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# SYNTHESIS OF SOME SUBSTITUTED IMIDAZO [5, 1-b] BENZOTHIAZOLES

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Cyclization of formylated and acetylated α-substituted 2-aminomethylbenzothiazoles with phosphorus oxychloride gives 3-substituted imidazo [5, 1-b] benzothiazoles, and 3-substituted 1-methylimidazo [5, 1-b] benzothiazoles. Treatment of 2-benzothiazolyl-4-pyridylaminomethane with formic acid gives 3-(4-pyridyl) imidazo [5, 1-b] benzothiazole. 1-Mercapto-3-phenylimidazo [5, 1-b] benzothiazole is converted into 3-phenylimidazo [5, 1-b] benzothiazole by elimination of the mercapto group.

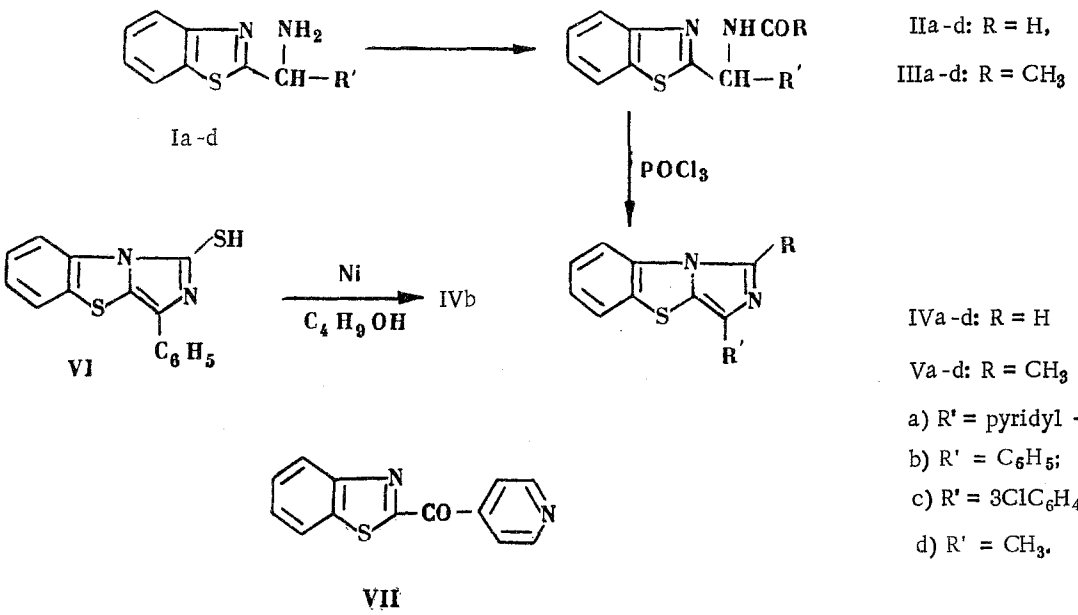
It has previously been stated [1], that α-substituted 2-aminomethylbenzothiazoles I are readily converted, by cyclization of their arylthiourea and arylurea derivatives, into 3-substituted 1-mercapto- or 1-hydroxyimidazo [5, 1-b] benzothiazoles, which are representatives of a new tricyclic system. Our aim was to obtain imidazo [5, 1-b] benzothiazoles IV, V, with position 1 unsubstituted, or carrying a methyl group, and to study their chemical behavior.

Compounds IVb-d and V were prepared by cyclizing the formyl and acetyl derivatives of the appropriate amines II, III, with phosphorus oxychloride in toluene. Actually compound IVa is prepared from the amine Ia in one stage; by refluxing Ia with 99% formic acid, imidazole ring closure is immediately effected. Obviously this peculiarity of the amine Ia is connected with the greater mobility of the hydrogen atom on its methane carbon atom, as compared with other compounds I, due to the electron-accepting effect of the pyridine portion.

It was previously stated [2] that acetylation of amine Ia with acetic anhydride gives a diacetyl derivative. It could be expected that treatment of amine Ia with glacial acetic acid or formic acid would immediately lead to cyclization or formation, indeed, of a monoacetyl derivative. However, heating Ia with acetic acid was found to give 35.4% of the monacetyl derivative IIIa, along with 33.9% of 2-benzothiazolyl-4-pyridylketone (VII) [2]. Actually VII arises by air-oxidation of amine to ketimine, followed by hydrolysis of the ketimine to ketone on treating the reaction products with water.

Compounds IV and V are crystalline, insoluble in water and ether, readily soluble in chloroform, more difficultly soluble in alcohol, methanol and benzene. They give comparatively stable hydrochlorides. Here hydrochlorides IVb, c and Vb, c are barely soluble in water, while the hydrochlorides of the other imidazo [5, 1-b] benzothiazoles are water-soluble. Their solutions are quite stable, and are not hydrolyzed in the cold.

Compound IVb was also prepared by eliminating the mercaptogroup of 1-mercapto-3-phenylimidazo [5, 1-b] benzothiazole VI, by refluxing it with Raney nickel in n-butanol.



## Experimental

2-(α-Formamidobenzyl)benzothiazole (IIb). 4 g (17 mmole) 2-(α-aminobenzyl) benzothiazole (Ib) was dissolved in 12 ml 99% formic acid, and refluxed for 4 hr. After cooling, the product was poured into 120 ml cold water, and the oil which separated was rubbed, to give colorless crystals of IIb. Yield 4.02 g (90%), mp 143-143.5° (from alcohol). Found: C 67.00; H 4.42; N 10.56; S 12.21%. Calculated for $C_{15}H_{12}N_2OS$: C 67.14; H 3.51; N 10.44: S 11.95%.

2-(α-Formamidoethyl-3-chlorobenzyl)benzothiazole (IIc) was prepared in a way similar to IIb. Yield 92.5%, mp 136.0-136.3° (from benzene). Found: C 59.47; H 3.61; Cl 12.03; N 9.27; S 10.71%. Calculated for $C_{15}H_{11}ClN_2OS$: C 59.50; H 3.66; Cl 11.71; N 9.25; S 10.59%.

2-(α-Formamidoethyl)benzothiazole (IId) was prepared in a way similar to IIb. Yield 70.0%, mp 112.5-113.5° (from benzene). Found: C 58.52; H 4.85; N 13.44; S 15.19%. Calculated for $C_{10}H_{10}N_2OS$: C 58.23; H 3.89; N 13.58; S 15.55%.

2-(α-Acetamidoethyl)benzothiazole (IIId). A mixture of 11.54 g (65 mmole) Id and 20 ml acetic anhydride was left overnight, and then mixed with 200 ml water. After three days the crystals which separated were filtered off, and washed with water. Yield 10.74 g (75%) IIId, mp 135-137° (from ethyl acetate). Found: C 60.00; H 5.57; N 12.59; S 14.55%. Calculated for $C_{11}H_{12}N_2OS$: C 59.97; H 5.49; N 12.72; S 14.56%

2-(α-Acetamidobenzyl)benzothiazole (IIIb), and 2-(α-acetamido-3-chlorobenzyl) benzothiazole (IIIc). See [1].

2-Benzothiazolyl-4-pyridylacetamidomethane (IIIa). 3.78 g (16 mmole) Ia was refluxed for 4 hr with 12 ml glacial acetic acid. After cooling the reaction products were poured into 120 ml cold water, and ammonia solution was added to bring the mixture to pH ~ 8. The yellow oil which separated was rubbed until it crystallized, the crystals filtered off, dried, and dissolved in boiling benzene (~ 100 ml). On cooling 1.56 g IIIa separated. Yield 35.4%. After recrystallizing from alcohol mp 173.0-173.5°, light yellow crystals, insoluble in water, soluble in alcohol, chloroform, boiling benzene. Found: C 63.51; H 4.66; N 15.30; S 11.25%. Calculated for $C_{15}H_{13}N_3OS$: C 63.58; H 4.63; N 14.83; S 11.32%. The benzene mother liquors were decolorized with active carbon, and evaporated. The residue (2.18 g) was recrystallized from methanol, to give a light yellow substance mp 130-131°. Mixed mp with authentic 2-benzothiazolyl-4-pyridylketone (VII) undepressed. The oxime of the substance had mp 230.5-231.5° (decomp). Mixed mp with the oxime of VII [1] undepressed.

3-(4-Pyridyl)-imidazo [5, 1-b] benzothiazole (IVa). 4 g (17 mmole) Ia was refluxed for 4 hr with 12 ml 99% formic acid, and after cooling the reaction products were poured into 120 ml cold water, after which the solution was brought to pH 9 with aqueous ammonia. 3.89 g (87.5%) IVa was obtained. Yellowish crystals (from benzene); insoluble in water, soluble in alcohol and chloroform. The Table gives properties and elementary analysis data of IVa, and of other IV and V compounds.

Substituted imidazo [5, 1-b] benzothiazoles (IV, V) (see table).

Method A. 0.01 mole of the appropriate formyl or acetyl derivative of the amine II, III, was dissolved in 18 ml dry boiling tolene, which was then cooled to 100°, 5 ml phosphorus oxychloride added, and refluxing continued until evolution of hydrogen chloride ceased. The products were evaporated to dryness in a vacuum, and the residue triturated with 20 ml water (acidified to pH ~ 1 with hydrochloric acid). The precipitate was filtered off, washed with 10% hydrochloric acid, pressed dry, suspended in 20 ml water which was then made alkaline with ammonia solution, the whole filtered, and the solid dried and purified by recrystallizing from alcohol.

Method B. Reaction was carried out in a way similar to that used in method A. The products were evaporated to dryness in a vacuum, the residue dissolved in water, and brought to pH ~ 1 with hydrochloric acid. The solution was decolorized with active carbon, made alkaline with ammonia, the precipitate filtered off, dried, and purified by recrystallizing from alcohol (Va), 50% alcohol (Vd), or ethyl acetate (IV d).

1-Methyl-3-phenyl-imidazo [5, 1-b] benzothiazole hydrochloride. 0.24 g (1 mmole) base Vb was dissolved in 2 ml alcohol-10% hydrochloric acid (1:1). On cooling colorless crystals separated (0.25 g), which were insoluble in cold water, moderately soluble in hot water, and soluble in hot alcohol, mp 260-262° (decomp). Found: Cl 12.32; S 10.96%. Calculated for $C_{16}H_{12}N_2S \cdot HCl$: Cl 11.79; S 10.66%.

Desulfurizing 1-mercapto-3-phenylimidazo [5, 1-b] benzothiazole (VI). 0.7 g (2.5 mmole) VI and about 1 g Raney nickel were refluxed together for 10 hr in 95 ml n-butanol. The catalyst was filtered off and washed with methylene chloride. The combined filtrates were evaporated to dryness in a vacuum, and the residue recrystallized from 5 ml alcohol, to give 0.22 g colorless crystals mp 158°. Mixed mp with 3-phenylimidazo [5, 1-b] benzothiazole undepressed.

Substituted Imidazo [5, 1 b] benzothiazoles (IV, V).

| R | R′ | Synthetic Method | Mp, °C | Formula | C, % | | H, % | | Cl, % | | N, % | | S, % | | $\lambda_{max}$ mμ in alcohol | Yield % |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Found | Calc. | Found | Calc. | Found | Calc. | Found | Calc. | Found | Calc. | | |
| H | $C_6H_5$ | A | 159.0—160.0 | $C_{15}H_{10}N_2S$ | 71.62 | 71.97 | 3.99 | 4.03 | — | — | 11.04 | 11.19 | 13.03 | 12.81 | 211<br>236<br>286 | 100 |
| H | 3-$ClC_6H_4$ | A | 172.0—172.5 | $C_{15}H_9ClN_2S$ | 63.26 | 63.26 | 3.02 | 3.19 | 12.84 | 12.45 | 10.01 | 9.84 | 11.46 | 11.26 | 210<br>232<br>297 | 100 |
| H | $CH_3$ | B | 133.2—133.4 | $C_{10}H_8N_2S$ | 63.83 | 63.80 | 4.13 | 4.28 | — | — | 14.99 | 14.88 | 16.83 | 17.03 | 208<br>230<br>312 | 87.6 |
| $CH_3$ | $C_6H_5$ | A | 140.0—141.0 | $C_{16}H_{12}N_2S$ | 72.62 | 72.69 | 4.57 | 4.58 | — | — | 11.03 | 10.60 | 12.01 | 12.13 | 210<br>235<br>290 | 94.0 |
| $CH_3$ | 3-$ClC_6H_4$ | A | 174.0—174.2 | $C_{16}H_{11}ClN_2S$ | 64.37 | 64.31 | 3.42 | 3.71 | 12.06 | 11.87 | 9.50 | 9.38 | 10.96 | 10.73 | 210<br>234<br>300 | 98.6 |
| $CH_3$ | $CH_3$ | B | 114.0—116.0 | $C_{11}H_{10}N_2S$ | 65.27 | 65.31 | 5.09 | 4.98 | — | — | 14.00 | 13.85 | 16.02 | 15.85 | 208<br>228<br>312 | 87.4 |
| $CH_3$ | 4-Pyridyl | B | 245.0—246.0 (decomp) | $C_{15}H_{11}N_3S$ | 67.76 | 67.90 | 4.22 | 4.18 | — | — | 15.70 | 15.84 | 11.69 | 12.08 | 208<br>234<br>332 | 73.7 |
| H | 4-Pyridyl | — | 216.0—221.0 (decomp) | $C_{14}H_9N_3S$ | 66.76 | 66.91 | 3.38 | 3.61 | — | — | 16.50 | 16.72 | 12.76 | 12.76 | 208<br>235<br>325 | 87.5 |

REFERENCES

1. V. V. Avidon and M. N. Shchukina, KhGS, 64, 1965.
2. V. V. Avidon and M. N. Shchukina, ZhOKh, 34, 2969, 1964.

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