325, 370 nm (4.57, 3.92; 3.79). PMR spectrum in $CHCl_3$, δ: 3.07 (N-$CH_3$, s), 3.40 ($OCH_3$, s), 5.79 (3'-H, d, 10 Hz), 6.1 ppm (br. s, 5'-H + 7'-H). IR spectrum: 3400, 3320, 3215, 3075, 3040, 2935, 1660, 1630, 1615 br, 1595, 1490 br, 1450, 1400, 1340, 1310, 1240, 1160, 1120, 1100, 1080, 1040, 1010, 990, 920, 865, 850, 825, 770, 750 $cm^{-1}$. Found: C 77.7; H 6.1; N 7.7%. $C_{23}H_{20}N_2O_2$. Calculated: C 77.5; H 5.7; N 7.9%.

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# SYNTHESIS OF DIHYDROTHIENO[3,4-b]INDOLES


N. A. Kogan



UDC 547.759.3'73.07



A new heterocyclic system – 3-imino-4-methyldihydrothieno[3,4-b]indole – was obtained by treatment of 1-methylindole-2-carboxylic acid thioamide with aldehydes or ketones in the presence of hydrogen chloride. Reactions involving saponification and acetylation of the imino group of the thieno ring and opening of the thieno ring by the action of $LiAlH_4$ to give a bis(indolylphenylmethyl) sulfide were carried out. A scheme is proposed in which the SH group of the thioamide adds to the carbonyl compound in the first step, after which the product undergoes intramolecular cyclization in the 3 position of indole.


An attempt to obtain dihydrothieno[3,4-b]indole by the Fischer reaction from 3-thiophanone and phenylhydrazine was unsuccessful and led exclusively to the formation of 2,3-dihydrothieno[3,2-b]indole [1]. Using the previously proposed principle of construction of three-ring indole-containing structures [2] we obtained dihydrothieno[3,4-b]indoles (II-XXI) by reaction of 1-methylindole-2-carboxylic acid thioamide in the presence of hydrogen chloride in alcohol, ether, or acetic acid at room temperature with aldehydes or ketones.


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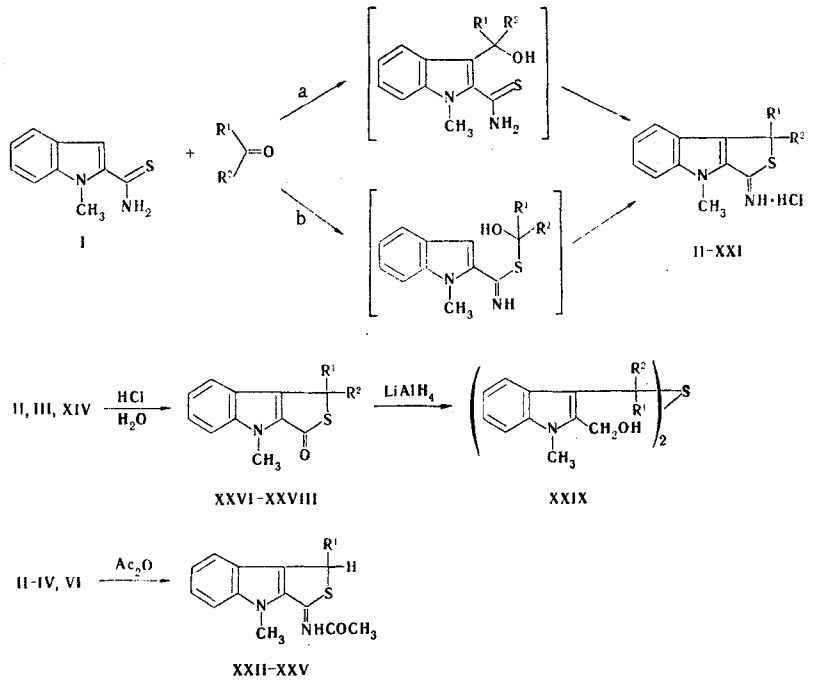


We were unable to subject benzophenone and some complex ketones (camphor and 3-cholestenone) to the reaction. When a mixture of thioamide I with the carbonyl compound is dissolved, crystallization of dihydrothienoindole hydrochlorides (II-XXI) begins after 5-15 min. These salts can be converted by the action of ammonia to bases, the $pK_a$ values of which range from 4.6 to 5.2. The composition of the isolated compounds indicates the addition of 1 mole of the carbonyl compound to 1 mole of thioamide I with the loss of 1 mole of water (Table 1).

The chemical properties and the IR and UV spectroscopic data for II-XXI constitute evidence for the formation of a dihydrothieno ring rather than a dihydropyrrole ring. The latter is formed when 1-methyl-2-carboxamide is treated with aromatic aldehydes [2]. The IR spectra of II-XXI do not contain the characteristic $\nu C=S$ band (1100 $cm^{-1}$) but do contain a $\nu C=N$ band (1610-1650 $cm^{-1}$). The hydrolysis of 3-iminodihydrothieno[3,4-b]indoles (II, III, and XIV) in an aqueous alcohol solution of HCl led [according to monitoring by thin-layer chromatography (TLC)] to dihydrothieno[3,4-b]indol-3-ones (XXVI-XXVIII, Table 2). The IR spectra of the latter differed from the IR spectrum of the nonhydrolyzed compounds only with respect to the 1600-1700 $cm^{-1}$ region, where the band at 1615 $cm^{-1}$ ($\nu C=N$) vanished but an intense band prepared at 1680 $cm^{-1}$ ($\nu C=O$), and also in the region of NH vibrations, when a sharp peak at 3200 $cm^{-1}$, which is not observed after hydrolysis for XXVI-XXVIII, was observed for 3-iminothieno[3,4-b]indoles II-XXI.

The UV spectrum of 3-iminothienoindole III in alcohol (Fig. 1) [$\lambda$ 305 nm (log $\varepsilon$ 4.18)] has the form characteristic for 1-methylindole-2-carboxylic acid amide [$\lambda_{max}$ 295 nm (log $\varepsilon$ 4.10)]; this provides evidence for retention of the 2-indolyl group conjugated with a double bond. Replacement of the imino group by a keto group in XXVIII leads to a hypsochromic shift. Because of lengthening of the conjugation chain, acetylation of III is accompanied by the appearance in the UV spectrum of XXIII of a maximum at 380 nm (log $\varepsilon$ 3.48). The reduction of thienoindole XXVI with $LiAlH_4$, which leads to the formation of isolated indole system XXIX, gives rise to a hypsochromic shift of $\lambda_{max}$ to 288 nm (log $\varepsilon$ 3.98). No effect of the substituents in the phenyl ring of 1-phenyl-3-imino-4-methyldihydrothieno[3,4-b]indoles II-XI on the position of $\lambda_{max}$ is observed; this confirms the absence of conjugation of the phenyl ring with the indole ring.

The PMR spectra of II-XXI differed from one another only because of a difference in the structures of $R^1$ and $R^2$ attached to 1-C. The spectra of aromatic aldehyde derivatives II-XI in trifluoroacetic acid contain a multiplet of aromatic protons at 7.2 ppm, a signal of an $N-CH_3$ group (s, 3H; 3.7 ppm), and a characteristic signal of a benzyl proton (s, 1H; 5.7 ppm).

The spectra of ketone derivatives XIV and XV contain, in addition to signals of aromatic protons at 7.2 ppm and of an $N-CH_3$ group (3.71 ppm), a signal of two geminal methyl groups (s, 6H; 1.71 ppm) in the case of XIV and, in the case of XV, which is the product of condensation of methyl ethyl ketone with thioamide I, two groups of signals of an ethyl fragment in the form of a triplet (3H, 0.6 ppm) and a quartet (2 H; 1.95 ppm) and a $C-CH_3$ signal (3H; 1.75 ppm).

TABLE 1. Characteristics of 3-Imino-4-methyldihydrothieno[3,4-b]indoles

| Compound | R¹ | R² | mp, °C | mp of the base [a] | Found, % Cl | Found, % N | Found, % S | Empirical formula | Calc., % Cl | Calc., % N | Calc., % S | Yield, % |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| II | H | $C_6H_5$ | 222 | 203 | 10,8 | 8,6 | 9,8 | $C_{17}H_{14}N_2S \cdot HCl$ | 11,3 | 8,9 | 10,2 | 95 |
| III | H | $o$-$ClC_6H_4$ | 220 | 145 | 20,3 | 8,0 | 9,1 | $C_{17}H_{13}N_2SCl \cdot HCl$ | 20,4 | 8,0 | 9,2 | 93 |
| IV | H | $p$-$ClC_6H_4$ | 225 | 210 | 20,1 | 7,6 | 9,1 | $C_{17}H_{13}N_2SCl \cdot HCl$ | 20,4 | 8,0 | 9,2 | 80 |
| Vb | H | $o$-$NO_2C_6H_4$ | 215 | 118 | — | 12,0 | 8,8 | $C_{17}H_{13}N_3O_2S \cdot HCl$ | 9,8 | 11,6 | 8,9 | 82 |
| VI | H | $p$-$OCH_3C_6H_4$ | 220 | 172 | 10,0 | 8,3 | — | $C_{18}H_{16}N_2OS \cdot HCl$ | 10,3 | 8,1 | 9,3 | 82 |
| VIIb | H | $p$-$N(CH_3)_2C_6H_4$ | 198 | 128 | 17,6 | 10,3 | 7,6 | $C_{19}H_{19}N_3S \cdot 2HCl$ | 18,1 | 10,7 | 8,1 | 90 |
| VIIIb | H | $p$-$OHC_6H_4$ | 230 | 206 | — | 8,3 | 9,6 | $C_{17}H_{14}N_2OS \cdot HCl$ | 10,7 | 8,5 | 9,7 | 64 |
| IX | H | $o$-$OHC_6H_4$ | 230 | 185 | — | 8,4 | 9,2 | $C_{17}H_{14}N_2OS \cdot HCl$ | 10,7 | 8,5 | 9,7 | 76 |
| Xb | H | $p$-$N(C_2H_4Cl)_2C_6H_4$ | 207 | — | 27,8 | 8,3 | 7,1 | $C_{21}H_{21}SCl_2 \cdot 2HCl$ | 28,4 | 8,4 | 7,1 | 55 |
| XI[c] | H | $p$-$BrC_6H_4$ | 240 | 202 | 31,7 | 6,4 | 7,9 | $C_{17}H_{13}N_2BrS \cdot HCl$ | 31,6 | 7,1 | 8,1 | 81 |
| XII | H | $CH{=}CH{-}C_6H_5$ | 205 | — | 10,0 | 7,6 | 9,3 | $C_{19}H_{16}N_2S \cdot HCl$ | 10,4 | 8,2 | 9,4 | 93 |
| XIII | H | $C_4H_9$ | 200 | — | 12,0 | 9,5 | 10,5 | $C_{15}H_{18}N_2S \cdot HCl$ | 12,1 | 9,5 | 10,9 | 90 |
| XIV | $CH_3$ | $CH_3$ | 240 | — | — | 10,1 | 11,9 | $C_{13}H_{14}N_2S \cdot HCl$ | 13,4 | 10,5 | 12,0 | 88 |
| XV | $CH_3$ | $C_2H_5$ | 172 | — | 11,9 | 9,8 | 10,8 | $C_{14}H_{16}N_2S \cdot HCl$ | 12,7 | 10,0 | 11,5 | 52 |
| XVI | Cyclohexylidene | | 245 | 148 | 11,7 | 8,7 | 10,1 | $C_{16}H_{18}N_2S \cdot HCl$ | 11,5 | 9,1 | 10,4 | 90 |
| XVII | Cyclopentylidene | | 230 | — | — | 9,4 | 10,2 | $C_{15}H_{16}N_2S \cdot HCl$ | 12,1 | 9,5 | 10,9 | 75 |
| XVIII | $CH_3$ | $CH_2C_6H_5$ | 204 | — | 10,0 | 8,1 | — | $C_{19}H_{18}N_2S \cdot HCl$ | 10,3 | 8,2 | 9,3 | 50 |
| XIX | H | 2-Furyl | 360 | — | 11,6 | 9,2 | 11,0 | $C_{15}H_{12}N_2OS \cdot HCl$ | 11,6 | 9,1 | 10,5 | 70 |
| XXb | $CH_3$ | $C_6H_5$ | 220 | — | — | 8,6 | 10,3 | $C_{18}H_{16}N_2S \cdot HCl$ | 11,1 | 8,5 | 9,7 | 90 |
| XXIb | H | H | 218 | — | 11,5 | 11,6 | 13,3 | $C_{11}H_{10}N_2S \cdot HCl$ | 14,8 | 11,7 | 13,4 | 90 |

[a]The results of elementary analysis of the bases are in agreement with the calculated values. [b]The reaction was carried out in alcohol saturated with HCl. [c]The calculation was made for the combined Br and Cl content.

TABLE 2. 1-Aryl-3-acetimido-4-methylhydrothieno[3,4-b]indoles

| Compound | R¹ | mp, °C | Found, % Cl | Found, % N | Found, % S | Empirical formula | Calc., % Cl | Calc., % N | Calc., % S | Yield, % |
|---|---|---|---|---|---|---|---|---|---|---|
| XXII | $C_6H_5$ | 208 | — | 9,6 | 9,4 | $C_{19}H_{16}N_2SO$ | — | 8,8 | 10,0 | 90 |
| XXIII | $o$-$ClC_6H_4$ | 198 | 9,5 | 7,6 | 9,0 | $C_{19}H_{15}N_2SOCl$ | 10,0 | 7,9 | 9,0 | 95 |
| XXIV | $p$-$ClC_6H_4$ | 240 | 9,7 | 7,1 | 9,0 | $C_{19}H_{15}N_2SOCl$ | 10,0 | 7,9 | 9,0 | 90 |
| XXV | $p$-$OCH_3C_6H_4$ | 195 | — | 7,6 | 9,1 | $C_{20}H_{18}N_2SO_2$ | — | 8,0 | 9,1 | 90 |

TABLE 3. 3-Oxo-4-methyldihydrothieno[3,4-b]indoles

| Compound | R¹ | R² | mp, °C | Found, % Cl | Found, % N | Found, % S | Empirical formula | Calc., % Cl | Calc., % N | Calc., % S | Yield, % |
|---|---|---|---|---|---|---|---|---|---|---|---|
| XXVI | H | $C_6H_5$ | 197 | — | 5,8 | 11,5 | $C_{17}H_{13}NOS$ | — | 5,0 | 11,5 | 65 |
| XXVII | $CH_3$ | $CH_3$ | 115 | — | 6,3 | — | $C_{13}H_{13}NOS$ | — | 6,1 | 13,8 | 60 |
| XXVIII | H | $o$-$ClC_6H_4$ | 164 | — | 4,9 | 9,8 | $C_{17}H_{12}NClOS$ | 11,3 | 4,4 | 10,0 | 88 |

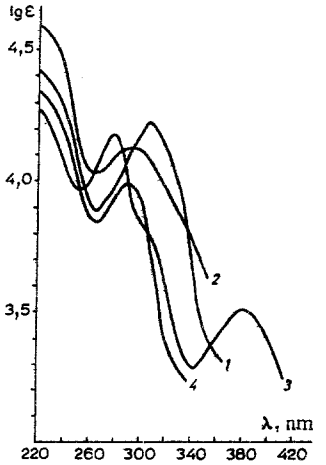
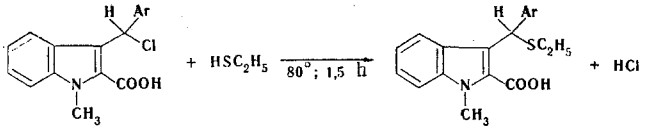
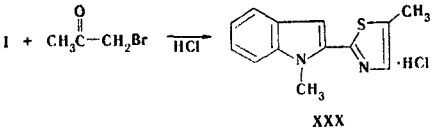



Fig. 1. UV spectra of III (1), XXVIII (2), XXXIII (3), and XXIX (4) in alcohol ($c = 1.5 \cdot 10^{-4}$ M).

Thioamides are widely used for the construction of five- and six-membered rings with the inclusion of nitrogen and sulfur atoms. At the same time, we did not find examples in the literature of the synthesis of a thieno ring by the action of carbonyl compounds on thioamides. The successful occurrence of this reaction in the indole series is evidently due to the absence of a deactivating effect of derivatives of the carboxyl group on the 3 position for electrophilic reagents. The mechanism of the formation of a thieno ring may commence both with electrophilic attack on the 3 position (path a) and at the sulfur atom (path b). The first path (path a) is realized in reactions with amides and anilides of 1-methylindole-2-carboxylic acid during the formation of dihydropyrrolo[3,4-b]indoles [2]. The second path (path b) is more likely during the formation of a thieno ring, since the sulfhydryl group is extremely sensitive to electrophilic agents. The substitution of chlorine by an alkylthio group, which takes place under more severe conditions (80°C for 1 h 30 min) [3] than those required for the formation of a thieno ring (0-10°C for 5-15 min), serves as a model for the formation of a thieno ring via path a.



Another piece of evidence in favor of path b is provided by the ease of the formation of a thieno ring with ketones, while other derivatives of 1-methylindole-2-carboxylic acid (esters, nitriles, amides, and anilides) do not react with ketones under the same conditions. The reaction of 1-methylindole-2-carboxylic acid thioamide (I) with bromoacetone leads to 2-(1-methyl-2-indolyl)-4-methylthiazole (XXX); this confirms path b as the first step in the synthesis of dihydrothieno[3,4-b]indoles.



XXX

## EXPERIMENTAL*

The UV spectra of alcohol solutions of the compounds were recorded with an SF-16 spectrophotometer. The IR spectra of mineral oil suspensions were recorded with a UR-20 spectrometer. The PMR spectra were recorded with a Varian-60 spectrometer. The homogeneity of all of the compounds was verified by TLC on Silufol in a cyclohexane–ethyl acetate system (3:1).

1-Methylindole-2-carboxylic Acid Thioamide (I). A 7.6-g (0.49 mole) sample of 1-methylindole-2-carboxylic acid was dissolved in 25 ml of pyridine and 7.5 ml of triethylamine, after which a stream of hydrogen sulfide was passed through the solution at 0-5°C for 30 min. The solution was poured over ice, and the separated crystals of thioamide I were recrystallized from ethanol to give 8.38 g (91%) of I with mp 145°C. Found: N 14.6; S 16.5%. $C_{10}H_{10}SN_2$. Calculated: N 14.4; S 16.8%.

1-Phenyl-3-imino-4-methyldihydrothieno[3,4-b]indole (II). A 0.5-g (0.026 mole) sample of thioamide I was mixed with 0.3 g (0.028 mole) of benzaldehyde, and 5 ml of ether saturated with HCl was added at 0°C. The crystalline precipitate of II hydrochloride that formed from the resulting solution after 3-5 min was removed by filtration, washed with ether, and crystallized from alcohol to give 0.7 g (95%) of product. To obtain base II, its hydrochloride was dissolved in 70% alcohol, and the solution was treated with $NH_4OH$ solution until the mixture was alkaline. Base II separated immediately as an oil, which crystallized rapidly when it was triturated. Workup gave 0.56 g (90%) of II. The product was recrystallized for analysis; TLC on Silufol showed one spot, namely, $Rf_{base}$ 0.53 ($Rf_{HCl}$ 0.31). The same method was used to obtain III-XXI (Table 1). The reaction was also carried out in alcohol saturated with HCl. Paraformaldehyde was used to obtain XXI.

1-Phenyl-3-acetimido-4-methyldihydrothieno[3,4-b]indole (XXII). A 2.5-g (0.09 mole) sample of base II was refluxed in 20 ml of acetic anhydride for 3 min, after which the mixture was cooled to precipitate XXII (Table 2). Compound XXII was crystallized from alcohol for analysis. The same method was used to obtain XXIII-XXV.

*E. P. Chernova, a student, participated in the experimental work.

1-Phenyl-3-oxo-4-methyldihydrothieno[3,4-b]indole (XXVI). A 0.7-g (0.0025 mole) sample of II·hydrochloride was refluxed in 20 ml of alcohol and 5 ml of concentrated HCl for 4 h, after which the mixture was cooled to precipitate XXVI (Table 3) with $R_f$ 0.56.

The same method was used to prepare XXVII and XXVIII.

Bis(1-methyl-2-hydroxymethyl-3-indolylphenylmethyl) Sulfide (XXIX). A 1.4-g (0.005 mole) sample of XXVI was reduced in ether with 0.40 g (0.012 mole) of $LiAlH_4$. After decomposition of the excess $LiAlH_4$ with water, the precipitate was removed by filtration, and the ether layer was dried with anhydrous $Na_2SO_4$ and evaporated to give XXIX, which was crystallized from cyclohexane. The yield of product with mp 75°C was 0.78 g (56%). Found: N 5.2; S 6.0%; $C_{34}H_{32}N_2SO_2$. Calculated: N 5.8; S 6.0%.

2-(1-Methyl-2-indolyl)-4-methylthiazole Hydrochloride (XXX). A 1.37-g (0.01 mole) sample of bromoacetone was added to 1.92 g (0.01 mole) of thioamide I in 15 ml of ethanol saturated with HCl, after which the mixture was refluxed for 5 min. It was then cooled to precipitate 2.4 g (86%) of XXX with mp 215°C (from alcohol). Substance XXX was not affected by refluxing in HCl. The 2-(1-methyl-2-indolyl)-4-methylthiazole base is incapable of forming acetyl derivatives under the influence of acetic anhydride. Found: Cl 12.6; N 4.9; S 11.0%. $C_{14}H_{10}NS \cdot HCl$. Calculated: Cl 12.7; N 5.0; S 11.4%.

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# DERIVATIVES OF CONDENSED SYSTEMS BASED ON PYRIMIDINE, PYRAZINE, AND PYRIDINE

## XXXVI.* SYNTHESIS OF PYRIMIDO[4,5-b]-1,4-THIAZIN-6-ONES AND PYRIMIDO[4,5-b]-1,5-THIAZEPIN-6-ONES


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Pyrimido[4,5-b]-1,4-thiazin-6-one and pyrimido[4,5-b]-1,5-thiazepin-6-one derivatives were obtained by reaction of 5-amino-6-chloropyrimidines with thioglycolic acid and 5-amino-6-mercaptopyrimidines with β-bromopropionyl chloride. The IR spectra of the compounds are presented.


We have previously reported the synthesis of pyrimido[4,5-b]-1,4-thiazin-6-ones by reaction of 5-amino-6-mercaptopyrimidines with α-halo acids [2]. During a biological study of these compounds it was observed that they inhibit the enzymes of folic acid metabolism and have antitumorigenic activity [3]. In this connection we obtained a number of new derivatives and homologs of pyrimido[4,5-b]-1,4-thiazin-6-one and investigated some of their properties.

4-Alkoxypyrimidothiazin-6-ones IV and V were obtained by reaction of 4-alkoxy-5-amino-6-chloropyrimidines I and II with thioglycolic acid. In the reaction of 4,6-dichloro-5-aminopyrimidine (III) with thioglycolic acid both chlorine atoms are replaced by carboxymethylthio groups to give derivative VI. This method for the synthesis of pyrimidothiazin-6-ones [4] has an advantage over the method described in [2] with respect to the number of steps involved.

*See [1] for communication XXXV.


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