INDOLE DERIVATIVES

C.* SYNTHESIS OF ω-(3-INDOLYL)ALKYL BROMIDES

B. Ya. Eryshev, A. G. Dubinin,
V. N. Buyanov, and N. N. Suvorov

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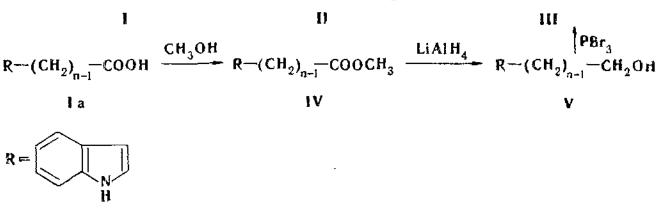
ω-(3-Indolyl)alkyl bromides, the structure of which was confirmed by alternative synthesis from ω-(3-indolyl)alkanols, were obtained by a modified Borodin–Hunsdiecker reaction from mercury salts of ω-(3-indolyl)alkanoic acids.

The Borodin–Hunsdiecker reaction is rather well known for various acids but has not been investigated at all in the indole series. In the present research we have studied the possibility of its use for the preparation of ω-(3-indolyl)alkyl bromides.



As pointed out in [2-6], a solvent that has a number of peculiarities is necessary for this reaction. It should not have nucleophilic properties [7], it should prevent bromination in the ring [8, 9], it should not react with bromine, it should have a low dielectric permeability in order to avoid dissolving of the $HgBr_2$ formed in the reaction, it should dissolve the starting acid and thereby promote the formation of the mercury salt, and it should prevent sedimentation of the mercury salt of the acid and HgO inasmuch as the reaction proceeds with the dispersed mercury salts [10].

It proved to be practically impossible to select an individual solvent with such an assemblage of properties for ω-(3-indolyl)alkanoic acids (I). The solvents that we investigated, such as $CHCl_3$, CCl_4, petroleum ether, benzene, diethyl ether, o-dichlorobenzene, and dimethylformamide (DMFA), did not give the desired results. We were able to establish that the best yield of bromide in the case of γ-(3-indolyl)-butyric acid is obtained by the use of a mixture of acetone and CCl_4 in a volume ratio of 1 : 1.33. The effect of the temperature and the ratio of bromine and red mercuric oxide on the yield of the indolylalkyl bromide and the dependence of the yield of the bromide on the use of oxides of various metals were studied for this same acid.

It was found that the optimum temperature was 55°C; lowering or raising the temperature by 5° leads to a decrease in the product yield. Of the oxides studied (cadmium oxide, lead oxide, and red mercuric oxide), red mercuric oxide showed the greatest activity. The best ratio of bromine to red mercuric oxide was 0.06 : 0.09 mole.

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* See [1] for communication XCIX.

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TABLE 1. ω-(3-Indolyl)alkyl bromides (III)

Compound	n[a]	mp, °C	Empirical formula	Found, %				Calc., %				Yield, %
				C	H	Br	N	C	H	Br	N	
IIIa	2	97—98[b]	$C_{10}H_{10}BrN$									42
IIIb	3	28,5—29[c]	$C_{11}H_{12}BrN$	55,2	5,3	33,5	6,0	55,5	5,0	33,6	5,9	54
IIIc	4	45—47	$C_{12}H_{14}BrN$	56,8	5,9	31,8	5,7	57,2	5,6	31,7	5,6	62
IIId	10	27—28	$C_{18}H_{26}BrN$	64,0	7,9	23,7	4,1	64,2	7,8	23,8	4,2	69

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[a] All of the products were obtained by crystallization from benzene–petroleum ether.

[b] According to [12], this compound has mp 98-99°.

[c] According to [11], this compound has n_D^{25} 1.625.

When all of the optimum conditions were observed, we were unable to succeed in having all of the acid introduced into the reaction react completely; a portion of it (19-34%) remains unchanged and can be recovered from the reaction mixture. In addition to the principal reaction, the hydrogen atoms in acetone are replaced by bromine; this is accompanied by the liberation of hydrogen bromide. Indole-ring substitution products were not detected.

The structure of the previously undescribed indolylalkyl bromides (III) was confirmed by alternative synthesis from indolylalkanoic acids (Ia) through the esters (IV) and alcohols (V) by the action of phosphorus tribromide, except for 3-indolylmethyl bromide (III, n = 1), which we were able to obtain only through the Borodin–Hunsdiecker reaction. Its structure was confirmed by elementary analysis and the PMR and IR spectra. γ-(3-Indolyl)propyl bromide (III, n = 3), which is described in the literature as an oily substance [11], was isolated, like all of the other bromides, in the crystalline form. The PMR and IR spectra of the indolylalkyl bromides obtained by various methods were completely identical. The IR spectra of the compounds obtained contained absorption bands at 3440 cm^{-1} (indole NH group), 1620 cm^{-1} (aromatic system of bonds of the indole ring), and 540 cm^{-1} (C–Br bond).

EXPERIMENTAL

The IR spectra of mineral oil suspensions of the compounds were recorded with a UR-10 spectrometer. The PMR spectra of $CDCl_3$ solutions were recorded with a JNM-4H spectrometer with an operating frequency of 100 MHz.

3-Indolylmethyl Bromide (III, n = 1). Carbon tetrachloride (10 ml) was added to a solution of 3.5 g (0.02 mole) of 3-indolylacetic acid (I, n = 1) in 9 ml of dry acetone, after which 9.5 g (0.045 mole) of red mercuric oxide was added slowly in small portions with vigorous stirring (the reaction was carried out in the dark). The mixture was then heated to 55°, and after 10-15 min a solution of 1.53 ml (0.03 mole) of bromine in 2 ml of carbon tetrachloride was added in the course of 30 min. After 10 min the reaction ceased; the mixture was cooled, and the $HgBr_2$ and HgO were removed by filtration. Ether (250 ml) was added to the mother liquor. The resulting precipitate was removed by filtration, and the mother liquor was washed successively with water (500 ml), 60% sodium bisulfite solution (200 ml), and water (100 ml), and the ether solution was dried with magnesium sulfate and evaporated to a volume of 16 ml. This residue was passed through a column filled with aluminum elution by chloroform to give 1.25 g (28%) of a product with mp 85-86° (benzene–petroleum ether). Found, %: C 49.0; H 4.1; Br 40.2; N 7.0. C_9H_8BrN. Calculated, %: C 49.0; H 4.0; Br 40.0; N 7.0.

Compounds IIIa-d, which were similarly obtained, are presented in Table 1.

δ-(3-Indolyl)butyl Bromide (III, n = 4). A solution of 1 g (3.7 mmole) of phosphorus tribromide in 70 ml of absolute ether was added with stirring and ice cooling to 1.89 g (10 mmole) of δ-(3-indolyl)butanol (V, n = 4) in 200 ml of absolute ether. The solution was held at room temperature for 24 h, after which it was washed successively with water, sodium bicarbonate solution, and dried with magnesium sulfate. It was then evaporated to a volume of 10 ml and passed through a column filled with aluminum oxide with elution by ether to give 0.76 g (31%) of a product with mp 45-47° (benzene–petroleum ether). Found, %: C 56.9; H 5.8; Br 31.9; N 5.7. $C_{12}H_{14}BrN$. Calculated, %: C 57.2; H 5.6; Br 31.7; N 5.6.

γ-(3-Indolyl)propyl Bromide (III, n = 3). This compound was similarly obtained in 30% yield and had mp 28.5-29° (benzene–petroleum ether) (n_D^{25} 1.625 [11]). Found, %: C 55.2; H 5.3; Br 33.5; N 6.0. $C_{11}H_{12}BrN$. Calculated, %: C 55.5; H 5.0; Br 33.6; N 5.9.

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