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SYNTHESIS OF SUBSTITUTED THIENO[2,3-d]THIAZOLES AND INDOLO[3,2-d]THIAZOLES

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Alkylene-, halo-, and aryl-substituted 2-methylthieno[2,3-d]thiazoles were obtained by the action of phosphorus pentasulfide on the corresponding 2-acetylamino-3-bromo- or 2-acetylamino-3-hydroxythiophenes in an organic solvent with heating. 2-Oximes of halo- and methyl-substituted isatins were converted by reduction and acylation into 2-hydroxy-3-acetylaminoindoles, from which 2-methylindolo[3,2-d]-thiazoles were obtained by the action of phosphorous pentasulfide with heating in xylene.

The spectral and photographic properties of polymethine dyes, derivatives of thieno- and indolothiazoles which do not contain substituents in the heterocyclic rings have already been studied in [1-3]. It is also known that the photographic effectiveness of sensitizing dyes, derivatives of benzothiazoles [4], is much higher than that of the corresponding unsubstituted compounds. In order to study the influence of substituents on the spectral and photographic properties of thieno- and indolothiazolocyanines, we carried out the synthesis of new thieno[2,3-d]- and indolo[3,2-d]-thiazoles, substituted in the annelated thiophene or benzene ring.

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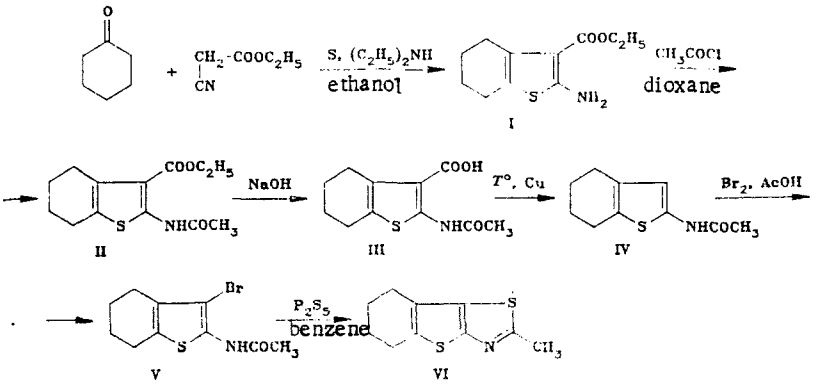
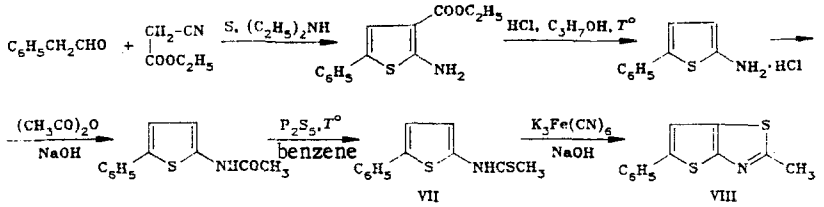
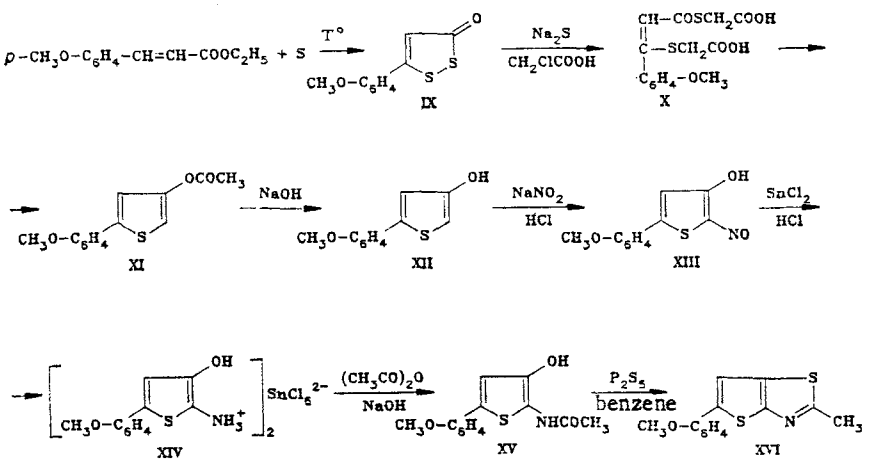
5,6-Tetramethylenethieno[2,3-d]thiazole (VI) was synthesized from cyclohexanone:



2-Amino-3-carbethoxy-4,5-tetramethylenethiophene (I) is obtained by condensing cyclohexanone with ethyl cyanoacetate in ethanol in the presence of sulfur and diethylamine, and is then acetylated by acetyl chloride in dioxane. The acetyl derivative (II) is hydrolyzed and the carboxylic acid (III) is decarboxylated at a temperature above 240°C in the presence of copper. 2-Acetylamino-4,5-tetramethylenethiophene (IV) is brominated in acetic acid, and the bromo derivative (V) is converted into base VI by heating with phosphorus pentasulfide in anhydrous benzene. 2-Methyl-5-phenylthieno[2,3-d]thiazole (VIII) was synthesized in a similar way from phenylacetaldehyde and ethyl cyanoacetate via 2-acetylamino- and, in contrast to the synthesis of thiazole VI, 2-thioacetylamino-5-phenylthiophene (VII):

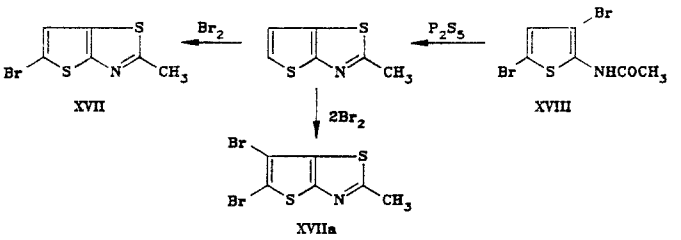


5-(p-Methoxypehnyl)thieno[2,3-d]thiazole (XVI) was synthesized from ethyl p-methoxycinnamate:



Heating ethyl p-methoxycinnamate with sulfur gives the cyclic disulfide IX, which, by reduction with sodium sulfide, followed by reaction with chloroacetic acid, is converted into compound X. The latter is subjected to cyclization in acetic anhydride; 5-p-methoxyphenyl-3-acetoxythiopene (XI) is hydrolyzed, the 3-hydroxy derivative XII is nitrosated, and the nitroso compound XIII is reduced by tin dichloride in hydrochloric acid. The binary tin salt (IV) is acetylated with acetic anhydride and 2-acetylamino-3-hydroxy-5-(p-methoxyphenyl)thiophene (XV) is reacted with phosphorus pentasulfide with heating in benzene.

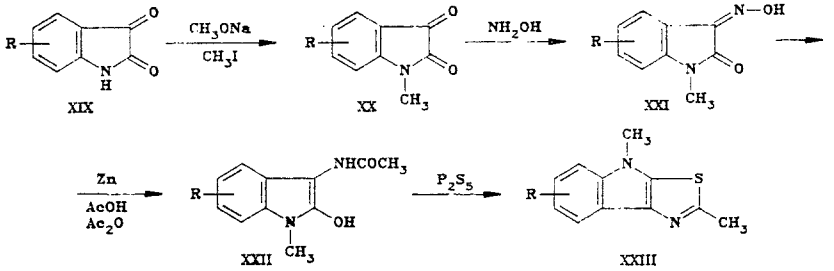
5-Bromo- and 5,6-dibromothieno[2,3-d]thiazoles (XVII, XVIIa) were obtained by the action of bromine on 2-methylthieno[2,3-d]-thiazole in acetic acid in the presence of sodium acetate.



It should be noted that base XVII is also formed in a low yield by the action of phosphorus pentasulfide on 2-acetylamino-3,5-dibromothiophene (XVIII) in an anhydrous solvent (benzene, toluene, xylene) or in its absence on heating, the main product of the reaction being the unsubstituted 2-methylthieno[2,3-d]-thiazole, i.e., the action of phosphorus pentasulfide on 3,5-dibromo-2-acetyl-aminothiophene leads to elimination of bromine at the 5-position.

As the starting materials for the synthesis of methyl- and halo-substituted indole-[3,2-d]thiazoles (XXIII), substituted anilines are used, which by reaction with hydroxylamine and chloral are converted in an acid medium into the corresponding isonitrosoacetanilides, and the latter into isatins XIX by heating in the presence of sulfuric acid [5].

Sodium salts of isatins are methylated by methyl iodide. In the synthesis of isatins from m-toluidine, a mixture of 4- and 6-methyl derivatives is obtained, which is methylated by methyl iodide and the isomeric N-methylisatins (XX) are separated by selective crystallization from water. Isatins XX are converted by the action of hydroxylamine, into 3-oximes XXI, which are reduced by zinc dust in a mixture of acetic acid and acetic anhydride. Reaction of N-methyl-2-hydroxy-3-acetylaminoindoles XXII with phosphorus pentasulfide with heating in xylene gives methyl- and haloindolothiazoles XXIII in 40-71% yield.



In the PMR spectrum of compound XXIII (R = 4-CH_3) there are signals of methyl group protons in the 2, 4, and 8-positions at 2.84, 2.89, and 3.83 ppm, respectively, and in the spectrum of compound XXIII (R = 6-CH_3) there are signals of 2-, 6-, and 8-methyl group protons at 2.81, 2.51, and 3.79 ppm.

In the mass spectra of the synthesized heterocycles, intense peaks of the molecular ion are observed. The presence of one or other substituents in the condensed (for example, thiophene) ring substantially influences the dissociation process, so that general paths characteristic for all the compounds can not be identified. Thus, splitting of the CH_3CN molecule, characteristic for 2-methyl-benzothiazoles, analogs of thienothiazoles, takes place only in the case of three out of five bases (experimental part) and proceeds only at the second stage of dissociation. The nature of the first step of the dissociative ionization is due to the presence of one or other substituent in the thiophene ring, and is manifested by the presence in the spectra of peaks of $[M-H]^+$, $[M-C_2H_4]^+$, $[M-CH_3]^+$, $[M-OCH_2]^+$, and $[M-Br]^+$ ions, respectively. The presence of an aryl substituent is evidenced by the formation of the $C_6H_5CS^+$ ion when the thiophene ring is split.

The results of the quantum-chemical calculations of the mobility of hydrogen atoms in the 2-methyl groups of substituted thieno- and indolothiazoles and their quaternary salts by the PPP method [6] show that the phenyl substituent and the bromine atom at the 5-position, and methyl and alkylene groups at the 5,6-positions, change the value of the electron

TABLE 1. Characteristics of Isatin Oximes, 2-hydroxy-3-acetyl-aminoindoles and Indolothiazoles

Compound	R	mp, °C[a]	Found, %			Empirical formula	Calculated, %			Yield, %
			C	H (S)	Hal (N)		C	H (S)	Hal (N)	
XXI	5-CH_3	212—213	63,4	5,6	(14,8)	$C_{10}H_{10}N_2O_2$	63,2	5,3	(14,7)	91
XXI	4-CH_3	169—170	63,2	5,3	—	$C_{10}H_{10}N_2O_2$	63,2	5,3	—	51
XXI	6-CH_3	192—193	63,1	5,5	(14,6)	$C_{10}H_{10}N_2O_2$	63,2	5,3	(14,7)	52
XXI	7-CH_3	229—230	62,2	6,2	—	$C_{10}H_{10}N_2O_2 \cdot 0,5C_2H_5OH$	62,0	6,1	—	76
XXI	5-Br	227—228	42,4	3,0	—	$C_9H_7BrN_2O_2$	42,3	2,7	—	84
XXI	5,7-di-Cl	>300	44,1	2,7	28,8	$C_9H_6Cl_2N_2O_2$	44,1	2,4	28,9	88
XXI	5,7-di-Br	>300	32,3	2,0	—	$C_9H_6Br_2N_2O_2$	32,3	1,8	—	86
XXII	5-CH_3	213—214	66,1	6,4	(12,8)	$C_{12}H_{14}N_2O_2$	66,3	6,2	(13,0)	80
XXII	4-CH_3	237—238	66,2	6,5	—	$C_{12}H_{14}N_2O_2$	66,3	6,2	—	53
XXII	6-CH_3	220—221	63,5	6,5	—	$C_{12}H_{14}N_2O_2 \cdot 0,5H_2O$	63,4	6,6	—	54
XXII	7-CH_3	>300	66,4	6,4	—	$C_{12}H_{14}N_2O_2$	66,1	6,4	—	61
XXII	5-Br	250—251	—	—	28,2	$C_{11}H_{11}BrN_2O_2$	—	—	28,2	66
XXII	5,7-di-Cl	233—234	—	—	25,8	$C_{11}H_{10}Cl_2N_2O_2$	—	—	26,0	69
XXII	5,7-di-Br	238—239	—	—	44,2	$C_{11}H_{10}Br_2N_2O_2$	—	—	44,2	78
XXIII	5-CH_3	80—82	66,4	5,8	—	$C_{12}H_{12}N_2S$	66,6	5,6	—	52
XXIIIa	4-CH_3	82—83	66,7	5,7	—	$C_{12}H_{12}N_2S$	66,6	5,6	—	41
XXIIIb	6-CH_3	55—56	66,5	5,5	—	$C_{12}H_{12}N_2S$	66,6	5,6	—	40
XXIII	7-CH_3	89—90	66,4	5,4	—	$C_{12}H_{12}N_2S$	66,6	5,6	—	45
XXIII	5-Br	113—114	—	(11,4)	28,4	$C_{11}H_9BrN_2S$	—	(11,5)	28,4	52
XXIIIc	5,7-di-Cl	149—150	—	(11,8)	25,9	$C_{11}H_8Cl_2N_2S$	—	(11,8)	26,2	45
XXIIId	5,7-di-Br	161—162	—	(8,7)	44,2	$C_{11}H_8Br_2N_2S$	—	(8,9)	44,4	71

[a]Compounds XXI) light-yellow needles; XXII, XXIIIc) snow-white prisms; XXIIId) light brown needles; remaining compounds) colorless needles.

density on the $C_{(2)}$ atom of the thiazole ring and the bond order $P_{C(2)=N}$ ($q_{C(2)}$ 0.137 and 0.138, $P_{C(2)=N}$ 0.842 and 0.844 for 2-methylthieno[2,3-d]thiazole and its 5-phenyl derivative, the signal of the 2-methyl group protons is at 2.64 and 2.75 ppm), exhibiting little influence on their reactivity. It should be noted that the 5-halo(aryl)-substituted thienothiazoles are more difficultly alkylated (with the formation of iodoalkylates and γ-sulfopropylbetains) than the 5,6-(methyl) (methylene) derivatives, which reflects their lower basicity. This is also characteristic of haloindolo-thiazoles in comparison with unsubstituted alkylindolothiazoles. In the mobility of the hydrogen atoms in their 2-methyl group, the alkylindolothiazoles and their quaternary salts are comparable with the derivatives of thieno- and benzothienothiazoles (2.84 ppm at R = 4-CH_3 and 2.81 ppm at R = 6-CH_3), while haloindolothiazoles show lower values ($q_{C(2)}$ and $P_{C(2)=N}$) 0.139 and 0.884, δ 2.73 ppm).

Substituted thieno- and indolothiazoles are crystalline compounds and on heating with alkylating agents form fairly reactive quaternary salts, which enter into condensation reactions with compounds used for the synthesis of polymethine dyes.

EXPERIMENTAL

The PMR spectra were run on a Bruker SCR-200 spectrophotometer (200 MHz) in deuterochloroform, using HMDS as internal standard, on the δ scale. The mass spectra were obtained on a Varian MAT-311A spectrometer at an ionizing voltage of 70 eV and emission current of 1.5 μA. The content of solvents in the reaction products was determined by gas chromatography on a Chrom-3A apparatus with an attachment for introducing solid samples (a Polysorb-1 column, l = 3 m, bp = 120°C, temperature of the evaporator 20°C lower than the melting point of the sample studied, flow rate of carrier gas 50 ml/min).

2-Acetylamino-3-carbethoxy-4,5-tetramethylenethiophene (II). A 13.3 g portion (0.17 mole) of acetyl chloride is added dropwise, with stirring, to a solution of 13.5 g (0.06 mole) of thiophene I in 30 ml of dioxane. The mixture is heated for 30 min at 110°C (in a bath), then cooled to 20°C and poured into 200 ml of ice water. After 1 h, the precipitate (yellowish prisms) is filtered, washed with water, and dried in air. Yield 14.8 g (92.5%), mp 119-120°C (from ethanol). Found, %: C 58.4, H 6.3, S 12.2. $C_{12}H_{15}NO_3S$. Calculated, %: C 58.4, H 6.4, S 12.0.

2-Acetylamino-3-carboxy-4,5-tetramethylenethiophene (III). A solution of 121 g (0.453 mole) of thiophene II and 36.2 g (0.906 mole) of sodium hydroxide in 500 ml of aqueous methanol (1:1) is boiled with stirring for 3 h. After cooling to 20°C, the solution is

TABLE 2. Spectral Characteristics of Compounds XXIIIa-d

Compound	PMR spectrum, ppm	Relative intensity, %			
		M^+	$[M-H]^+$	$[M-CH_3]^+$	M^{++}
XXIIIa	2,84 (3H, s, 2-CH_3); 2,89 (3H, s, 4-CH_3); 3,88 (3H, s, 8-CH_3); 6,99 (1H, br, d, d, J=3,0 and 5,2 Hz, 5-H); 7,18 (2H, m, 6-H and 7-H)	100	25	13	13
XXIIIb	2,51 (3H, s, 6-CH_3); 2,81 (3H, s, 2-CH_3); 3,79 (3H, s, 8-CH_3); 7,03 (1H, d.d, J=8,0 and 5 Hz, 5-H); 7,12 (1H, br.s, 7-H);	100	21	10	10
XXIIIc	7,83 (1H, d, J=8,0 Hz, 4H)	100		11	
XXIIId		100		9	

poured into 3 liters of ice water and acidified with HCl to an acid reaction to Congo. The precipitate (light brown needles) is filtered, washed with water, and dried in air. Yield 67 g (62%), mp 222°C (from methanol). Found, %: C 53.4, H 5.6, N 5.8. $C_{11}H_{13}NO_3S \cdot 0.5H_2O$. Calculated, %: C 53.2, H 5.7, N 5.6.

2-Acetylamino-4,5-tetramethylenethiophene (IV). A mixture of 71.7 g (0.3 mole) of thiophene III and 7.2 g of copper is heated at 250°C (in a bath) for 40 min (until carbon dioxide ceases to evolve), is then cooled to 70°C, and 350 ml of ethanol are added. The mixture is boiled for 15 min, the hot solution is filtered and poured into 1 liter of ice water. The precipitate (light-brown prisms) is filtered and dried in air. Yield 30 g (51.2%), mp 151-152°C (from 50% ethanol). Found, %: C 61.6, H 6.6, S 16.5. $C_{10}H_{13}NOS$. Calculated, %: C 61.5, H 6.7, S 16.4.

2-Acetylamino-3-bromo-4,5-tetramethylenethiophene (V). A solution of 10 ml of bromine in 50 ml of acetic acid is added dropwise, with stirring to a suspension of 40.15 g (0.206 mole) of thiophene IV in 300 ml of acetic acid. The mixture is stirred for 2 h, poured into 3 liters of ice water, the precipitate (pinkish prisms) is filtered and dried in air. Yield 51 g (90%), mp 124-125°C (from ethanol). Found, %: C 44.4, H 5.4, Br 26.9. $C_{10}H_{12}BrNOS \cdot 0.5C_2H_5OH$. Calculated, %: C 44.5, H 5.1, Br 26.9.

2-Methyl-5,6-tetramethylenethieno[2,3-d]thiazole (VI). Phosphorous pentasulfide (40 g, 0.18 mole) is added in portions, with stirring, to a suspension of 51 g (0.19 mole) of thiophene V in 330 ml of dry benzene. The mixture is boiled for 1.5 h, then cooled to 40-50°C, 90 ml of hot water is added in portions, and then at 45-55°C, a solution of 40 g (1 mole) of sodium hydroxide in 330 ml of water is added in the course of 10 min, and the mixture is stirred for 1 h. The benzene layer is separated and the aqueous layer is extracted by 150 ml of benzene. The benzene solutions are combined, washed with water, dried over potassium carbonate, and benzene is distilled off at reduced pressure. The residue (oil) is distilled at 165-170°C (5 mm). Yield 14.5 g (36.5%), mp 35-36°C. (from 50% ethanol). Mass spectrum, m/z (%): 209 (M^+, 57), 208 ($[M-H]^+$, 26), 181 ($[M-C_2H_4]^+$, 110), 140 ($[M-C_2H_4, -CH_3CN]^+$, 10). Found, %: C 57.2, H 5.2. $C_{10}H_{11}NS_2$. Calculated, %: C 57.4, H 5.3.

2-Acetylamino-5-phenylthiophene. A mixture of 6.5 ml of acetic anhydride and 12 ml of ether is added at 0-5°C, with stirring, to a mixture of 7.7 g (0.037 mole) of 2-amino-5-phenylthiophene hydrochloride and 50 ml of water and then a solution of 4 g (0.10 mole) of sodium hydroxide in 12 ml of water is added. The mixture is stirred for 30 min at 5°C and for 3 h at 20°C. The precipitate is filtered, washed with water and dried. Yield 5.38 g (67%). Colorless plates (from benzene); mp 178-179°C (178-180°C [7, 8]).

2-Thioacetylamino-5-phenylthiophene (VII). A 1.12 g portion of phosphorus pentasulfide is added with stirring to a boiling mixture of 2.16 g (0.01 mole) of 2-acetylamino-5-phenylthiophene and 30 ml of dry benzene, and the mixture is boiled for 1 h. The solution is separated from the precipitate and shaken with 25 ml of a 4% NaOH solution. The aqueous layer is acidified with ice-cooling by concentrated HCl to an acid reaction, and the precipitate that separates (light-yellow prisms), is filtered, washed with water to a neutral reaction, and dried in air. Yield 1.04 g (44.4%), mp 162-163°C (from benzene). Found, %: C 61.6, H 4.7, N 5.9. $C_{12}H_{11}NS_2$. Calculated, %: C 61.7, H 4.7, N 6.0.

2-Methyl-5-phenylthieno[2,3-d]thiazole (VIII). A solution of 1.4 g of thiophene VII in 1.5 ml of 4% NaOH is added dropwise, with stirring and cooling to 0°C (in a bath), to 40 ml of a 10% solution of potassium ferricyanide. The mixture is stirred for 2 h at 20°C. The

precipitate is filtered and steam-distilled. Yield 0.42 g (30.5%). Colorless prisms, mp 118-119°C. Mass spectrum, m/z (%): 231 (M^+, 100), 230 ($[M-H]^+$, 16), 145 (14), 121 ($[C_6H_5CS]^+$, 19). PMR spectrum (in CCl_4): 2.75 ppm (3H, s, 2-CH_3); 7.06 (6-H). Found, %: N 6.1. $C_{12}H_9NS_2$. Calculated, %: N 6.0.

5-(p-Methoxyphenyl)dithia[1,2]cyclopenten-3-one (IX). A mixture of 20.6 g (0.10 mole) of ethyl p-methoxycinnamate and 9.6 g (0.15 mole) of sulfur is heated for 16 h at 220-230°C in a bath. After cooling, the reaction mixture is boiled in 100 ml of acetone. The precipitate is filtered and boiled in 180 ml of acetone. The acetone solutions are combined, acetone is distilled off, the residue is treated with 100 ml of diethyl ether and the precipitate is filtered. Yield 6.72 g (30%); pinkish plates, mp 103-104°C (from 50% acetic acid). Found, %: C 53.5, H 3.7. $C_{10}H_8O_2S_2$. Calculated, %: C 53.5, H 3.6.

(β-p-Methoxyphenyl-β-carboxymethylthio)acryloylthioglycolic acid (X). A 17.92 g portion (0.08 mole) of ketone IX is added to 80 g (0.64 moles) of molten sodium sulfide. The mixture is heated for 20 min on a boiling water bath, then cooled, diluted with 30 ml of water and added with ice-water cooling to a solution of 66 g (0.7 mole) of chloroacetic acid, neutralized by a sodium hydroxide solution, and then allowed to stand for 2 days at 20°C. It is then filtered and the filtrate acidified with hydrochloric acid with ice water cooling. After a few hours, the precipitate is filtered and dried in air. Yield 12 g (43.9%); colorless needles (from acetic acid), mp 157-159°C. Found, %: C 49.1, H 4.3. $C_{14}H_{14}O_6S_2$. Calculated, %: C 49.1, H 4.1.

5-p-Methoxy-3-acetoxythiophene (XI). A 23.94 g portion (0.07 mole) of acid X is introduced into a hot mixture of 22 g of anhydrous sodium acetate and 80 ml of acetic anhydride, and the mixture is heated on a water bath to completion of evolution of carbon dioxide. The solution is evaporated in vacuo and the residue is treated with water. The crystalline produce is filtered, dissolved in ether (800 ml) at 20°C, the ether is evaporated and the residue is treated with water. The precipitate is filtered and dried in air. Yield 13.6 g (78.1%); gray plates, mp 80-82°C (from 50% ethanol). Found, %: C 61.4, H 5.3. $C_{13}H_{12}O_3S \cdot 0.33\ H_2O$. Calculated, %: C 61.4, H 5.0.

5-p-Methoxyphenyl-3-hydroxythiophene (XII). A solution of 14.88 g (0.06 mole) of thiophene XI in 300 ml of ethanol is added to 300 ml of 10% NaOH at 80°C (in a bath), and the mixture is stirred. After 10 min, the solution is cooled, acidified with hydrochloric acid, and allowed to stand overnight. The precipitation is filtered, washed with water, and dried in air. Yield 10.75 g (86.7%); pinkish leaves, mp 114-115°C (from petroleum ether, bp 40-70°C). Found, %: C 64.2, H 5.2. $C_{11}H_{10}O_2S$. Calculated, %: C 64.0, H 4.9.

2-Nitroso-3-hydroxy-5-(p-methoxyphenyl)thiophene (XIII). A 16.48 g portion (0.08 mole) of thiophene XII and 6.07 g (0.088 mole) of sodium nitrite are added to a solution of 3.8 g (0.095 mole) of sodium hydroxide in 180 ml of water. The solution is added dropwise, with cooling, to 158 ml of dilute (1:1) hydrochloric acid. The precipitate is filtered, washed with water and dried. Yield 18 g (95.7%); yellow prisms (from ethanol, mp 209-210°C (dec.). Found, %: C 56.4, H 4.1, N 5.8. $C_{11}H_9NO_3S$. Calculated, %: C 56.2, H 3.9, N 5.9.

2-Acetylamino-3-hydroxy-5-(p-methoxyphenyl)thiophene (XV). A 9.40 g portion (0.04 mole) of thiophene XIII is added at 40°C to a solution of 40 g (0.176 mole) of tin dichloride in 50 ml of hydrochloric acid. At the end of the addition, the mixture is stirred at the same temperature for 3 h and then cooled. The precipitate is filtered, washed with ethanol, ether, and dried in air. Yield of 2-amino-3-hydroxy-5-(p-methoxyphenyl)thiophene hexachlorostannate (XIV) is 9.75 g (62.8%). A solution of 5.2 ml of acetic anhydride in 10 ml of ether is added with vigorous stirring at 0-5°C to a suspension of 7.76 g (0.1 mole) of hexachlorostannate XIV in 50 ml of water, and then a solution of 10 g of sodium hydroxide in 15 ml of water is added in small portions at a temperature not higher than 10°C. At the end of the addition, the mixture is stirred for 20 min with cooling, and ether is removed by a current of air. The precipitate is filtered, treated with a 5% HCl solution, and filtered again. The filtrate is acidified with hydrochloric acid, the precipitate is washed with water, and dried. Yield 4.93 g (93.7%); light yellow prisms, mp 149-151°C (from 50% ethanol). Found, %: C 55.9, H 5.4. $C_{13}H_{13}NO_3S \cdot H_2O$. Calculated, %: C 55.5, H 5.4.

2-Methyl-5-(p-methoxyphenyl)thieno[2,3-d]thiazole (XVI). Phosphorous pentasulfide (5.7 g, 0.027 mole) is added in portions, with stirring, to a solution of 5.7 g (0.027 mole) of thiophene XV in 115 ml of boiling benzene. The mixture is stirred at the boiling point for 2 h, then cooled, and 13 ml of water, and then a solution of 5.7 g of sodium hydroxide

in 50 ml of water, are added. The benzene layer is separated, washed with water, and evaporated. The compound is purified by reprecipitation by water from a solution in 100 ml of ethanol. Yield 1.78 g (31.6%). After distillation in vacuo [bp 180-200°C (3 mm)] and recrystallization from ethanol, colorless leaves, mp 123-124°C. Mass spectrum, m/z (%): 261 (M^+, 100), 246 ($[M - CH_3]^+$, 73), 231 ($[M - OCH_2]^+$, 44), 218 (21), 145 (12), 121 ($[C_6H_5CS]^+$, 11). Found, %: C 60.0, H 4.2. $C_{13}H_{11}NOS_2$. Calculated, %: C 59.7, H 4.2.

2-Methyl-5-bromothieno[2,3-d]thiazole (XVII). A solution of 2.1 g (0.013 mole) of bromine in 6 ml of acetic acid is added with stirring to a solution of 1.16 g of anhydrous sodium acetate in 20 ml of acetic acid and 1.86 g (0.012 mole) of 2-methyl-thieno[2,3-d]-thiazole. The mixture is stirred for 1.5 h and poured into water. The precipitate is filtered, washed with water, and dried in air. Yield 2.7 g (96.4%). After crystallization from petroleum ether, colorless prisms, mp 89-90°C. Mass spectrum, m/z (%): 235/233 (M^+, 100), 234/232 ($[M-H]^+$, 20), 154 ($[M - Br]^+$, 22), 113 ([M − Br, $-CH_3CN]^+$, 32), 101 (55), 69 (58). Found, %: C 30.6, H 1.6, N 5.7. $C_6H_4BrNS_2$. Calculated, %: C 30.8, H 1.8, N 5.9.

2-Methyl-5,6-dibromothieno[2,3-d]thiazole (XVIIa). A solution of 2.1 g (1.3 mmole) of bromine in 1.3 ml of acetic acid is added dropwise at 110-120°C (in a bath) to a solution of 1.16 g of anhydrous sodium acetate and 0.93 g (6 mmoles) of 2-methylthieno[2,3-d]thiazole in 10 ml of acetic acid. The mixture is stirred for 1.5 h and then evaporated in vacuo to dryness. The residue is treated with 100 ml of water, and the precipitate is filtered, dried in air, and treated with ether, added in 10 ml portions. The combined ether solutions are evaporated to half their volume. The precipitate that separates is filtered. Yield 1 g (53.2%). After recrystallization from ethanol, greyish prisms. Mass spectrum, m/z (%): 315/313/311 (M^+, 100), 234/232 ($[M - Br]^+$, 21), 193/191 ([M − Br, $-CH_3CN]^+$, 14), 149/147 ([M − Br, $-CS]^+$, 34). Found, %: C 23.9, H 1.3, N 4.8. $C_6H_3Br_2NS_2 \cdot 0.2C_2H_5OH$. Calculated, %: C 23.8, H 1.33, N 4.4.

1,5-Dimethylisation (XX, R = 5-CH_3). A solution of 2.76 g of the sodium in 50 ml of methanol is added at 20°C, with stirring, to a suspension of 17.5 g (0.11 mole) of 5-methyl-isatin in 60 ml of anhydrous methanol. The precipitate is filtered, washed with 30 ml of cold methanol, and dried in air. The yield of the sodium salt is 15.3 g. The mixture of the sodium salt and 50 ml of methyl iodide is boiled for 70 h and then evaporated. The residue is treated with water and filtered, and the precipitate is washed with water and dried in air. Yield 13.6 g (72%). Red-orange plates (from ethanol), mp 150-151°C (152°C [5]).

1,7-Dimethyl, 1-methyl-5-bromo-, 1-methyl-5,7-dichloro-, and 1-methyl-5,7-dibromoisatins (XX) are obtained similarly as the preceding compound. Red-orange plates (from ethanol). Yield 71-81%.

1,4- and 1,6-Dimethylisatins are obtained from a mixture of 4- and 6-methylisatins. The isomers are separated by selective crystallization from water. Reddish-orange plates (from ethanol). The yield of 1,4-dimethylisatin is 54%, mp 164-165°C (165°C [5]); PMR spectrum: 2.55 (3H, s, 4-CH_3); 3.22 (3H, s, 1-CH_3); 6.68 (1H, d, J = 7.8 Hz, 2-H); 6.88 (1H, d, J = 7.8 Hz, 5-H); 7.43 (1H, t, J = 7.8 Hz, 3-H). The yield of 1,6-dimethylisatin is 29%, mp 150-151°C (150°C [5]).

3-Oximes of Dimethylisatins (XXI). A 0.052 mole portion of hydroxylamine hydrochloride and a few drops of concentrated HCl are added to a solution of 0.51 mole isatin XX in a mixture of 350 ml of hot water and 100 ml of ethanol. The mixture is boiled for 1 h, and then cooled, The precipitate is filtered, dried in air, and crystallized (Table 1).

2-Hydroxy-3-acetylaminoindoles (XXII). A mixture of 0.03 mole of isatin-3-oxime XXI and 12 g of zinc dust is added at 50-55°C, with stirring, to a mixture of 65 ml of acetic acid and 30 ml of acetic anhydride. The mixture is heated for 1 h, then cooled and filtered. The precipitate is washed with 50 ml of acetic acid, and the solutions are combined and evaporated to dryness. The residue is treated with water, and the precipitate is filtered, dried in air, and crystallized from ethanol (Table 1).

Indolo[3,2-d]thiazoles (XXIII). A 4.3 g portion of phosphorus pentasulfide is added with stirring and boiling to a suspension of 0.02 mole of 2-hydroxy-3-acetylaminoindole XXII in 150 ml of anhydrous xylene. The mixture is stirred at the boiling point for 2 h, and the solution is decanted and evaporated. The residue is treated twice with 4% NaOH and extracted by chloroform. The extracts are combined and evaporated. The precipitate is

crystallized from petroleum ether (bp 40-70°C) with active charcoal. Dihaloindolothiazoles are isolated similarly by evaporating the chloroform extract and treating the concentrate with ether. The precipitate is filtered and crystallized from ethanol (Tables 1 and 2).

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