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5-bromo-1-methylindole

Figure 1: Fig. 1. Ultraviolet spectra of indolines (a) and indoles (b). 1—5-bromo-1-methylindole

Abstract

Full Text

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CHEMISTRY

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SYNTHESIS OF DERIVATIVES OF 5-MERCAPTOINDOLE AND 5-MERCAPTO-1-METHYLINDOLE

In connection with the high physiological activity of various indole compounds containing a hydroxy—or alkoxy—group in the benzene nucleus (serotonin, alkaloids, reserpine, eserine, etc.), the synthesis and study of the chemical properties and physiological activity of various derivatives of 5-mercaptoindole is of considerable interest. Until recently, not a single substituted indole had been described containing, in the 4, 5, 6, or 7 position, an atom of divalent sulfur. Indeed, by Fischer' s method, by Reissert' s method, or by other methods used for the synthesis of indoles substituted in the benzene nucleus, it is very difficult to obtain such compounds.

The application of the new route we have developed for the synthesis of indoles substituted in the benzene nucleus ([1]) made it possible to obtain a number of derivatives of 5-mercaptoindole and 5-mercapto-1-methylindole. The synthesis was carried out according to the following scheme. Indole (or 1-methylindole) was reduced to the corresponding dihydroindole (indoline). Indoline, like any aromatic amine, enters into the rhodanation reaction. The rhodanindoline obtained was dehydrogenated with formation of rhodanindole.

Fig. 1. Ultraviolet spectra of indolines (*a*) and indoles (*b*). 1—5-bromo-1-methylindole

Thus 5-rhodanindoline (I), 5-rhodan-1-methylindoline (II), 5-rhodanindole (III), and 5-rhodan-1-methylindole (IV) were obtained.

(I) $R = H$ (III) $R = H$
(II) $R = CH_3$ (IV) $R = CH_3$

(V)

The yield of (III), calculated on the starting indole, was 57%; the yield of (IV) was 34%. The rhodan group enters the 5 position of the indoline ring analogously to the way in which, upon rhodanation of *o*-toluidine, 5-rhodan-*o*-toluidine (V) is formed ([2]). In the bromination of indolines, the hydrogen atom attached to the 5 carbon atom is likewise substituted. By brominating 1-methylindoline we obtained 5-bromo-1-methylindoline, dehydrogenated to 5-bromo-1-methylindole. Upon oxi-

oxidation of the latter with chromic acid, 5-bromo-1-methylisatin was isolated, identical with 5-bromo-1-methylisatin synthesized from isatin.

It is interesting to note that the absorption spectra in the ultraviolet region of 5-bromo-1-methylindoline and of rhodanindolines are not identical, whereas the absorption spectra of (III) and (IV) are analogous to the spectrum of 5-bromo-1-methylindole* (see Fig. 1).

On boiling with alkali, rhodan compounds form disulfides. In this way—starting from (II)—the corresponding disulfide (VI) was obtained. The nitrogen-unsubstituted disulfide (VII) could be isolated only in the form of its diacetyl derivative (VIII). Starting from (IV), 5,5-disulfide-1-methylindole (IX) was obtained.

$(\text{indoline disulfide structure})_2$
(VI) $R = \mathrm{CH_3}$
(VII) $R = \mathrm{H}$
(VIII) $R = \mathrm{COCH_3}$
$(\text{1-methylindole disulfide structure})_2$ (IX)

By reduction and subsequent benzoylation of (II), 5-benzoylmercapto-1-methylindoline (X) was synthesized; its dehydrogenation with chloranil in xylene gave 5-benzoylmercapto-1-methylindole (XI). The yield of (XI), calculated on 1-methylindole, was 14%.

$\mathrm{C_6H_5COS}$-1-methylindoline (X) $\mathrm{C_6H_5COS}$-1-methylindole (XI)

Work with these substances requires a number of precautions, since they cause severe dermatitis appearing 2–3 weeks after work has begun.

Experimental Part

5-Rhodanindoline (I). To a solution of 11.9 g of indoline in 50 ml of methyl alcohol, 40 g of potassium thiocyanate was added; to the resulting reaction mixture, with cooling below 0° and stirring, a solution of 16 g of bromine in 20 ml of methyl alcohol saturated with sodium bromide was added dropwise. After completion of the addition, the reaction mixture was poured into an aqueous solution of sodium carbonate (500 ml). An oil separated, which crystallized after several minutes. Yield 17.1 g (97%). M.p. 64.5-65° (from methyl alcohol).

Found, %:	C 61.46; H 4.53
$C_9H_8N_2S$. Calculated, %:	C 61.33; H 4.58.

UV absorption spectrum of (I): $\lambda_{\max} = 272$ mμ; $\lg \varepsilon_{\max} = 4.38$.

0.6 g of (I) was dissolved in 50 ml of acetic anhydride and heated to boiling for 15 min.; the solution was poured into water. 0.6 g of crystalline 1-acetyl-5-rhodanindoline was obtained. M.p. 102.5–103.5° (from heptane).

Found, %:	C 60.32; H 4.59; S 14.54
$C_{11}H_{10}ON_2S$. Calculated, %:	C 60.52; H 4.62; S 14.69.

5-Rhodan-1-methylindoline (II). The preparation of (II) was carried out under the same conditions as the preparation of (I). 13.3 g of methylindoline was rhodanated. After completion of the addition of the bromine solution, the reaction mixture was poured onto ice. The substance was obtained as an oil, which crystallized after several hours[**].

[*] The spectra were recorded on an SF-4 spectrophotometer. Solvent—methyl alcohol.

[**] In order for the oil to crystallize, it is usually necessary to introduce a seed crystal. To obtain a small quantity of crystalline (II), 2–3 g of the substance was distilled in vacuo. 5-Rhodan-1-methylindoline distills at a temperature above 150° at 2 mm Hg with decomposition; however, the red liquid that distills over crystallizes readily. It is not possible to distill larger quantities in vacuo (complete decomposition occurs before the start of distillation).

The crystals were filtered off, and from the mother liquor, by extraction with ether, an additional several grams of 5-rhodan-1-methylindoline were obtained. Total yield 15.9 g (84%). After recrystallization from methanol, 13 g of (II) were obtained. Mp 45–45.5°.

$C_{10}H_{10}N_2S$.	Found, %:	C 63.20; H 5.14;
	Calculated, %:	C 63.11; H 5.30.

UV absorption spectrum (II): $\lambda_{\max} = 286$ mμ; $\lg \varepsilon_{\max} = 4.16$.

5-Rhodanindole (III). A solution of 4.1 g of 5-rhodanindoline and 5.7 g of chloranil in xylene (100 ml) was heated to boiling for 2 hr. After cooling, the reaction mixture was shaken several times with aqueous alkali (20%), the xylene solution was filtered and washed successively with water, hydrochloric acid (1:1), and again with water. After removing the xylene in vacuo, 2.8 g of 5-rhodanindole (68%) were obtained. Mp 104-105° (from heptane).

$C_9H_6N_2S$.	Found, %:	C 62.16; H 3.46
	Calculated, %:	C 62.04; H 3.47.

UV absorption spectrum (III): $\lambda_{\max} = 282$ mμ; $\lg\varepsilon_{\max} = 3.66$; $\lambda_{\max} = 330$ mμ; $\lg\varepsilon_{\max} = 2.04$.

5-Rhodan-1-methylindole (IV). 4.8 g of 5-rhodan-1-methylindoline and 6.2 g of chloranil in 100 ml of xylene were heated to boiling for 20 min. After cooling, the solution was shaken several times with 20% alkali, filtered, washed successively with water, hydrochloric acid (1:1), and water; the xylene was removed in vacuo and the remaining oil was distilled. The substance distilled at 160-180° at 2 mm Hg. A red oily liquid, which rapidly crystallized, 2.4 g (51%). Mp 57-57.5° (from heptane).

$C_{10}H_8N_2S$.	Found, %:	C 63.69; H 4.36
	Calculated, %:	C 63.78; H 4.28.

UV absorption spectrum (VI): $\lambda_{\max} = 235$ mμ; $\lg\varepsilon_{\max} = 4.72$; $\lambda_{\max} = 288$ mμ; $\lg\varepsilon_{\max} = 3.74$. It should be noted that a mixed sample with 5-rhodan-1-methylindoline does not give a depression of the melting point. Mp of the mixture (II)–(IV) (1:1) 46-47°.

1,1′-Dimethyl-5,5′-diindolinyl disulfide (VI). A suspension of 1.9 g of (II) in 100 ml of concentrated alkali was heated to boiling for 6 hr; the separated oil was extracted with ether. After evaporation of the ether, 1 g of disulfide (VI) was obtained. For analysis, the substance was purified by dissolution in dilute hydrochloric acid and precipitation with sodium bicarbonate, and then by recrystallization from acetone. Bright yellow crystals. Mp 96.5-98°.

$C_{18}H_{20}N_2S_2$.	Found, %:	C 65.88; H 6.06
	Calculated, %:	C 65.81; H 6.14.

UV absorption spectrum: $\lambda_{\max} = 268$ mμ; $\lg\varepsilon_{\max} = 4.18$; $\lambda_{\max} = 312$ mμ; $\lg\varepsilon_{\max} = 4.19$. In an analogous manner, starting from 5-rhodan-1-methylindole, 1,1′-dimethyl-5,5′-diindolyl disulfide (IX) was obtained. Mp 101-102° (from heptane).

5,5′-Diindolinyl disulfide (VII). Obtained in the form of an oil by boiling 6-rhodanindoline with concentrated alkali. Upon heating it with acetic anhydride, a crystalline diacetyl derivative, 1,1′-diacetyl-5,5′-diindolinyl disulfide (VIII), was isolated. Mp 201-203° (from octane).

$C_{20}H_{20}O_2N_2S_2$. Found, %: C 62.56; H 5.20
Calculated, %: C 62.47; H 5.25.

5-Benzoylmercapto-1-methylindoline (X). 5.1 g of (II) was dissolved in 100 ml of concentrated hydrochloric acid, 10 g of metallic tin was added, and the mixture was heated on a boiling water bath. The reaction mixture first turned red and then gradually became decolorized. On cooling, a viscous oil separated (apparently the tin complex of 5-mercapto-1-methylindoline). The oil was dissolved in acetone, precipitated with water, and extracted with chloroform. To the viscous reddish mass obtained after evaporation of the solvent were added benzene, benzoyl chloride, and aqueous alkali, and the reaction mixture was shaken for 30 min. The benzene layer was separated, filtered, washed with water, and the benzene was distilled off in vacuo. 5-Benzoylmercapto-1-methylindoline was obtained, 2.8 g (33%). Yellow crystals, m.p. 104-106.5° (from isooctane). For analysis the substance was purified as follows: it was dissolved in dilute hydrochloric acid, the hydrochloric acid solution was filtered, washed with benzene, neutralized with sodium bicarbonate, and the crystals that separated were recrystallized several times from isooctane. M.p. 105.5-106.5°.

Found, %: C 71.43; H 5.63
$C_{16}H_{15}ONS$. Calculated, %: C 71.33; H 5.61.

UV absorption spectrum (X): $\lambda_{\max} = 239$ mμ; $\lg \varepsilon_{\max} = 4.06$; $\lambda_{\max} = 275$ mμ; $\lg \varepsilon_{\max} = 4.37$.

5-Benzoylmercapto-1-methylindole (XI). A solution of 1.8 g of (X) and 1.64 g of chloranil in xylene was boiled for 15 min; after cooling it was washed successively with 20% alkali, water, dilute hydrochloric acid, and water. After distillation of the solvent in vacuo, an oily liquid was obtained, which crystallized upon addition of heptane. 1.1 g of a dark crystalline substance (61%) was obtained. The substance is readily purified by boiling the heptane solution with charcoal. Colorless crystals. M.p. 118.5-119.5°.

Found, %: C 71.72; H 5.14; N 5.06
$C_{16}H_{13}ONS$. Calculated, %: C 71.86; H 4.90; N 5.25.

UV absorption spectrum: $\lambda_{\max} = 237$ mμ; $\lg \varepsilon_{\max} = 4.70$; $\lambda_{\max} = 276$ mμ; $\lg \varepsilon_{\max} = 4.03$.

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