INDOLE DERIVATIVES

XXXIV. Synthesis of 2-Substituted 4-(3'-Indolyl)thiazoles*

Yu. I. Smushkevich, Ts. M. Babueva, and N. N. Suvorov

Khimiya Geterotsiklicheskikh Soedinenii, Vol. 5, No. 1, pp. 91–93, 1969

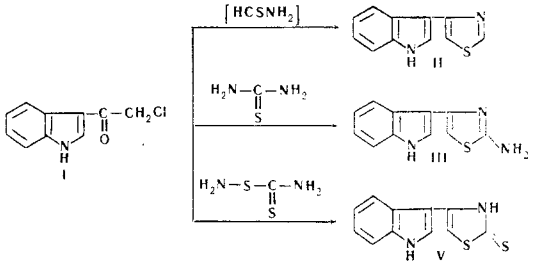
UDC 547.759.2'789.07:543.422.4.6

The reaction of 3-chloroacetylindole (I) with thioformamide, thiourea, and ammonium dithiocarbamate has given, respectively, 4-(3'-indolyl)thiazole (II), 2-amino-4-(3'-indolyl)thiazole (III), and 4-(3'-indolyl)-2-mercaptothiazole (V), identified by the preparation of derivatives and UV and IR spectra.

Recently, interest in derivatives of indole and of thiazole and analogs of the latter from the pharmacological and biochemical points of view has been increasing. However, compounds containing both these rings in one molecule have so far been completely unknown.

In this paper we describe the synthesis of 4-(3'-indolyl)thiazole and some of its derivatives and their properties. Compounds of the thiazole series containing alkyl, aryl, and heterocyclic substituents are synthesized by the reaction of α-halo-substituted carbonyl compounds with thioamides [2].

We obtained 4-(3'-indolyl)thiazole (II) from 3-chloroacetylindole (I) and thioformamide with a yield of 40%:



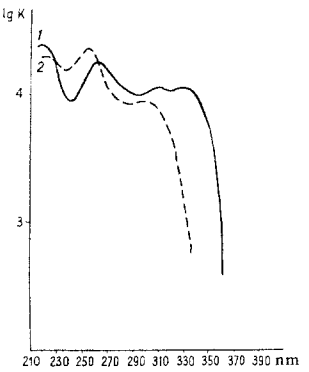
The completion of the reaction and the purity of the product were checked by chromatography in a non-fixed layer of alumina in the benzene—ethanol (9 : 1) and benzene—ether (1 : 1) systems.

The structure of 4-(3'-indolyl)thiazole was confirmed by the results of elementary analysis and NMR and IR spectra. In the NMR spectrum of compound II there is a broad peak at δ = 8.8 which must probably be ascribed to the proton of the NH of the indole ring, and a group of lines in the range δ = 7.15–8.05 corresponding to the CH protons of the aromatic nuclei. The thiazole II was characterized by the preparation of derivatives: picrate and hydrochloride.

2-Amino-4-(3'-indolyl)thiazole (III) was obtained by condensing 3-chloroacetylindole with thiourea. The structure of the thiazole III was shown by the results of elementary analysis and by IR spectroscopy. It was chromatographed in the universal benzene—methanol (9 : 1) system.

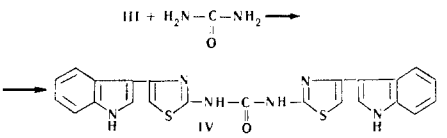
*For part XXXIII, see [1].

In order to study the pharmacological properties of the aminothiazole III, its adipate was prepared,



UV absorption spectra of 4-(3'-indolyl)-2-mercaptothiazole: (1) in ethanol; (2) in 0.05 M KOH.

this having the structure of a basic salt regardless of the method of preparation, which is confirmed by elementary analysis. The reaction of the aminothiazole III with urea gave the disubstituted urea IV:



The action of ammonium dithiocarbamate on 3-chloroacetylindole (I) in absolute methanol gave 4-(3'-indolyl)-2-mercaptothiazole (V), the structure of which was shown by the results of elementary analysis and by UV and IR spectroscopy.

It is known that 2-mercaptothiazoles exist in two tautomeric forms—thiol and thione; the latter may predominate quantitatively in solutions in certain organic solvents [3].

The absence of the absorption band of the SH group (2600–2550 cm^{-1}) from the IR spectrum (mull in paraffin oil) indicates that 4-(3'-indolyl)-2-mercaptothiazole has the thione structure in the solid state.

In an ethanolic medium, according to the UV spectrum (see figure), the thiazole V has an absorption maximum in the 332 nm region (thione form) and in an alkaline medium this maximum disappears, since the thione-thiol equilibrium is displaced in the direction of the thiol form. A similar displacement of the absorption maximum has been observed in a study of thione-thiol tautomerism [4]. 4-(3'-Indolyl)-2-mercaptothiazole readily dissolves in aqueous solutions

of alkalies. The purity of the product was established chromatographically in the ether—ethyl acetate (1 : 1) system.

It is known that substituted mercaptothiazoles are converted under the action of Raney nickel into thiazoles or, with degradation of the thiazole nucleus, into ketones [5, 6], the predominance of one process or the other depending on the medium and the activity of the catalyst, [7]. In the case of the mercaptothiazole V, regardless of the activity of the Raney nickel the thiazole ring was cleaved with the formation of 3-acetylindole, the structure of which was confirmed by elementary analysis and IR spectroscopy.

EXPERIMENTAL

All the **UV spectra** were measured on an SF-4 spectrophotometer in ethanolic solution. The **IR spectra** were recorded on a UR-10 instrument in paraffin oil. The **NMR spectra** were obtained on an INM-4H-100 spectrometer with a working frequency of 100 MHz. Deuterochloroform ($CDCl_3$) was used as the solvent and tetramethylsilane (TMS) as the intern. l standard. We take this opportunity of expressing our gratitude to Prof. Yu. N. Sheinker and to K. F. Turchin for performing the NMR spectroscopic investigations.

4-(3'-Indolyl)thiazole (II). With stirring, 5 g (26 mM) of 3-chloroacetylindole (I) was added in small portions to a mixture of 1.78 g (8 mM) of phosphorus pentasulfide, 50 ml of dry dioxane, and 1.51 ml (38 mM) of formamide. The temperature was raised gradually to 90° C and the mixture was heated at 85-90° C for 4 hr, after which 15 ml of 6.5% HCl was added and the reaction mixture was heated at 85-90° C for another hour. Then it was distilled with steam and the residue in the flask was filtered from resin and, with cooling, made alkaline with a 50% solution of NaOH. The precipitate that deposited was filtered off, washed with 50 ml of water, and dried. Yield 2 g, mp 134-135° C (from water or CCl_4). Found, %: C 66.22, 66.20; H 4.29, 4.05; N 14.04, 13.97; S 16.28, 16.21. Calculated for $C_{11}H_8N_2S$ %: C 66.00; H 4.02; N 13.97; S 16.00. IR spectrum: 3450 cm^{-1} (NH bond of indole—3490 cm^{-1}); 1570 and 1475 cm^{-1} (thiazole ring—1630, 1520 cm^{-1}) [8].

4-(3'-Indolyl)thiazole picrate, mp 217-218° C (from ethanol). Found, %: N 16.50, 16.34. Calculated for $C_{11}H_8N_2S \cdot C_6H_3(NO_2)_3OH$, %: N 16.35.

4-(3'-Indolyl)thiazole hydrochloride (VI). Absolute ether saturated with dry HCl was added to a solution of the thiazole **II** in absolute ether. The precipitate that deposited was filtered off and washed with absolute ether, mp 168-170° C (after reprecipitation from absolute ethanol with absolute ether). Found, %: N 12.12, 11.99. Calculated for $C_{11}H_8N_2S \cdot HCl$, %: N 11.83.

2-Amino-4-(3'-indolyl)thiazole (III). A suspension of 0.98 g (13 mM) of thiourea in 25 ml of distilled water was treated with 2.5 g (13 mM) of the chloroketone **I**, and the mixture was boiled for 3 hr. The hot solution was filtered and, after cooling, a 25% aqueous ammonia solution was added. An oil separated out which crystallized on trituration. The product was filtered off, washed with a large amount of water, and dried. Yield 2.43 g (mp 163-164° C, from a mixture of benzene and methanol). Found, %: C 61.53, 61.38; H 4.39, 4.36; N 19.09; 19.11; S 14.55, 14.70. Calculated for $C_{11}H_9N_3S$, %: C 61.45; H 4.19, N 19.53; S 14.88. IR spectrum: 3450, 3320, 3130 cm^{-1} (N—H and $-NH_2$ bonds) and 1650 and 1540 cm^{-1} (thiazole ring).

2-Amino-4-(3'-indolyl)thiazole adipate. A solution of 1.5 g (~10 mM) of adipic acid in 30 ml of ethanol was added to a cold solution of 4.5 g (21 mM) of the aminothiazole **III** in 30 ml of ethanol. The precipitate that deposited was filtered off, washed with 10 ml of ethanol, and dried. Yield 6.5 g, mp 208-210° C (from ethanol). Found, %: C 58.13, 58.43; H 4.89, 4.92; N 14.20, 14.31; S 10.56, 10.65. Calculated for $C_{28}H_{28}N_6O_4S_2$, %: C 58.31; H 4.89; N 14.57; S 11.12.

N, N'-Bis[4-(3'-indolyl)-2-thiazolyl]urea (IV). A solution of 1 g (4.7 mM) of the thiazole **III** in 30 ml of ethanol was treated with 0.28 g of urea and the mixture was boiled for 2 hr 30 min. The solvent was driven off in vacuum and the product dried. Yield 1 g, mp 172-174° C (from water). Found, %: C 60.48, 59.90; H 3.80, 3.70; N 18.61, 18.43; S 14.40, 14.37. Calculated for $C_{23}H_{16}N_6OS_2$, %: C 60.47; H 3.53; N 18.41; S 14.05. IR spectrum: 3420, 3220, 3130 cm^{-1} (NH bond of indole and a substituted urea); 1650 cm^{-1} (C=O). It was chromatographed in the ether—ethanol (5%) system giving $R_f = 0.45$.

4-(3'-Indolyl)-2-mercaptothiazole (V). In portions, 3 g (~16 mM) of the chloroketone I was added to a suspension of 1.7 g of ammonium dithiocarbamate [9] in 50 ml of absolute methanol. The mixture was heated in the water bath for 3 hr, and the solvent was distilled off in vacuum. With vigorous stirring, water was added to the residue until crystallization took place. The solid matter was filtered off and dried. Yield 3.5 g, mp 200-202° C (after repeated reprecipitation from a 15% solution of NaOH with 10% acetic acid). Found, %: C 56.74, 56.77; H 3.50, 3.37; N 12.26, 12.13. Calculated for $C_{11}H_8N_2S_2$, % C 56.85, H 3.47; N 12.06.

Desulfuration of 4-(3'-indolyl)-2-mercaptothiazole with Raney nickel. A mixture of 1.85 g (~11 mM) of the mercaptothiazole V and 6.65 g of Raney nickel [10] in 100 ml of methanol was boiled for 3 hr. The hot mixture was filtered and the catalyst was washed with hot methanol (2 × 30 ml). The filtrate and the methanol from the washing process were combined and the solvent was distilled off in vacuum to give 1.2 g of 3-acetylindole, mp 187-188° C (from aqueous methanol or benzene). A mixture with an authentic sample of 3-acetylindole gave no depression of the melting point. Found, %: C 75.85, 75.71; H 5.90, 5.72; N 9.00, 8.84. Calculated for $C_{10}H_9NO$, %: C 75.47; H 5.70; N 8.80. The IR spectrum: 3205 cm^{-1} (NH indole bond), 1615 cm^{-1} (C=O).

REFERENCES

1. N. N. Suvorov, V. P. Gorbunova, and K. F. Turchin, KhGS [Chemistry of Heterocyclic Compounds], 4, 1029, 1968.

2. K. Canapathi and A. Venkataraman, Proc. Indian Acad. Sci., 22A, 363, 1945.

3. Heterocyclic Compounds, Vol. 5 [Russian translation], IL, Moscow, p. 448, 1961.

4. A. Gillem and E. Stern, An Introduction to Electronic Absorption Spectroscopy in Organic Chemistry [Russian translation], IL, Moscow, p. 317, 1957.

5. C. M. Badger and N. Kowanco, J. Chem. Soc., 1652, 1957.

6. C. D. Hurd and B. Rudner, J. Am. Chem. Soc., 73, 5157, 1951.

7. H. Hauptman and W. F. Walter, Chem. Rev., 62, 347, 1962.

8. S. G. Bogomolov, Yu. N. Sheinker, and I. Ya. Postovskii, DAN, 93, 277, 1953.

9. P. L. Julian and B. M. Sturgis, J. Am. Chem. Soc., 57, 1126, 1935.

10. A. Pavlic and H. Adkins, J. Am. Chem. Soc., 68, 1471, 1946.

24 October 1966

Mendeleev Chemical and Technological Institute, Moscow