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XXVII.* 2-HALOACETYLINDOLES

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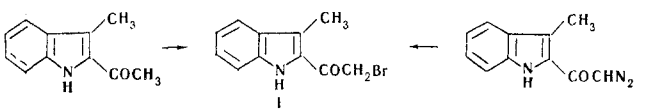
A number of 2-haloacetylindoles were synthesized from substituted 2-diazoacetylindoles. The direct bromination of 3-methyl-2-acetylindole proceeds at the acetyl group of form 3-methyl-2-bromaoacetylindole. In 2-acetylindole, the CH_3 group and the 3-position of the pyrrole ring are simultaneously brominated.

Halo ketones of the indole series are used for the synthesis of amino ketones, ketonitriles, hydroxy ketones, and other difunctional derivatives (for example, see [2,3]). Among these compounds, those with a haloacyl group in the 2 position of the indole ring have received comparatively little study. Only the conversion of 2-diazoacetylindole to 2-bromoacetylindole is known [4]. A communication regarding the synthesis of 2-chloroacetylindole by the reaction of indolylmagnesium halide with chloroacetyl chloride [5] was subsequently refuted [6].

We have performed a number of experiments on the synthesis of 2-haloacetylindoles by both the direct halogenation of the appropriate ketones and by the decomposition of substituted 2-diazoacetylindoles in acid media. A number of difficulties were encountered in the direct halogenation of 2-acetylindoles, since the 2-acylindoles themselves are rather hard to obtain (for example, see [7]). A particularly large number of complications are encountered in the case of ketones that do not have substituents in the 3 position, since halogenation in the side chain may be complicated by substitution of a hydrogen atom in the 3 position.

We obtained the starting 2-acetylindole by the reduction of 2-diazoacetylindole with stannous chloride in a mixture of hydrochloric acid and alcohol, while 3-methyl-2-acetylindole was obtained by the action of acetic anhydride on skatole in the presence of boron trifluoride etherate. We used a solution of bromine in methanol or a solution of trimethylphenylammonium tribromide in tetrahydrofuran for the bromination of 3-methyl-2-acetylindole. The latter reagent was previously successfully used for the bromination of 3-acetylindoles [8, 9]. Both reagents brominated only the acetyl group without affecting the benzene ring, and this made is possible to obtain 3-methyl-2-bromoacetylindole (I) in completely satisfactory yields. According to its physical constants, I was identical to the sample obtained by an alternative route by the decomposition of 3-methyl-2-diazoacetylindole in hydrobromic acid. The PMR spectrum of I contains singlets at 2.87 and 4.53 ppm with an intensity ratio of 3:2 (CH_3 and CH_2 groups) and a multiplet of aromatic protons (4H), which confirms its structure.



*See [1] for communication XXVI.

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TABLE 1. 2-Diazoacetylindoles (IV)

R	Decomp. point, °C[a]	R_f	IR spectrum, cm^{-1} C=O	IR spectrum, cm^{-1} NH	IR spectrum, cm^{-1} N_2	UV spectrum, λ_{max}, nm (log ε)	Empirical formula	Found, % C	Found, % H	Found, % N	Calc., % C	Calc., % H	Calc., % N	Yield, %[b]
H	175—188[c]	0,47	1583	3270	2110	238 (4,08) 333 (4,49)	$C_{10}H_7N_3O$	—	—	—	—	—	—	75
3-CH_3	165—166	0,47	1570	3265	2113	331 (4,41)	$C_{11}H_9N_3O$	66,3	4,8	21,3	66,3	4,6	21,1	80
5-CH_3	210—215	0,28	1565	3280	2108	338 (4,34)	$C_{11}H_9N_3O$	66,4	4,8	21,2	66,3	4,6	21,1	80
5-OCH_3	166—168	0,21	1590	3250	2100	336 (4,35)	$C_{11}H_9N_3O_2$	61,1	4,3	19,0	61,4	4,2	19,5	72
6-Br	176—177	0,47	1579	3250	2120	336 (4,32)	$C_{11}H_6BrN_3O$	45,6	2,5	15,5	45,5	2,3	15,9	83
3-Br	185—190[d]	0,47	1585	3270	2100	247 (4,09) 331 (4,43)	$C_{10}H_6BrN_3O$	45,5	2,6	15,6	45,5	2,3	15,9	85

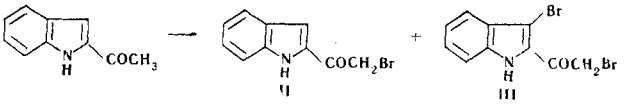
[a]Recrystallization from alcohol. [b]Based on the indole-2-carboxylic acids. [c]Decomposition point 165-175° [11]. [d]From aqueous dimethylformamide.

TABLE 2. 2-Haloacetylindoles (V)

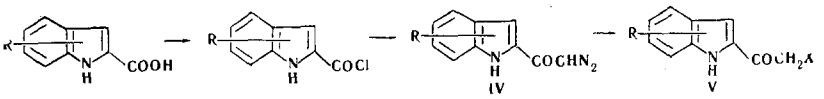
R	X	mp, °C	R_f	IR spectrum, cm^{-1} C=O	IR spectrum, cm^{-1} NH	UV spectrum, λ_{max}, nm (log ε)	Empirical formula	Found, % C	Found, % H	Found, % N	Calc., % C	Calc., % H	Calc., % N	Yield, %
H	Cl	138—139[a]	0,66	1670	3330	232 (4,04) 313 (4,31)	$C_{10}H_8ClNO$	61,5	4,2	7,5	62,0	4,1	7,2	65
H	Br	130—131[b]	0,66	1665	3320	315 (4,29)	$C_{10}H_8BrNO$	—	—	—	—	—	—	70
H	I	149—150[a]	0,66	1640	3300	324 (4,35)	$C_{10}H_8INO$	42,1	2,8	4,6	42,1	2,8	4,9	45
3-CH_3	Br	168—169[a]	0,58	1645	3330	239 (4,22) 318 (4,34)	$C_{11}H_{10}BrNO$	52,9	3,3	5,5	52,4	3,6	5,6	82
5-CH_3	Br	175—176[c]	0,58	1660	3320	317 (4,32)	$C_{11}H_{10}BrNO$	52,1	3,4	5,5	52,4	3,6	5,6	74
5-OCH_3	Br	150—152[c]	0,51	1650	3340	321 (4,32)	$C_{11}H_{10}BrNO_2$	50,1	4,1	5,5	49,3	3,8	5,2	70
6-Br	Cl	154—155[c]	0,65	1700	3320	304 (4,34)	$C_{10}H_7ClBrNO$	44,4	2,5	5,0	44,2	2,5	5,2	69
3-Br	Br	178—179[c]	0,58	1660	3320	241 (4,16) 317 (4,39)	$C_{10}H_7Br_2NO$	37,7	2,4	4,3	37,9	2,2	4,4	73

[a]From benzene–hexane. [b]mp 130-131° [4]. [c]From alcohol.

Only traces of 2-bromoacetylindole (II) were detected chromatographically during the bromination of 2-acetylindole with bromine in methanol at room temperature. A mixture of 2-bromoacetylindole (II) (40%), starting material (~15%), and 3-bromo-2-bromoacetylindole (III) (25%) is obtained when the reagents are refluxed. The bromination with trimethylphenylammonium tribromide, even at 15-18°, leads to partial substitution of a hydrogen atom in the CH_3 group. The starting compound (53%) and 2-bromoacetylindole (II) (38%) could be isolated by means of preparative thin-layer chromatography. Substitution in the 3 position also begins to occur appreciably as the temperature is raised. Thus the starting ketone (15-18%), II (55%), and dibromide III (~20%) were isolated chromatographically after refluxing the reagents for 1 h. It was possible to chromatographically demonstrate that the formation of III occurs at 37-40°. Thus the introduction of a halogen in the side chain requires precise selection of the conditions and is, as a rule, accompanied by side halogenation of the ring.



The synthesis of haloacetylindoles via 2-diazoacetylindoles (IV) is considerably more unambiguous. It is known that diazo ketones IV can be obtained from the comparatively readily accessible indole-2-carboxylic acids [10, 11]. We have synthesized a number of these compounds (see Table 1), like the other diazo ketones of the indole series [10, 11], through the acid chlorides of the appropriate acids by the action of diazomethane. In concentrated hydrohalic acids, diazo ketones IV decompose to form 2-haloacetylindoles (Table 2) in yields of up to 50% based on the starting acids.



The IR spectra of diazo ketones IV contain an intense absorption band at 2100-2120 cm^{-1}, which is characteristic for the stretching vibrations of the diazo group [12]. The stretching vibrations of the indole NH group are found at 3250-3280 cm^{-1}, while the vibrations of the carbonyl group are shifted to the absorption region of the double bonds of the pyrrole ring (intense bands at 1565-1590 cm^{-1}) because of conjugation with the diazo group.

The stretching vibrations of the NH group are situated at 3300-3340 cm^{-1} in the IR spectra of the 2-haloacetylindoles (Table 2), while the absorption band at 1640-1700 cm^{-1} can be related to a carbonyl group conjugated with the indole ring. The several deviations of the various structures from the average value may be associated with the conformation of the acyl group, but we do not have sufficient data for a definitive answer to this problem.

The UV spectra of 2-diazoacetylindoles contain an absorption band at 331-338 nm, while the spectra of 2-haloacetylindoles contain an absorption band at 304-321 nm. As in the case of indole-2-carboxylic acids [13], the introduction of an electron-donor substituent into the ring does not substantially change the physicochemical characteristics of the molecule, while the introduction of a bromine atom with its strong -I effect induces an appreciable hypsochromic shift of the absorption band. This is also observed in the IR spectra, in which the frequency of the carbonyl group of 6-bromo-2-chloroacetylindole is shifted to 1700 cm^{-1}.

EXPERIMENTAL

The UV spectra of methanol solutions were recorded with an EPS-3 spectrophotometer (c 10^{-5} M). The IR spectra of mineral oil suspensions were recorded with a UR-10 spectrometer. The PMR spectrum of a trichloroacetonitrile solution was recorded with an RS-60 spectrometer with hexamethyldisiloxane as the internal standard. The purity of the compounds obtained was monitored by chromatography in a thin layer of silical gel with a hexane–ethyl acetate system (4:1). The spots were developed with iodine vapors.

2-Diazoacetylindoles (Table 1). Thionyl chloride (25 ml) was added with stirring and cooling to 0.1 mole of indole-2-carboxylic acid in 150 ml of dry ether, and the resulting solution was held at room temperature for 3 h and overnight in a refrigerator. It was then filtered, and the filtrate was evaporated to dryness in vacuo at 25°. The residue was dissolved in 30 ml of dry ether, 70 ml of petroleum ether was added, and the mixture was stirred for 1 h and filtered. The filtrate was evaporated to dryness in vacuo at a bath temperature of 30°. The acid chlorides thus obtained (75-85%) were used in the synthesis without further purification.

A solution of 0.1 mole of the acid chloride of the appropriate indole-2-carboxylic acid in 50 ml of dry ether was added with stirring at 10-15° to 300 ml of an ether solution of diazomethane (from 45 g of nitrosomethylurea). The solution was held at room temperature for 24 h and evaporated to dryness. The residue was recrystallized.

2-Haloacetylindoles from 2-Diazoacetylindoles. Concentrated hydrohalic acid (30 ml) was added to a suspension of 0.1 mole of 2-diazoacetylindole in 50 ml of ether, and the mixture was held at room temperature for 2 h and evaporated to dryness in vacuo. The residue was diluted with 100 ml of water, and the precipitate was removed by filtration, washed with water, and recrystallized from alcohol. The yields and physical constants of the substances obtained are presented in Table 2.

1-Butylindole-2-carboxylic Acid. A solution of 52 g (0.29 mole) of N-nitrosobutylaniline in 80 ml of glacial acetic acid was added with stirring at 10-20° to a suspension of 80.5 g (0.87 g-atom) of zinc dust in

120 ml of water. The mass was stirred at room temperature for 1 h and then heated up to 80°. The hot solution was filtered, and the solid was washed with hot 5% hydrochloric acid. The filtrate and wash liquids were combined and cooled to 5°, and 500 ml of 40% sodium hydroxide was added. The oil that was liberated was extracted with ether, and the ether was removed by distillation on a water bath. The residue of 1-butyl-1-phenylhydrazine was dissolved in 200 ml of 20% hydrochloric acid, and 14.2 ml (0.2 mole) of freshly distilled pyruvic acid in 20 ml of water was added dropwise. The mixture was stirred at room temperature for 15 min, heated for 2 h at 65°, and cooled to 10°. The resulting precipitate was removed by filtration and dried at room temperature to give 10.8 g (17%) of 1-butylindole-2-carboxylic acid with mp 120.5-122° (from benzene–hexane). UV spectrum (in methanol), λ_{max}, nm (log ε): 221 (5.03); 289 (4.76). Found: C 71.8; H 6.9; N 6.5%. $C_{13}H_{15}NO_2$. Calculated: C 71.9; H 6.9; N 6.5%.

The other indole-2-carboxylic acids were synthesized via the method in [13].

2-Acetylindole. Anhydrous stannous chloride [5.6 g (0.03 mole)] was added to a suspension of 1.85 g (0.01 mole) of 2-diazoacetylindole in 20 ml of absolute methanol, and 9.2 ml (0.12 mole) of concentrated hydrochloric acid was added dropwise with stirring. The mixture was then stirred at 45-50° for 1 h, cooled to room temperature, and diluted with 30 ml of water. The resulting precipitate was removed by filtration and recystallized from benzene–hexane to give 1 g (66%) of 2-acetylindole with mp 150-152° and R_f 0.40. IR spectrum: 1648 (C=O), 3275 cm^{-1} (N-H). UV spectrum (in methanol), λ_{max}, nm (log ε): 307 (4.33); 226 (4.10). According to [7], the compound has mp 154-155° and λ_{max}, nm (log ε) in ethanol: 305 (4.33); 225 (4.10).

Bromination of 2-Acetylindole. A) A solution of 2.36 g (0.006 mole) of trimethylphenylammonium tribromide in 4 ml of absolute tetrahydrofuran was added dropwise at room temperature to a solution of 1 g (0.006 mole) of 2-acetylindole in 7 ml of absolute tetrahydrofuran. The mixture was held at room temperature for 30 min, refluxed for 1 h, and cooled. The resulting precipitate of trimethylphenylammonium bromide was removed by filtration, and the filtrate was vacuum-evaporated to dryness. The residue was separated by means of preparative chromatography in a thin layer of KSK silica gel with a hexane–ethyl acetate system (4:1) to give 0.75 g (55%) of 2-bromoacetylindole (II) with mp 128-129° (from alcohol), 0.41 g (20%) of 3-bromo-2-bromoacetylindole (III) with mp 178-180° (from alcohol), and 0.2 g (20%) of 2-acetylindole with mp 149-150° (from dilute alcohol). A similar experiment carried out at room temperature yielded 35% of 2-bromoacetylindole and 53% of 2-acetylindole.

B) A solution of 0.32 ml (0.006 mole) of bromine in 3 ml of absolute methanol was added dropwise at 0-5° to a solution of 1 g (0.006 mole) of 2-acetylindole in 6 ml of absolute methanol, and the mixture was held at room temperature for 1 h and at 37-40° for 1 h. The solution was vacuum-evaporated to dryness, and the residue was separated by means of preparative chromatogrphy in a thin layer of silica gel to give 0.62 g (40%) of 2-bromoacetylindole (II) with mp 128-130°, 0.5 g (25%) of 3-bromo-2-bromoacetylindole (III) with mp 178-180°, and 0.2 g (20%) of 2-acetylindole with mp 149.5-150.5°.

3-Methyl-2-acetylindole. Boron trifluoride etherate (2.6 ml) was added dropwise to a cold solution of 2.6 g (0.02 mole) of 3-methylindole in 26 ml of acetic anhydride and 10.3 ml of acetic acid. The mixture was then vacuum-evaporated, and the residue was diluted with water to give 2.24 g (66%) of 3-methyl-2-acetylindole with mp 144-145° (from aqueous alcohol) [14].

Bromination of 3-Methyl-2-acetylindole. A solution of 3.75 g (0.01 mole) of trimethylphenylammonium tribromide was added in 20 min at 40° to a solution of 1.73 g (0.01 mole) of 3-methyl-2-acetylindole in 8 ml of absolute tetrahydrofuran, and the reaction mixture was refluxed for 1 h. The precipitate was removed by filtration, and the filtrate was vacuum-evaporated to dryness. The residue was diluted with 10 ml of cold absolute methanol to give 1.8 g (72%) of 3-methyl-2-bromoacetylindole (I) with mp 155.5-157° (from alcohol).

In a similar experiment, 1.5 g (63%) of I with mp 154-155° was obtained by the action of equimolar amounts of bromine in methanol at 0-5° and subsequent refluxing for 2 h, followed by vacuum evaporation and dilution of the residue with water.

1-Butyl-2-bromoacetylindole. A solution of 1-butylindole-2-carboxylic acid chloride in 50 ml of dry ether was added with stirring at 5-10° to 150 ml of an ether solution of diazomethane (from 23 g of nitrosomethylurea), and the solution was held at room temperature for 24 h and evaporated to dryness. The oily residue was dissolved in 50 ml of ether, and 15 ml of concentrated hydrobromic acid was added to it at 5-10°. The mixture was held at room temperature for 2 h and vacuum-evaporated to dryness at a bath

temperature no higher than 25-30°. The residue was reprecipitated three times from benzene solution by the addition of hexane to give 6 g (40%) of 1-butyl-2-bromoacetylindole as a yellow oil. IR spectrum: 1640 cm^{-1} (C=O). UV spectrum (in methanol), λ_{max}, nm (log ε): 237 (4.16); 315 (4.31). Found: C 56.5; H 5.3; N 5.0%. $C_{14}H_{16}BrNO$. Calculated: C 57.2; H 5.4; N 4.7%.

1-Butylindacyl-2-pyridinium bromide with mp 239-240° (from absolute methanol) was formed when 1-butyl-2-bromoacetylindole was refluxed for 1 h with dry pyridine. IR spectrum: 1668 cm^{-1} (C=O). Found: C 61.4; H 6.0; N 7.7%. $C_{16}H_{21}BrN_2O$. Calculated C 61.1; H 5.7; N 7.5%.

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