[CONTRIBUTION FROM THE CHEMICAL INSTITUTE, UNIVERSITY OF ZÜRICH]

Some *Ind-N*-methyl-3-alkyl-β-carbolines and *Ind-N*-ethyl-3-alkyl-β-carbolines*

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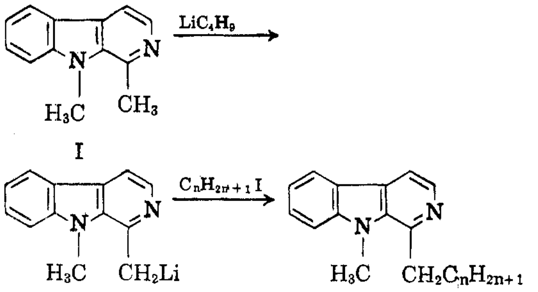
In the course of the experimental investigation of the indole alkaloids, which in the last few years have become of increasing importance, simple β-carboline derivatives were sometimes obtained, the constitution of which could not easily be elucidated on account of the small amounts available. Therefore, some of the compounds which could be expected as degradation (dehydration) products of indole and β-carboline alkaloids, respectively, were synthesized. Knowledge of these compounds may facilitate their identification.

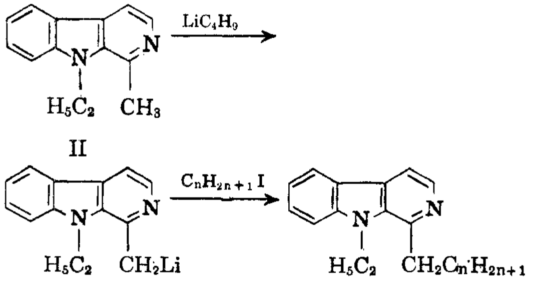
These syntheses were carried out by alkylation of the lithium derivatives of *ind-N*-methylharman and *ind-N*-ethylharman with alkyl halides.

All compounds were characterized as picrates. Furthermore, their quaternary ammonium salts were made by heating them with methyl iodide. Finally the R_f values of the corresponding chlorides were determined on paper chromatograms. These qualities, which are essential contributions to the characterization of the various *ind-N*-methyl-3-alkyl-β-carbolines and *ind-N*-ethyl-3-alkyl-β-carbolines respectively, are listed in Table I.



I

III. $C_nH_{2n+1} = CH_2CH(CH_3)CH_2CH_3$
IV. $C_nH_{2n+1} = CH_2CH_2CH_2CH_3$
V. $C_nH_{2n+1} = CH_2CH_2CH_3$



II

VI. $C_nH_{2n+1} = CH_2CH_2CH_2CH_3$
VII. $C_nH_{2n+1} = CH_2CH_2CH_3$
VIII. $C_nH_{2n+1} = CH(CH_3)_2$
IX. $C_nH_{2n+1} = CH_2CH_3$
X. $C_nH_{2n+1} = CH_3$

EXPERIMENTAL

Ind-N-methylharman. Ten mg. of dry liquid ammonia was distilled with exclusion of moisture and oxygen into 220 mg. of potassium and 2 mg. $Fe(NO_3)_3$. After short stirring at room temperature the deep blue colors of the solution disappeared and potassium amide precipitated. To this mixture was added 1 g. harman which dissolved immediately giving a yellow color. Then 10 ml. of dry 1,2-dimethoxyethane was added and the ammonia was removed by warming the solution to 80° in a current of nitrogen. To the yellow solution of the harman potassium salt in 1,2-dimethoxyethane was added dropwise at ordinary temperature within 40 min. a solution of 0.33 ml. of dry methyl iodide in 4 ml. of the same solvent. During the reaction the mixture was stirred; heated shortly to its boiling point, diluted with ether, and the separated potassium iodide was filtered off. The residue was boiled out several times with ether and chloroform. The extracts were combined and evaporated, and the residue was distilled in the "Kugelrohr" under high vacuum, whereupon the substance distilled at 120–150° (temperature of the air bath) as a light yellow oil which crystallized after a short time. After two crystallizations from ether/pentane we obtained 634 mg. *ind-N*-methylharman, m.p. 102–104°.

Alkylation of ind-N-methylharman with 1-bromo-2-methylbutane. A solution of 200 mg. *ind-N*-methylharman in 3 ml. of dry ether was added dropwise at room temperature with stirring and exclusion of moisture to the solution of 1.0 g. *n*-butyllithium. The apparatus was filled with nitrogen. Immediately a dark yellow precipitate appeared. After having stirred the mixture for 15 min. at room temperature the solution of 0.130 ml. of dry 1-bromo-2-methylbutane in 1 ml. ether was added dropwise within 15 min. Then it was boiled for 1 hr. with stirring and exclusion of oxygen. After this time was added again 0.015 ml. of the bromide dissolved in 1 ml. ether and the mixture was boiled again for 2 hours. It was at first green but became finally light yellow. After having reached room temperature it was decomposed by water and the ether layer was separated. The water layer was extracted again with ether, the ether extracts combined, dried, the solvent evaporated, and the residue distilled in high vacuum. It went over at 125–145°/0.03 mm. (temperature of the air bath). The first drops of the distillate were removed. The distilled product was dissolved in methanol and picric acid was added. A mixture of picrates precipitated when the mixture was boiled with methanol, *ind-N*-methyl-3-(3′-methylpentyl)-β-carboline picrate went into solution while some *ind-N*-methylharman picrate remained undissolved. The former was crystallized from methanol several times; m.p. 165–166°.

Anal. Calcd. for $C_{24}H_{25}N_5O_7$: C, 58.17; H, 5.08; N, 14.12. Found: C, 57.97; H, 5.04; N, 14.17.

Alkylation of ind-N-methylharman with various alkyl halides. For the preparation of the following compounds the same method was applied as in the example mentioned above. *Ind-N*-methyl-3-*n*-pentyl-β-carboline picrate, m.p. 191°.

Anal. Calcd. for $C_{23}H_{23}N_5O_7$: C, 57.37; H, 4.82; N, 14.54. Found: C, 56.98; H, 4.91; N, 14.32.

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* This paper is a contribution in honor of Lyndon F. Small, former Editor of the Journal.

TABLE I.

PROPERTIES OF *ind*-*N*-ALKYL-β-CARBOLINES

Compound	*ind*-*N*-alkyl	C(3)-alkyl	M.P. of Picrate	R_f Values of the Chlorides of the Quaternary Ammonium Bases: On washed paper	R_f Values of the Chlorides of the Quaternary Ammonium Bases: On unwashed paper
III	CH_3	$—CH_2CH_2CH(CH_3)CH_2CH_3$	165°	0.42	0.38
IV	CH_3	$—CH_2CH_2CH_2CH_2CH_3$	191°	0.37	0.34
V	CH_3	$—CH_2CH_2CH_2CH_3$	195°	0.34	0.30
	CH_3	$—CH_3$		0.18	0.17
VI	C_2H_5	$—CH_2CH_2CH_2CH_2CH_3$	156°	0.44	0.37
VII	C_2H_5	$—CH_2CH_2CH_2CH_3$	181°	0.39	0.33
VIII	C_2H_5	$—CH_2CH(CH_3)CH_3$	186°	0.34	0.29
IX	C_2H_5	$—CH_2CH_2CH_3$	206°	0.30	0.26
X	C_2H_5	$—CH_2CH_3$	236°	0.22	0.20
	C_2H_5	$—CH_3$		0.198	0.19

Ind-*N*-methyl-3-*n*-butyl-β-carboline picrate, m.p. 195°. Anal. Calcd. for $C_{22}H_{21}N_5O_7$: C, 56.53; H, 4.52; N, 14.96. Found: C, 56.89; H, 4.89; N, 14.67.

Ind-*N*-*ethylharman.* This substance was prepared in the same way as described for the synthesis of *ind*-*N*-methylharman. The substance crystallizes from ether/pentane in colorless leaflets, m.p. 74°; yield 800 mg. from 1 g. harman.

Alkylation of ind-*N*-*ethylharman with n*-*butyl*-*bromide.* The solution of 200 mg. *ind*-*N*-ethylharman in 3 ml. ether was added dropwise at room temperature to the solution of 1.0 *g. n*-butyllithium. The liquid was stirred and nitrogen was passed through the apparatus. A deep yellow precipitate appeared. After having stirred the mixture for 15 min. at room temperature, the solution of 0.12 ml. dry *n*-butyl bromide in 1 ml. ether was added. Then it was boiled for an hour with stirring and exclusion of oxygen. After this time we added 0.034 ml. *n*-butyl bromide dissolved in 1 ml. ether and boiled the mixture again for 2 hr. at which time it had become colorless. It was kept for 2 hr. at room temperature and then decomposed by water, and the ether layer was separated. The water layer was extracted again with ether, the ether extracts combined, dried, the solvent removed, and the residue distilled in high vacuum (Kugelrohr, 125–150°/0.04 mm.).

When picric acid was added to the distilled compound dissolved in methanol, a mixture of two picrates precipitated. It was extracted with boiling methanol. The picrate of *ind*-*N*-ethyl-3-*n*-pentyl-β-carboline went into solution while some *ind*-*N*-methylharman-picrate remained undissolved. *Ind*-*N*-ethyl-3-*n*-pentyl-β-carboline-picrate melted at 156° after several crystallizations from methanol.

Anal. Calcd. for $C_{24}H_{25}N_5O_7$: C, 58.17; H, 5.08; N, 14.12. Found: C, 58.21; H, 5.29; N, 14.48.

Other ind-*N*-*ethyl*-*3*-*alkyl*-β-*carbolines.* For the syntheses of the following compounds the same method was applied as for the preparation of *ind*-*N*-ethyl-3-*n*-pentyl-β-carboline.

Ind-*N*-ethyl-3-*n*-butyl-β-carboline picrate, m.p. 181°. *Anal.* Calcd. for $C_{23}H_{23}N_5O_7$: C, 57.37; H, 4.86; N, 14.56. Found: C, 57.64; H, 5.01; N, 14.71.

Ind-*N*-ethyl-3-isobutyl-β-carboline-picrate, m.p. 186°. *Anal.* Calcd. for $C_{23}H_{23}N_5O_7$: C, 57.37; H, 4.86; N, 14.56. Found: C, 57.63; H, 4.88; N, 14.74.

Ind-*N*-ethyl-3-*n*-propyl-β-carboline-picrate, m.p. 206°. *Anal.* Calcd. for $C_{22}H_{21}N_5O_7$: C, 56.6; H, 4.69; N, 15.02. Found: C, 56.73; H, 4.76; N, 15.06.

Ind-*N*-ethyl-3-ethyl-β-carboline-picrate, m.p. 236°. *Anal.* Calcd. for $C_{21}H_{19}N_5O_7$: C, 55.52; H, 4.19; N, 15.88. Found: C, 55.41; H, 4.31; N, 15.78.

R_f-values of the chlorides of the quaternary ammonium bases. From the picrates (3 mg.) the free bases of the β-carbolines were recovered as lacquers by treating them with 2*N*-NaOH, extracting with ether, and distilling at 110–120° (temperature of the air bath). Then these bases were combined with a few drops of methyl iodide and kept for 12 hr. in a sealed tube at 30°. After having removed the excess of CH_3I with a stream of nitrogen the crude methyl iodides were transformed in acetone–water solution (7:3) into the chlorides with the chloride form of Amberlite IRA 400. These quaternary β-carbolinium salts can be made visible on paper strips by their intensive blue fluorescence in ultraviolet light.

Several test chromatograms served to find a solvent with satisfactory separation activity.

The paper chromatograms were made on Whatman No. 1 paper at 18–20° with the mixture: ethyl acetate–pyridine–water (7.5:2.3:1.6) (descending method). For comparison purposes all the compounds were put side by side on the same paper strip and their chromatograms developed simultaneously.

In the chromatograms of some of the investigated substances there appeared beside the main spot a very small second spot, which was caused by traces of the methochlorides of the starting materials (*ind*-*N*-methylharman methochloride and *ind*-*N*-ethylharman methochloride, respectively) which, in spite of the repeated crystallizations of the picrates, were not completely removed.

SUMMARY

With the intention of facilitating the identification of simple β-carboline-derivatives, which are often obtained as degradation products of indole alkaloids, the following substances were synthesized: *ind*-*N*-methyl-3-(3′-methylpentyl)-β-carboline picrate (III), *ind*-*N*-methyl-3-*n*-pentyl-β-carboline picrate (IV), *ind*-*N*-methyl-3-*n*-butyl-β-carboline picrate (V), *ind*-*N*-ethyl-3-*n*-pentyl-β-carboline picrate (VI), *ind*-*N*-ethyl-3-*n*-butyl-β-carboline picrate (VII), *ind*-*N*-ethyl-3-isobutyl-β-carboline picrate (VIII), *ind*-*N*-ethyl-3-*n*-propyl-β-carboline picrate (IX), and *ind*-*N*-ethyl-3-ethyl-β-carboline picrate (X).

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