} 342 nm (log ε 4.39). Found: C 71.5; H 5.8; N 10.3%. $C_{16}H_{16}N_2O_2$. Calculated: C 71.6; H 6.0; N 10.4%.

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SYNTHESIS OF AMINOINDOLES BY THE BUCHERER REACTION

A. N. Kost, V. I. Terenin, and L. G. Yudin

UDC 547.754.07

The reaction of 5-hydroxyindoles with ammonia, alkylamines, or dialkylamines in the presence of sulfites leads to the corresponding 5-aminoindoles. Partial or complete elimination of the substituent is observed in the case of indoles that have an electron-acceptor substituent ($COOC_2H_5$, $COCH_3$).

The Bucherer reaction is well known as a method for the conversion of aromatic amines to hydroxy compounds or the conversion of hydroxy compounds to primary, secondary, or tertiary amines. It has been studied systematically in the naphthalene series and among heterocyclic compounds has been used in the synthesis of quinoline and isoquinoline derivatives [1]. There are also data regarding similar transformations of 4-hydroxy- and 4-aminobenzo-2,1,3-thiadiazoles, as well as 4-hydroxybenzofuran and 4-aminobenzofuran [2-4].

We have attempted to use this method for 5-hydroxyindoles, which are quite easily obtainable but are extremely unstable under the influence of extraneous agents. In particular, one might have expected that addition to the C_2–C_3 bond, as described for some indoles under the influence of sulfurous acid [5], would occur under the conditions of the Bucherer reaction. Our attempts showed that when the conditions are selected successfully, one can convert 5-hydroxyindoles (I) to the corresponding 5-amino- or 5-alkylaminoindoles (II) in good yields. In contrast to the classical conditions of the Bucherer reaction, better re-

M. V. Lomonosov Moscow State University, Moscow 117234.

Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 6, pp. 786-789, June, 1979. Original article submitted July 5, 1978.

0009-3122/79/1506-0639$07.50