BENZIDOLES. SYNTHESIS OF (5,6-BENZINDOL-3-YL)-ACETAMIDINES

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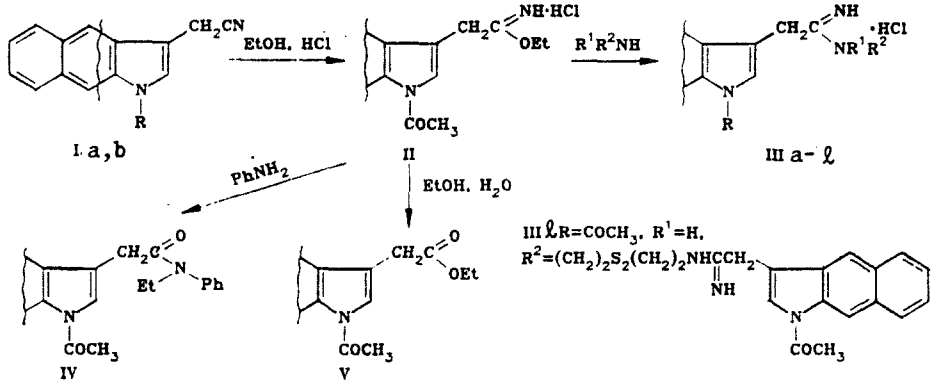
Various compounds derived from the nitrile group were synthesized by conventional methods by carrying out consecutive transformations of (1-acetyl-5,6-benzindol-3-yl)acetonitrile.

In continuation of our investigations in the field of benzindole derivatives [1], we synthesized hydrochlorides of (5,6-benzindolyl)acetamidines IIIa-l according to the classical scheme:



I a R=H, b R=$COCH_3$; III a—c R=H, g—ℓ R=$COCH_3$; a-j, ℓ R^1=H, k R^1+R^2= $=(CH_2)_2O(CH_2)_2$; a R^2=H, b $R^2=CH_3$, c $R^2=C_2H_5$, d R^2=H, e $R^2=CH_3$, f $R^2=C_2H_5$, g $R^2=C_4H_9$, h $R^2=CH_2C_6H_5$, i $R^2=C_2H_4OH$, j $R^2=C_6H_{11}$.

The starting (1-acetyl-5,6-benzindol-3-yl)acetonitrile (Ib) was previously synthesized by us [2]. By its consecutive treatment with sodium ethylate, ammonia, and HCl, instead of the expected amidine IIIa, the deacylated (5,6-benzindol-3-yl)acetonitrile (Ia) was isolated. The imino-ether hydrochloride II was obtained from the acylated nitrile Ib by a conventional method – the treatment of the latter by gaseous hydrogen chloride in ether. Reaction of imino-ether II with ammonia and various amines leads to the formation of amidines IIIa-l in a yield of 40-90% (Table 1). It was noted that when gaseous ammonia, methyl- and ethylamine are reacted with imino-ether II, deacylation of the amidines formed takes place, which can be attributed to overalkalifying of the reaction mixture as a result of the difficulty of regulating the pH during addition of the gaseous reagents. Therefore, in further operations with gaseous reagents, we introduced an alcoholic solution of the amine at a given concentration into the reaction with imino ether II. This made it possible to carry out a dosed introduction of the amine, which enabled the preparation of acylated amidines. As a result of the reaction of imino-ether II with aniline, instead of the expected N-phenyl (1-acetyl-5,6-benzindol-3-yl)amidine, N-ethyl, N-phenyl (1-acetyl-5,6-benzindol-3-yl)acetamide (IV) was isolated, the formation of which can be attributed by the extraordinary instability of the intermediate amidine which, in the presence of traces of acid and moisture, is saponified to amide IV. After treatment of imino-ether II with aqueous alcohol, ethyl (1-acetyl-5,6-benzindol-3-yl)acetate (V) was isolated.

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TABLE 1. Characteristics of Synthesized Compounds I-V

Compound	Empirical formula	Mp, °C	IR spectrum (in KBr), cm^{-1}	Yield, %
Ia	$C_{14}H_{10}N_2$	150...151	2260 (C≡N); 3400 (NH)	70
II	$C_{18}H_{19}ClN_2O_2$	215...216	1700 ($COCH_3$); 1650 (—OC=NH); 1605, 320...2700 (NH)	96
IIIa	$C_{14}H_{14}ClN_3$	183	1685, 1650 (H_2N—C—NH); 1636*; 3400...2800 (NH)	41
IIIb	$C_{15}H_{16}ClN_3 \times C_2H_5OH$	143	1685, 1650 (NC=NH); 3400...2800 (NH, OH)	50
IIIc	$C_{16}C_{18}ClN_3 \times CH_3COC_2H_5$	90**	1710 (C=O of methyl ethyl ketone) 1685, 1645 (NC=NH); 3400...2800 (NH)	93
IIId	$C_{16}H_{16}ClNO$	283...285	1700 ($COCH_3$); 1680, 1630 (NC=NH); 1600; 3300...2900 (NH)	71
IIIe	$C_{17}H_{18}ClN_3O \cdot H_2O$	233...235	1700 ($COCH_3$); 1685, 1650 (NC=NH); 1600; 3500...2900 (NH)	47
IIIf	$C_{18}H_{20}ClN_3O$	260...261	1700 ($COCH_3$); 1685 1640 (—NC=NH); 1600; 3300...2850 (NH)	58,4
IIIg	$C_{20}H_{21}ClN_3O$	242...243	1695 ($COCH_3$); 1685 1645 (—NC=NH); 1605; 3400...2800 (NH)	61
IIIh	$C_{25}H_{22}ClN_3O$	246...248	1695 ($COCH_3$); 1685, 1645 (—NC=NH); 1605; 3300...2800 (NH)	74
IIIi	$C_{18}H_{20}ClN_3O_2$	188...190	1705 ($COCH_3$); 1675, 1625 (NC=NH); 3400...2900 (NH)	60,5
IIIj	$C_{22}H_{26}ClN_3O$	283...285	1705 ($COCH_3$); 1680, 1625 (NC=NH); 3400...2850 (NH)	57,7
IIIk	$C_{20}H_{22}ClN_3O$	268...270***	1705 ($COCH_3$); 1670, 1625 (NC=NH); 3400...2900 (NH)	66,7
IIIl	$C_{36}H_{38}Cl_2N_6O_2S_2 \times 3H_2O$	210	1695 ($COCH_3$); 1675, 1630 (NC=NH); 1600, 3200...2800 (NH)	21
IV	$C_{24}H_{22}N_2O_2$	130...131	1700 ($COCH_3$); 1680 (=N—C=O); 1605	37
V	$C_{18}H_{17}NO_3$	108...110	1720 (COO^-); 1695 ($COCH_3$)	55

*In $CHCl_3$.

**From methyl ethyl ketone.

***From ethanol.

A broad intense absorption band is observed in the IR spectra of compounds IIIa-l at 1680 cm^{-1}, which we assigned to the amidine grouping. The latter masks the characteristic band of the $COCH_3$ group at 1695 cm^{-1} (compounds IIId-l) appearing in the form of a shoulder. The imino-ether grouping in compound II is characterized by a sharp intense absorption band at 1650 cm^{-1}. We should note that that the presence of an acyl substituent at the nitrogen atom in the 5,6-benzindole ring generally is accompanied by the appearance of a sharp band at 1605 cm^{-1}, which can be used for the identification of compounds II, IIId-l, IV, and V.

PMR spectra of the synthesized compounds were obtained (Table 2). The signals of the aromatic protons were assigned on the basis of a comparison of the chemical shifts and multiplicity of signals of the compounds obtained by us with an unsubstituted linear benzindole [3]. The noticeable spin-spin interaction (0.5 Hz) of the 2-H proton and the pyrrole NH for compounds IIIa-c enabled the unequivocal assignment of the 2-H proton signals. A general characteristic of the PMR spectra of the hydrochlorides and esters of the compounds obtained is the weak field shift (~1.0 ppm) of the 9-H signal when the NH group proton is replaced by the anisotropic acetyl group. Thus, for the hydrochlorides with the series of substituents studied at the 3-position, the signal of the 2-H proton is also shifted by 0.4-0.6 ppm to the weak field. In ester V and amide IV, the position of the 2-H signal changes little, which may be due to the mutual compensation of the contributions of the substituents at the 1- and 3-positions. The signal of the methylene protons CH_2 of the substituent at the 3-position is a singlet, which does not change its position much (the 4.0-4.3 ppm region for hydrochlorides and 3.7-3.9 ppm for the ester and amide). In their chemical shifts and multiplicity, the proton signals of the alkyl radicals in the substituent at the β-position agree well with the known literature data. The signals of the alkyl protons are broadened because of the spin-spin interaction with the neighboring proton of the NH group for compound IIIb, $J_{NHCH_3} = 3.3$ Hz. The NH proton signal for the hydrochloride II containing an ether group, is shifted to the weak field. In the spectra of other hydrochlorides, either one broad signal is observed

TABLE 2. PMR Spectral Data of 5,6-Benzindole Derivatives

Compound	1-H	$COCH_3$	CH_2	NH·HCl	NH	2-H	4-H	5-H	6-H	7-H	8-H	9-H	Other protons
5,6-BI*	11,02	—	—	—	—	7,55	8,02	7,84	7,28	7,15	7,84	7,82	
II	—	2,67	4,28	11,92 (1H)	—	8,08	8,22	7,98	7,46	7,46	7,98	8,85	
IIIa	11,16	—	3,93	8,90 (4H)	8,90	7,62	8,16	7,88	7,23	7,23	7,88	7,81	
IIIb	11,27	—	4,03	9,31 (1H); 8,76 (1H)	9,73	7,71	8,22	7,93	7,32	7,32	7,93	7,89	
IIIc	11,28	—	4,03	9,28 (1H); 8,84 (1H)	9,95	7,73	8,31	7,90	7,25	7,25	7,90	7,86	
IIId	—	2,68	4,05	8,27 (1H); 8,16 (1H)	—	8,20	8,31	8,00	7,49	7,49	8,07	8,80	
IIIe	—	2,68	4,09	9,58 (1H); 8,93 (1H)	10,15	8,27	8,38	8,00	7,49	7,49	8,06	8,87	2,87 (CH_3)
IIIf	—	2,68	4,08	9,47 (1H); 8,99 (1H)	10,20	8,26	8,39	7,99	7,49	7,49	8,06	8,87	1,17 (CH_3); 3,32 (CH_2)
IIIg	—	2,69	4,07	9,30 (1H); 8,90 (1H)	10,00	8,18	8,30	8,08	7,50	7,50	7,98	8,88	
IIIh	—	2,65	4,16	9,53 (3H)	9,53	8,25	8,36	7,97	7,46	7,46	7,97	8,84	
IIIi	—	2,67	4,05	—	—	8,17	8,31	8,01	7,44	7,44	8,01	8,85	3,59 (OCH_2); 3,40 (NCH_2)
IIIj	—	2,67	4,06	9,27 (1H); 8,23 (1H)	10,09	8,19	8,34	7,99	7,46	7,46	7,99	8,84	3,48; 3,65 (C_6H_{11})
IIIk	—	2,68	4,30	9,88 (1H); 9,41 (1H)	—	8,01	8,25	8,00	7,47	7,47	8,00	8,87	3,75 (OCH_2); 3,66 (NCH_2)
IV	—	2,62	3,71	—	—	7,57	7,86	8,04	7,47	7,47	7,95	7,86	
V	—	2,65	3,86	—	—	7,90	8,03	7,97	7,44	7,44	7,97	8,85	

*5,6-BI = 5,6-Benzindole.

(the NH, NH_2, and HCl protons) with an intensity of 4-H (IIIa) or 3-H (IIIh); compound IIIb-g, j, k have two broad signals of the NH and HCl protons.

EXPERIMENTAL

The PMR spectra were obtained on a Varian HA-100 spectrometer in DMSO-D_6 solutions, using TMS as internal standard. The IR spectra were run on a Perkin–Elmer 180 spectrophotometer in KBr tablets and in solutions in standard cuvettes. The mass spectrum was recorded on a Varian MAT-311A spectrometer in an electron impact regime. The TLC was carried out on Silufol UV-254 plates in a benzene–acetone, 4:1, and ethyl acetate–alcohol–ammonia, 1:1:1 systems.

(5,6-Benzindol-3-yl)acetonitrile (Ia). A 1.18-g portion (4.76 mmoles) of nitrile Ib in a solution of a 5:1 mixture of absolute ethanol and chloroform was added to a solution of 0.35 g (5 mmoles) of sodium ethylate in 100 ml of absolute ethanol, and the reaction mixture was allowed to stand for 10-12 h at 20-25°C. At the end of the reaction, the solvent was evaporated to yield 0.69 g of compound Ia.

(1-Acetyl-5,6-benzindol-3-yl)acetiminoethyl Ether Hydrochloride (II). A 3.2-ml portion (53 mmoles) of absolute ethanol was added to 6.6 g (26.5 mmoles) of nitrile Ib in 350 ml of absolute ether. The mixture was cooled to 0°C and the solution was saturated with a dry gaseous HCl. The reaction mixture was allowed to stand for 8-10 days at –10°C to a total completion of the reaction (according to TLC). The imino-ether II was filtered in the form of a white fibrous precipitate, which was washed with dry ether. Yield 8.4 g of compound II.

(5,6-Benzindol-3-yl)acetamidine Hydrochloride (IIIa). Dry ammonia was passed at 0°C through a heterogeneous mixture of 2.4 g (7.2 mmoles) of compound II in 350 ml of absolute ethanol to pH 8. The reaction mixture was allowed to stand for 12 h at –10°C, was then filtered, evaporated to a volume of 10 ml, and precipitated by methyl ethyl ketone (2:1). The oily amidine IIIa that was formed was crystallized at 0°C from 1:2 ethanol–methyl ethyl ketone mixture, and then from a 1:10 ethanol–ether mixture. Yield 0.73 g of product IIIa.

N-Methyl (5,6-Benzindol-3-yl)acetamidine Hydrochloride (IIIb). Dry gaseous methylamine was passed through a heterogeneous mixture of 2.4 g (7.1 mmoles) of compound II in 350 ml of absolute ethanol to complete dissolution, pH 8. The reaction mixture was allowed to stand for 2 days at 0°C, then evaporated and reprecipitated from a 1:10 ethanol–ether mixture. Yield 0.9 g of compound IIIb.

N-Ethyl (5,6-Benzindol-3-yl)acetamidine hydrochloride (IIIc) was obtained from 1 g (3 mmoles) of compound II and gaseous ethylamine under conditions similar to those used in the preceding example. Yield 0.81 g.

(1-Acetyl-5,6-benzindol-3-yl)acetamidine Hydrochloride (IIId). A 10.8-ml portion of an alcoholic solution containing 0.05 g (3 mmoles) of ammonia was added dropwise at –5°C to a suspension of 1.0 g (3 mmoles) of iminoether II in 100 ml of absolute ethanol. After dissolution of iminoether II (pH 7), the solution was allowed to stand for 18 h at 0-5°C. The precipitate was filtered and reprecipitated from an aqueous ethanol–ether (1:1) mixture. Yield of compound IIId 0.64 g.

N-Methyl (1-acetyl-5,6-benzindol-3-yl)acetamidine hydrochloride (IIIe) was obtained from 3.5 g (10 mmoles) of compound II in 350 ml of absolute ethanol and 0.31 g (10 mmoles) of methylamine in 52 ml of absolute ethanol under conditions similar to those used in the preceding example. Yield 2.52 g (75%). After reprecipitation from an aqueous ethanol–diethyl ether (2:1) mixture, the yield of compound IIe was 1.57 g.

N-Ethyl (1-acetyl-5,6-benzindol-3-yl)acetamidine hydrochloride (IIIf) was obtained from 2.2 g (6.6 mmoles) of imino-ether II in 220 ml of absolute ethanol and 0.3 g (6.6 mmoles) of ethylamine in 52 ml of absolute ethanol. Yield 1.28 g.

N-Butyl (1-Acetyl-5,6-benzindol-3-yl)acetamidine Hydrochloride (IIIg). A solution of 0.2 g (3 mmoles) of n-butylamine in 10 ml of absolute ethanol was added dropwise at 0°C to a suspension of 1 g (3 mmoles) of imino-ether II in 100 ml of absolute ethanol. The imino-ether II dissolved progressively as the amine solution was added. After 1 h, the reaction mixture was filtered and evaporated in vacuo. The white precipitate of amidine IIIg was separated and washed with dry ether. Yield 0.68 g.

N-Benzyl (1-acetyl-5,6-benzindol-3-yl)acetamidine hydrochloride (IIIh) was obtained from 1 g (3 mmoles) of compound II and 0.32 g (3 mmoles) of benzylamine under conditions similar to those used in the preceding example. Yield 0.87 g.

N-Hydroxyethyl (1-acetyl-5,6-benzindol-3-yl)acetamidine hydrochloride (IIIi) was obtained from 1.5 g (4.5 mmoles) of iminoether II in 150 ml of absolute ethanol and 0.3 g (4.5 mmoles) of hydroxyethylamine in 15 ml of absolute ethanol under conditions similar to those used in the synthesis of IIIg. After cooling, 0.95 g of compound IIIi was obtained from the reaction mixture.

N-Cyclohexyl (1-acetyl-5,6-benzindol-3-yl)acetamidine hydrochloride (IIIj) was obtained from 2.0 g (6 mmoles) of compound II in 200 ml of absolute ethanol and 0.6 g (6 mmoles) of cyclohexylamine in 14 ml of absolute ethanol under the conditions of synthesis of IIIg. After cooling, 1.34 g of amidine IIIj was obtained from the reaction mixture by precipitation with hexane.

(1-Acetyl-5,6-benzindolyl-3-yl)morpholylacetamidine hydrochloride (IIIk) was obtained from 1.26 g (4 mmoles) of imino-ether II in 126 ml of absolute ethanol and 0.32 g (4 mmoles) of morpholine in 6 ml of absolute ethanol. Yield 0.94 g.

N,N-Cystaminyl di[1-acetyl-5,6-benzindol-3-yl)acetamidine] dihydrochloride (IIIl) was obtained from 0.5 g (1.5 mmoles) of imino-ether II in 50 ml of absolute ethanol and 0.23 g (1.5 mmoles) of cystamine in 32 ml of dry ether. Yield 0.25 g.

N-Ethyl, N-phenyl (1-acetyl-5,6-benzindol-3-yl)acetamide (IV) was obtained from 1 g (3 mmoles) of imino-ether II and 0.28 g (3 mmoles) of aniline under conditions similar to those used in the synthesis of IIIg. Yield 0.4 g.

Ethyl (1-acetyl-5,6-benzindol-3-yl)acetate (V) was obtained from 0.1 g (0.3 mmole) of imino-ether II and 15 ml of 20% aqueous ethanol at 20-25–C. Yield 0.05 g.

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TAUTOMERISM AND METHYLATION OF 2-IMINO-4-IMIDAZOLIDINONES

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5-Benzylidenecreatinine and 2'-phenylglycocyamidine exist in DMSO-D_6 in the imino form. In basic medium, the two compounds exhibit a dual reactivity with respect to methylating agents, forming $N_{(2')}$- and $N_{(3)}$-methyl derivatives.

We have previously shown that in basic medium, 2-imino-4-thiazolidinones (pseudothiohydantoins) and 2-imino-4-oxazolidinones exhibit dual reactivity with respect to alkylating agents [1, 2]. The tautomerism of these compounds was also studied [2, 3]. It was of interest to clarify whether anions of 2-imino-4-imidazolidinones (glycocyamidines, creatinines, cyclic derivatives of guanidine) are capable of reacting in dual manner, i.e., whether this mode of reaction is a general property of 2-imino-4-azolidinone anions, the charge of which is delocalized over the amidine system of bonds.

The subjects of the present investigation are 2-imino-5-benzylidene-1-methyl-4-imidazolidinone (I, 5-benzylidenecreatinine) and 2-phenylimino-4-imidazolidonone (II, 2'-phenylglycocyamidine). It is known [4] that in a basic medium compound I is alkylated with the formation of a 2'-methyl derivative. The alkylation of compound II was not previously studied. Since in the investigation of the dual reacting, methylated derivatives were obtained modeling tautomeric forms of compounds I and II, we also studied the tautomeric composition of these compounds, the information on which has not yet been given in the literature.

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