UDC 547.789.6

STRUCTURE AND PROPERTIES OF SUBSTITUTED IMIDAZO [5, 1-b] BENZOTHIAZOLES

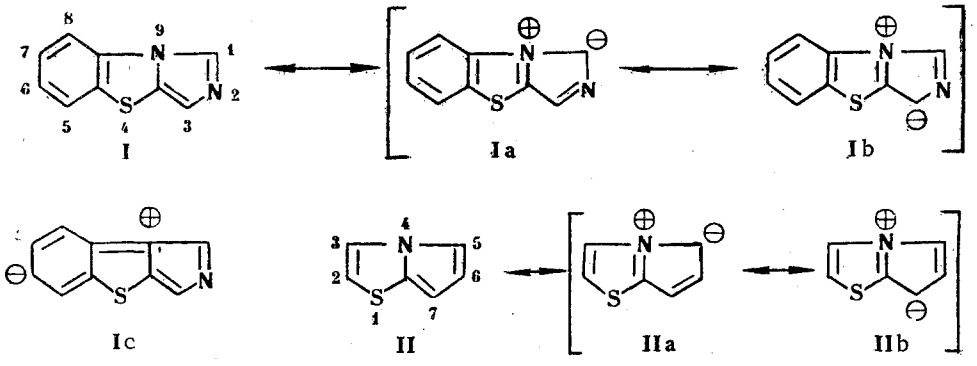
V. V. Avidon and M. N. Shchukina

Khimiya Geterotsiklicheskikh Soedinenii, Vol. 2, No. 2, pp. 292-298, 1966

The properties of 3-phenylimidazo [5, 1-b] benzothiazole (III) are investigated; bromination, nitration, and mercuration are effected, as well as the Mannich and Wilsmeyer reaction, at position 1. Oxidation gives 2-benzoylbenzothiazole (IV). The bromine in 1-bromo-3-phenylimidazo [5, 1-b] benzothiazole (V) is replaced by nitro, butoxy, and sulfide groups. Hydrogen sulfide reduced V to III. The disulfide XVI is obtained from 1-mercapto-3-phenylimidazo- [5, 1-b] benzothiazole (XV).

The new heterocyclic system imidazo [5, 1-b] benzothiazole (I) was previously synthesized by us [1, 2]. The present work aimed to study the properties and reactions of this system, and in particular, the possibility of introducing various functional groups into the molecule of I.

The system I studied is a benz- and aza-analog of pyrrolothiazoles (II), whose reactions have been investigated [3]. Like II, I can also be represented by two polar formulas (Ia and b), where both the thiazole and imidazole rings have an aromatic sextet of π-electrons. In other structures, where maximum electron density would occur at atoms in the benzene ring (e.g., Ic), the aromatic sextet would be broken in all 3 rings, so that shift of electron density in the direction of formation of a structure of such a type seems less probable to us.

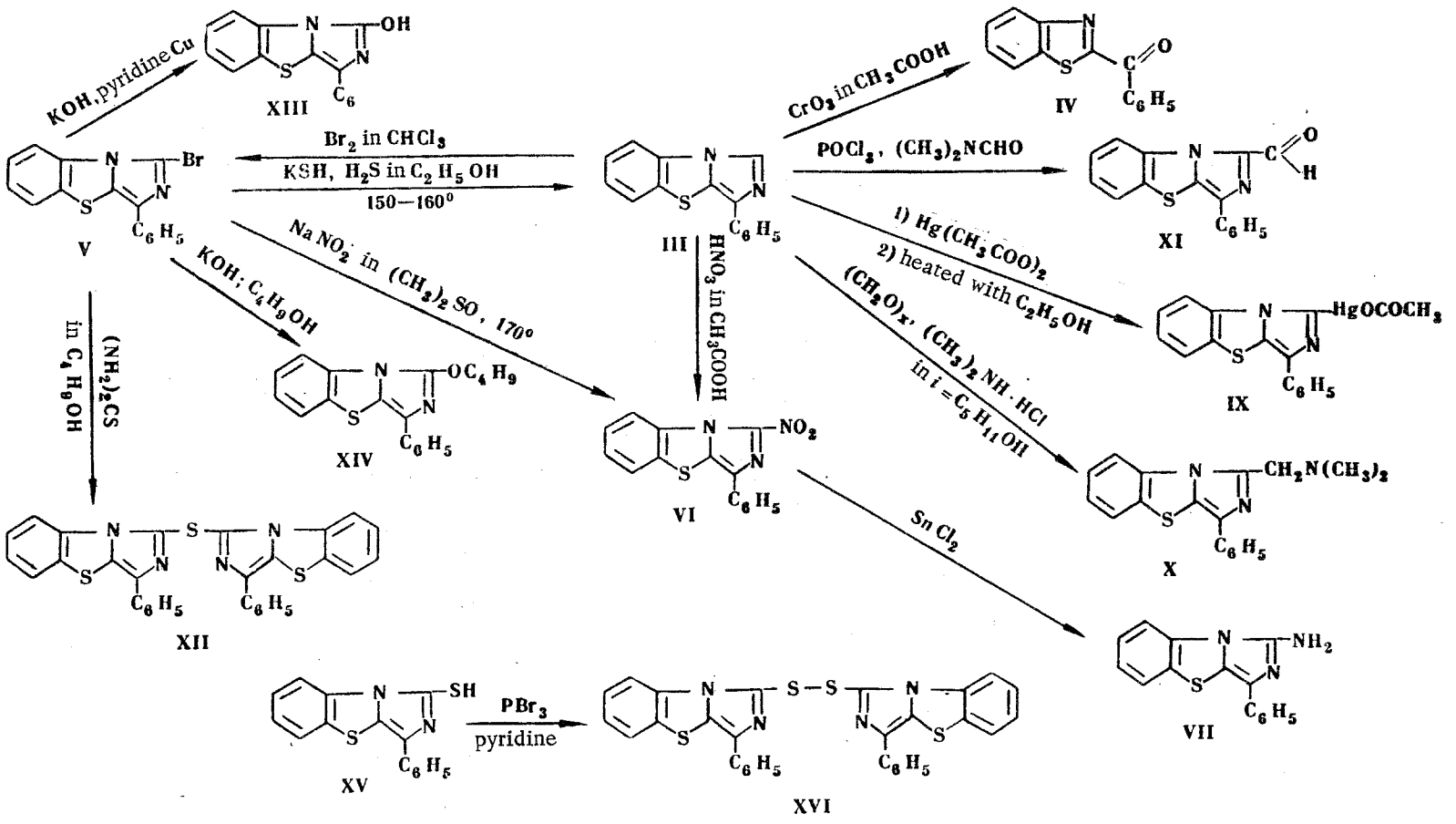


From what has been said above, it can be assumed that the maximum electron density in I should obviously be at positions 1 and 3, and that the imidazole ring must be the one most enriched in π-electrons. Basically the present experimental results are in accord with these views.

System I was studied using, as a type, substance 3-phenylimidazo [5, 1-b] benzothiazole (III). The great chemical stability of system I is shown: compound III is unchanged when treated with 74% sulfuric acid at 95° C, as well as by boiling with 20% ethanolic alkali.

When a polycyclic system is oxidized it is to be expected that the ring most enriched in π-electrons will be oxidized. Actually, oxidation of III with chromic anhydride in acetic acid gave a good yield of 2-benzoylbenzothiazole (IV).

I being the aza-analog of II, it would be expected that electrophilic substitution in I would be less energetic than in II, as introduction of the $-N=$ group into the ring in place of $-CH=$ usually lowers the π-electron excess of the ring. Actually it proved impossible to nitrosate III, though the reaction proceeds readily with II type compounds. If in the case of II dibenz-analogs, isoindolobenzothiazoles, acetylation takes place readily even in boiling acetic anhydride [4], it was found impossible to acetylate III even by heating with aluminum chloride in chlorobenzene. However, other substitution reactions of III take place quite readily, always in a well defined way, and to give good yields. Bromination of III in chloroform gave 1-bromo-3-phenylimidazo [5, 1-b] benzothiazole (V). Nitration of III in acetic acid with a small excess of fuming nitric acid gave 1-nitro-3-phenylimidazo [5, 1-b] benzothiazole (VI). Reduction of VI with stannous chloride gave a good yield of 1-amino-3-phenylimidazo [5, 1-b] benzothiazole (VII). The amine VII forms a monohydrochloride, sparingly soluble in water, and readily hydrolyzed. Attempts to diazotize amine VII either in hydrochloric acid, or by treatment with nitrosylsulfuric acid, gave only high-melting sparingly soluble mix-


KOH, pyridine Cu
XIII
Br_2 in $CHCl_3$
KSH, H_2S in C_2H_5OH
150—160°
V
III
CrO_3 in CH_3COOH
IV
$POCl_3$, $(CH_3)_2NCHO$
XI
1) $Hg(CH_3COO)_2$
2) heated with C_2H_5OH
IX
$(CH_2O)_x$, $(CH_3)_2NH \cdot HCl$
in $i\text{-}C_5H_{11}OH$
X
HNO_3 in CH_3COOH
VI
$Sn Cl_2$
VII
$NaNO_2$ in $(CH_3)_2SO$, 170°
KOH; C_4H_9OH
XIV
$(NH_2)_2CS$
in C_4H_9OH
XII
PBr_3
pyridine
XV
XVI

tures, which were not identified. Attempts to replace the amino group with hydroxyl by diazotization were also unsuccessful. Compound III undergoes mercuration. When, at room temperature, aqueous ethanolic mercuric acetate and a solution of III are poured into acetone, a copious white precipitate forms, its composition and IR spectrum corresponding to the complex III · $Hg(CH_3COO)_2$ · C_2H_5OH (VIII). When VIII is boiled in ethanol, heated at about 100° C in acetic acid, or the solid heated above its melting point, ready conversion to 1-acetylmercur-3-phenyl-imidazo [5, 1-b] benzothiazole (IX) ensues. It is a high-melting solid, insoluble in water and organic solvents. Compound IX was quite inert chemically, and the mercuracetyl group could not be replaced by bromine even under very drastic conditions.

Characteristic Frequencies of Valence Vibrations of NO_2 and CO Groups in RNO_2 and RCHO

R	ν_{NO_2}(asymm.) in RNO_2, cm^{-1}	ν_{CO} in RCHO, cm^{-1}	References
Pyridyl-4	1535	1721	5, pp. 310—318
C_6H_5	1524	1705	the same
4-HOC_6H_4	1515	—	6
3-Phenylimidazo [5, 1-b] benzothiazolyl-1	1515	1680	
3-Methyl-6-phenylpyrrolothiazolyl-5	—	1640	3
Indolyl-3	—	1631	5, pp. 310—318
Isoindolobenzothiazolyl-11	—	1620	4

The Mannich reaction of III with formaldehyde and dimethylamine gave 1-(N, N-dimethylaminomethyl)-3-phenylimidazo [5, 1-b] benzothiazol-1-aldehyde (X).

With III Wilsmeyer formylation takes place at 90–95° C. The resultant 3-phenylimidazo [5, 1-b] benzothiazol-1-aldehyde, unlike type II structure aldehydes [3], is stable to acids, and when it is boiled with hydrochloric acid (1:1) the formyl group is not split off.

In all the above reactions the substituent enters at position 1, and this is fully confirmed by the PMR spectra. The spectrum of compound III consists of a broad multiplet with center at $\delta = 7.1$, and singlet at $\delta = 8.5$. The spectrum of 1-methyl-3-phenylimidazo [5, 1-b] benzothiazole lacks the singlet at $\delta \approx 8.5$ so that signal corresponds to a proton at position 1, and the multiplet at $\delta = 7.1$ to phenyl protons. The signal of a proton at position 1 is also lacking with compounds V, VI, VII, IX, X, and XI, clearly indicating a substituent at position 1.

Under rather drastic conditions the bromide V undergoes replacement. The bromine in the compound can be replaced by a nitro group by treatment with sodium nitrite in dimethylsulfoxide at 170° C, and bis (3-phenylimidazo [5, 1-b]-benzothiazolyl-1) sulfide (XII) is also obtained by boiling V with thiourea in butanol. Prolonged boiling of bromide V with alkali in butanol gives, instead of the expected 1-hydroxy-3-phenylimidazo [5, 1-b]-benzothiazole (XIII) [1], a good yield of 1-butoxy-3-phenylimidazo- [5, 1-b) benzothiazole (XIV). XIII could not be obtained by prolonged refluxing of V with alkali in pyridine, only the starting compound was isolated. Attempts to replace the bromine in V by a mercapto group by heating in a sealed tube with ethanolic potassium hydrosulfide and hydrogen sulfide, resulted only in reduction of V to compound III. It is possible that this phenomenon is connected with the much higher electron density at C^1 in comparison with that in most other aryl halides. The bromide V could not be obtained by heating the hydroxy compound XIII with phosphorus tribromide in pyridine, and only the starting compound was isolated. Under the same conditions 1-mercapto-3-phenylimidazo [5, 1-b] benzothiazole [1] is converted to bis(3-phenylimidazo- [5, 1-b] benzothiazolyl-1) disulfide (XVI).

It should be mentioned that the above-stated assumption regarding the character of the system of I is in agreement with IR spectrum data. It may be considered that the lowering of the frequencies of the assymetric valence vibrations of the nitro group in nitro compounds, and of C=O bond vibrations in aldehydes, as compared with the corresponding values for benzene derivatives is usually due to electron-donor properties of the aromatic group as compared with the substituent [5]. Comparison of these frequencies in the spectra of compounds VI and XI with the corresponding frequencies of other nitro compounds and aldehydes (table) leads one to conclude that the electron-donating properties of the 3-phenylimidazo [5, 1-b]-benzothiazole group are greater than those of phenyl, and closely approximate to those of 4-hydroxyphenyl.

Experimental

Action of sulfuric acid on 3-phenylimidazo [5, 1-b] benzothiazole (III). A suspension of 2 g (8.1 mmole) III in 27 ml 74% H_2SO_4 was heated and stirred for 2 hr on a boiling water bath, then cooled, poured into 75 ml water, and the mixture made alkaline to pH ~ 9 with aqueous ammonia. The white precipitate was filtered off, washed and dried. Yield 1.89 g compound mp 158.5–159.5°C, undepressed mixed mp with starting compound III.

Action of alkali on 3-phenylimidazo [5, 1-b] benzothiazole (III). 1.82 g (7.4 mmole) III was refluxed for 2 hr with 50 ml ethanolic 20% NaOH. The cooled mixture was poured into 600 ml water, and 1.8 g substance filtered off, mp 159-159.5° C, undepressed mixed mp with starting III.

Oxidation of 3-phenylimidazo [5, 1-b] benzothiazole. 3.3 g CrO_3 were added in small portions to a solution of 2 g (8.1 mmole) III in glacial AcOH, with stirring, the mixture heated for 1 hr on a boiling water bath. During heating, the color changed from brown to green. After cooling the products were poured into 500 ml cold water, and left overnight. The precipitate which formed was filtered off, and 1.21 g colorless compound obtained, mp 102-102.6° C (yield 63.8%). Undepressed mixed mp with authentic 2-benzoylbenzothiazole IV.

1-Bromo-3-phenylimidazo [5, 1-b] benzothiazole (V). 0.42 g bromine in 5 ml $CHCl_3$ was added dropwise to a solution of 2 g (8.1 mmole) III in 75 ml $CHCl_3$ at 20° C. After adding the bromine the mixture was stirred for 1 hr, filtered, and the solid washed with $CHCl_3$. The yellow crystals (2.96 g), were triturated with 10 ml water, 1 ml $NaHSO_3$ solution added, then 2 ml concentrated aqueous ammonia, trituration repeated, and the mixture left for 1 hr, until the precipitate was fully decolorized. The mixture was then filtered, to give 2.27 g (86.6%) bromide V. Colorless needles ex MeOH, mp 171-172° C, λ_{max} 234 and 286 mμ; log ε 4.26 and 4.29. Found: C 54.83; H 2.70; Br 24.50; N 8.54; S 9.90%. Calculated for $C_{15}H_9BrN_2S$: C 54.72; H 2.76; Br 24.27; N 8.51; S 9.74%.

1-Nitro-3-phenylimidazo [5, 1-b] benzothiazole (VI). a) A solution of 1 ml HNO_3 (d 1.51) in 7 ml AcOH was added dropwise to a solution of 2.5 g (10.1 mmole) compound III in 80 ml glacial AcOH, the mixture stirred for 2 hr, the solid filtered off, yield 2.31 g (78.5%) compound VI, bright orange needles ex iso-BuOH., mp 202-202.5° C. λ_{max} 266, 310, and 429 mμ, lg ε 4.28; 4.22, and 4.04, ν_{NO_2} 1332 and 1514 cm^{-1}. Found: C 60.75; H 3.08; N 14.28; S 10.76%. Calculated for $C_{15}H_9N_3O_2S$: C 61.00; H 3.07; N 14.23; S 10.86%.

b) A mixture of 0.39 (1.2 mmole) bromide V, 0.2 g $NaNO_2$, and 4 ml dimethylsulfoxide was heated for 2 hr in a bath at 160-170° C. The crystalline precipitate formed on cooling (0.15 g) was filtered off and recrystallized from isobutane, mp 198.5-199.5°C, undepressed mixed mp with nitro compound VI. The IR spectrum is identical with that of compound VI.

1-Amino-3-phenylimidazo [5, 1-b] benzothiazole (VIII). A solution of 6.5 g $SnCl_2$ in 25 ml ethanolic HCl was added dropwise to a suspension of 2 g (~ 7 mmole) nitro compound VI in 25 ml boiling EtOH, the mixture refluxed for 6 hr, cooled, and 2.87 g orange powder (tin complex) filtered off, mp 255-260° C (decomp). 2.87 g complex was treated with 5% NaOH solution at 60°, the mixture filtered, the solid washed with water, yield 1.74 g (96.7%) amine VII. Rose crystals, after recrystallizing from EtOH-hexane (1:1), mp 192-194°; λ_{max} 236 and 307 mμ; lg ε 4.28 and 4.22, ν_{NH} 3400 cm^{-1}. Found: C 68.02; H 4.48; N 15.94; S 11.81%. Calculated for $C_{15}H_{11}N_3S$: C 67.90; H 4.18; N 15.84; S 12.08%.

0.05 g (0.15 mmole) amine VII was dissolved in 10 ml EtOH, 0.5 ml ethanolic HCl added, the precipitate formed filtered off to give the amine VII hydrochloride, mp 250-254° C (decomp). Found: Cl 11.78%. Calculated for $C_{15}H_{12}ClN_3S$: Cl 11.75%.

1-Acetylmercur-3-phenylimidazo [5, 1-b] benzothiazole (IX). A solution of 2.68 g $Hg(OAc)_2$ in 200 ml Me_2CO + 2 ml glacial AcOH + 30 ml water was added to a solution of 2 g (8.1 mmole) compound III in 200 ml Me_2CO. A white crystalline precipitate immediately began to form; it was a complex of compound III with $Hg(OAc)_2$, composition $C_{15}H_{10}N_2S \cdot Hg(OAc)_2 \cdot$ ETOH, yield 3.29 g (67%). For analysis a specimen of compound VIII was obtained by precipitation from solution in cold AcOH. Colorless prisms, mp 178-179° C (with transformation into IX), ν_{OH} 3120 cm^{-1}. Found: C 41.05; H 3.61; Hg 32.74; S 5.15%. Calculated for $C_{12}H_{22}HgN_2O_5S$: C 41.01; H 3.37; Hg 32.62; S 5.21%.

0.7 g complex VIII was dissolved in 16 ml boiling EtOH, containing 0.7 ml AcOH, and the mixture boiled for 3 min. White flakes separated, the mixture was filtered hot, the precipitate washed with hot EtOH, to give 0.46 g (79.7%) compound IX, white finely crystalline powder, mp > 360° C, in insoluble in water and in all organic solvents. Found: C 40.06; H 2.60; Hg 38.95; N 5.23; S 6.01%. Calculated for $C_{17}H_{12}HgN_2S$: C 40.11; H 2.38; Hg 39.42; N 5.50; S 6.30%.

1-(N, N-Dimethylaminomethyl)-3-phenylimidazo [5, 1-b] benzothiazole (X). A solution of 1.5 g (6.2 mmole) compound III, 0.36 g paraformaldehyde, and 0.6 g $Me_2NH \cdot HCl$ in 15 ml iso-AmOH was refluxed for 15 min, and the white precipitate which came down from the hot solution filtered off, washed with iso-AmOH, and then treated with dilute aqueous ammonia to give 0.98 g compound X. On cooling the mother liquor deposited a small further quantity of precipitate, which was treated in the same way, to give a further 0.24 g pure X, total yield 66.3%. Colorless crystals, mp 124-125° C (ex EtOH), λ_{max} 236 and 286 mμ, lg ε 4.33 and 4.32. Found: C 70.20; H 5.37; N 13.79; S 10.37%. Calculated for $C_{18}H_{17}N_3S$: C 70.32; H 5.57; N 13.67; S 10.43%.

Dihydrochloride: mp 246-248° C (ex 10% HCl). Found: Cl 17.95%. Calculated for $C_{18}H_{19}Cl_2N_3S$: Cl 18.65%.

3-Phenylimidazo [5, 1-b] benzothiazol-1-aldehyde (XI). 1.5 ml freshly-distilled $POCl_3$, and a solution of 1.5 g (6.2 mmole) compound III in 12 ml dimethylformamide, were added to 10 ml dimethylformamide at 0-5° C, and the mixture stirred for 2 hr at 90-92° C. After cooling the products were poured on to 60 g ice and 40 ml water, a bright yellow precipitate formed, and the whole, after adjusting to pH 6 with saturated KOAc solution, was left overnight. The precipitate was filtered off, washed with water, yield of aldehyde XI 1.51 g (91.4%), pale yellow needles, mp 203-203.5° C (ex iso-BuOH), λ_{max} 280 and 371 mμ; lg ε 4.48 and 4.12; ν_{CO} 1680 cm^{-1}. Found: C 68.86; H 3.75; N 9.88; S 11.55%. Calculated for $C_{16}H_{10}N_2OS$: C 69.04; H 3.62; N 10.07; S 11.52%.

0.1 g (~ 0.4 mmole) aldehyde XI was refluxed for 2 hr with 2 ml HCl (1 : 1). The mixture was cooled, the precipitate filtered off, washed with water, treated with aqueous ammonia, then again carefully washed with water. The solid was dried, mp 203-203.5° C, undepressed mixed mp with the starting IX.

Bis (3-phenylimidazo [5, 1-b) benzothiazolyl sulfide (XII). 0.55 g (1.7 mmole) compound V and 0.17 g thiourea in 7.5 ml BuOH were refluxed for 3 hr, boiling being accompanied by formation of a precipitate. The mixture was filtered hot, yield 0.17 g (38.3%) sulfide XII, mp 262-263° C (decomp). Found: C 67.74; H 3.55; N 10.37; S 18.28%. Calculated for $C_{30}H_{18}N_4S_3$: C 67.89; H 3.42; N 10.56; S 18.13%.

1- Butoxy-3-phenylimidazo [5, 1-b] benzothiazole (XIV). A solution of 0.6 g (1.84 mmole) compound V and 2.12 g KOH in 50 ml BuOH was refluxed for 20 hr, cooled, filtered, and 0.38 g (65.0%) compound XIV obtained, colorless crystals, mp 130-130.5° C (ex EtOH), λ_{max} 234 and 300 mμ, lg ε 4.30 and 4.26. Found: C 70.31; H 5.67; N 9.01; S 10.14%. Calculated for $C_{19}H_{18}N_2OS$: C 70.77; H 5.63; N 8.69; S 9.95%.

Reaction between 1-bromo-3-phenylimidazo [5, 1-b] benzothiazole (V) and hydrogen sulfide. A suspension of 1 g (~ 3 mmole) compound V in 60 ml of a saturated solution of H_2S in EtOH and 2.78 g KSH were heated together in a sealed tube for 20 hr at 156-160° C. The tube was cooled, opened, the yellow solution filtered to remove a small amount of inorganic impurity, and then poured into 120 ml water. The resultant white precipitate was filtered off, and dried, mp 123-146° C. Its IR and PMR spectra were identical with those of compound III. The substance prepared was treated with ethanolic HCl, twice extracted with 10 ml portions of boiling xylene, the residue treated with aqueous ammonia, when white crystals mp 157-158.8° C were obtained. Undepressed mixed mp with III.

Bis (3-phenylimidazo [5, 1-b] benzthiazolyl-1) disulfide (XVI). A solution of 2 g 1-mercapto-3-phenylimidazo [5, 1-b] benzothiazole (XV) and 1.5 ml PBr_3 in 25 ml dry pyridine, was heated on a boiling water bath for 3 hr 30 min, the products cooled, poured into 150 ml water, and the yellow precipitate (XVI) filtered off. Yield 1.97 g (98.5%), mp 274-275° C (ex AcOH). Found: C 63.40; H 3.42; N 10.03; S 22.70%. Calculated for $C_{30}H_{18}N_4S_4$: C 64.03; H 3.22; N 9.96; S 22.79%.

The PMR spectra were determined in dimethylsulfoxide and trifluoroacetic acid, using a JEOL spectrometer M = 60 (60 Mc).

The authors thank Yu. N. Sheinker and G. Yu. Pek of the Institute of the Chemistry of Natural Compounds, AS USSR, for determining and analyzing the PMR spectra.

REFERENCES

1. V. V. Avidov and M. N. Shchukina, KhGS [Chemistry of Heterocyclic Compounds], 64, 1965.
2. V. V. Avidov and M. N. Shchukina, KhGS [Chemistry of Heterocyclic Compounds], 349, 1965.
3. V. K. Kiberev and F. S. Babichev, Ukr. khim.zhurn., 30, 488, 1963.
4. F. S. Babichev and V. K. Kiberev, ZhOKh, 33, 2000, 1963.
5. Physical Methods in Heterocyclic Chemistry, N.Y.-London, vol. II, 1963.
6. R. D. Kross and V. A. Fassel, J. Am. Chem. Soc., 78, 4225, 1956.

10 February 1965

Ordzhonikidze All-Union Pharmaceutical Chemistry Institute, Moscow