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# Reactions with 2-Mercaptopyridoimidazole

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2-Mercaptopyridoimidazole **(1)** reacts with monochloroacetic acid to give **2**, which in turn reacts with aromatic aldehydes or aryldiazonium chloride to give **3** and **4**. On reaction with maleic anhydride **1** affords **6**. Cyanoethylation of **1** leads to the compounds **7** and **8**.

**Umsetzungen mit 2-Mercaptopyridoimidazol**

2-Mercaptopyridoimidazol **(1)** reagiert mit Monochloressigsäure und liefert das Produkt **2**. Die Verbindung **2** reagiert mit aromatischen Aldehyden und Aryldiazoniumchloriden und liefert die Verbindungen **3** und **4**. **1** reagiert auch mit Maleinsäureanhydrid und liefert **6**. Die Verbindungen **7** und **8** wurden durch Cyanoethylierung von **1** erhalten.

The fungicidal action of several organic sulphur compounds may be attributed to the presence of a N-C-S linkage, characteristic of thiazole compounds which posses considerable activity[1,2]. This work is an extension of our previous investigations[3-6]with the aim of preparing new compounds for pharmacological studies.

In this study, the action of α-halogenated acids on 2-mercaptopyridoimidazole **(1)** has been found to yield thiazolo[3,2-a]pyridoimidazol-3(2H)-one **(2)**.

Aromatic aldehydes condense readily with **2** to give the chalcones **3a–d**. The structure of **3** has been elucidated from analytical data and the IR spectrum of **3a** which shows a maximum at 1740 $cm^{-1}$ charactistic for carbonyl absorption. Hydrogen peroxide easily oxidises the sulphur atom in the thiazole ring of compound **3** to give the corresponding sulphone derivative **4**. **4** shows two short peaks in the IR spectrum at 1150 and 1350 $cm^{-1}$ characteristic for the $SO_2$ group.

In addition, comound **2** is readily coupled with diazotized amines to give the 2-arylazothiazolo[3,2–a]pyridoimidazol-3(2H)-ones **5a, b.** The structure of **5** was confirmed from analytical data. The IR spectrum of **5a** presents absorption bands at 1570 $cm^{-1}$ for the N=N group and at 1740 $cm^{-1}$ for the carbonyl group of the thiazolone ring.

It was found[7] that benzimidazole reacted with maleic anhydride to give thiazolyl[3,2–*a*]benzimidazol-3(2*H*)-one. In a similar manner **1** reacts with maleic anhydride to give thiazolyl[3,2–*a*]pyridoimidazole-3(2*H*)-one acetic acid **(6)**. The structure of **6** is established by the presence of the pyridoimidazolyl moiety of the parent compound **2** together with the carboxylic group. The IR spectrum of compound **6** shows an absorption band at 1740 $cm^{-1}$ representing the thiazolone carbonyl group and another band at 1580 $cm^{-1}$ for the carboxylate ion.

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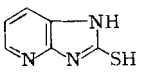
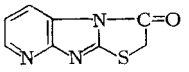
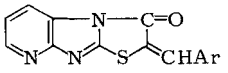
Cyanoethylation of **1** with acrylonitrile in aqueous pyridine gives 3-N-(β-cyanoethyl)-2-mercaptopyridoimidazole **(7)**. Compound **7** is readily confirmed from analytical data and the IR spectrum which shows an absorption band at 2220 $cm^{-1}$ characteristic for CN group. Similarly, ethylacrylate reacts with **1** in aqueous pyridine to give thiazino[3,2-a]pyridoimidazol-3(2*H*)-one **(8)**. Compound **7** is readily converted to **8** by hydrolysis and cyclization with hydrochloric acid acetic mixture.



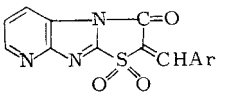
**1**



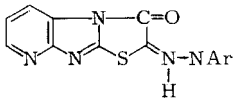
**2**



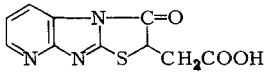
**3a**: Ar = $C_6H_5$
**b**: Ar = $C_6H_4$–$OCH_3$(o)
**c**: Ar = $C_6H_3$–$Cl_2$, (3,4)
**d**: Ar = $C_6H_4$–Br(p)



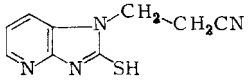
**4a**: Ar = $C_6H_5$
**b**: Ar = $C_6H_4$–Br(p)



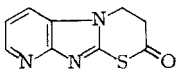
**5a**: Ar = $C_6H_5$
**b**: Ar = $C_6H_4$–Cl(p)



**6**



**7**



**8**

## Experimental Part

*MP:* uncorr. *IR spectra:* KBr) Pye Unicam SP 1000.

*Thiazolo[3,2-a]pyridoimidazol-3(2H)-one* **(2)**

A solution of 0.1 mole **1**, 0.01 mole monochloroacetic acid, 5 g anhydrous sodium acetate and 30 ml acetic anhydride was boiled under reflux for 2 h. The reaction mixture was cooled in ice. **2**: colourless crystals from ethanol, m.p. 235°C, yield 60 %. $C_8H_5NOS$ (163) Calcd. C 58.8 H 3.1 N 8.6 S 19.8; Found C 59.1 H 3.2 N 8.1 S 19.3.

*2-Arylidene-thiazolo[3,2-a]pyridoimidazol-3(2H)-ones* **3a–d**

A mixture of 0.1 mole **1**, 0.1 mole monochloroacetic acid, 0.1 mole of the appropriate aldehyde, 5 g anhydrous sodium acetate and 30 ml acetic anhydride was heated under reflux for 2 h. The reaction mixture was poured on ice. **3a:** grey crystals from acetic acid, m.p. 243°C, yield 72 %. $C_{15}H_9NOS$ (251) calcd. C 71.7 H 3.6 N 5.6 S 12.7; Found C 71.5 H 3.4 N 5.5 S 12.5. **3b:** green crystals from acetic acid, m.p. 240°C, yield 74 %. $C_{16}H_{11}NO_2S$ (281) Calcd. C 68.3 H 3.9 N 5.0 S 11.4; Found C 68.1 H 3.7 N 4.9 S 11.2. **3c:** green crystals from acetic acid, m.p. 337°C, yield 70 %. $C_{15}H_7NOSCl_2$ (320) Calcd.: C 56.4 H 2.2 N 4.4 S 10.0; Found C 56.1 H 2.1 N 4.5 S 9.8. **3d:** dark green crystals from acetic acid m.p. 310°C,

yield 67 %. $C_{15}H_8NOSBr$ (330) Calcd.: C 54.5 H 2.4 N 4.2 S 9.7; Found C 54.3 H 2.5 N 4.1 S 9.3.

*2-Arylidene-sulphothiazolo[3,2–a]pyridoimidazol-3(2H)-ones* **(4a, b)**

To a solution of 5 g **3** in glacial acetic acid, 10 ml $H_2O_2$ was added and the reaction mixture was refluxed for 2 h. The reaction mixture was cooled and poured in ice cold water. **4a:** colourless crystals from ethanol, m.p. 275°C, yield 50 %. $C_{15}H_9NO_3S$ (283) Calcd.: C 63.6 H 3.2 N 4.9; Found C 63.4 H 3.1 N 4.6. **4b:** colourless crystals from dioxane, m.p. 280°C, yield 66 %. $C_{15}H_8NO_3SBr$ (362) Calcd.: C 49.7 H 2.2 N 3.9; Found C 49.5 H 2.1 N 3.7.

*2-Arylazothiazolo[3,2–a]pyridoimidazol-3(2H)-ones* **5a, b**

**5a, b** were prepared by the action of arydiazonium salts on **2** using the same procedure described previously[8]. **5a:** red crystals from dilute acetic acid, m.p. 280°C, yield 60 %. $C_{14}H_9N_5SO$ (295) Calcd.: C 56.9 H 3.1 N 23.7 S 10.8; Found C 56.7 H 3.0 N 23.5 S 10.6. **5b:** orange crystals from acetic acid, m.p. 260°C, yield 54 %. $C_{14}H_8N_5SOCl$ (329.5) Calcd.: C 50.9 H 2.4 N 21.2 S 9.7; Found C 50.6 H 2.3 N 21.1 S 9.5.

*2-Carboxymethylthiazolo[3,2–a]pyridoimidazol-3(2H)-one* **(6)**

A mixture of 0.1 mole **1** and maleic anhydride were heated in an oil bath at 160°C for 6 h. The reaction mixture was cooled and triturated with ethanol. **6**: colourless crystals from DMF, m.p. 290 °C, yield 55 %. $C_{10}H_7N_3O_3S$ (249) Calcd.: C 48.2 H 2.8 N 16.9; Found C 48.1 H 2.6 N 16.7.

*2-N-(β-cyanoethyl)-2-mercaptopyridoimidazole* **(7)**

A mixture of 0.1 mole **1** and 0.1 mole acrylonitrile was added to 50 ml pyridine and 10 ml water. The reaction mixture was heated under reflux for 4 h, evaporated i. vac. and the resulting oily product was triturated with petroleum ether 60–80°C. The solid product was crystallized from acetic acid. **7:** colourless crystals, m.p. 240°C, yield 60 %. $C_9H_8N_4S$ (204) Calcd.: C 52.9 H 3.9 N 27.5; Found C 52.7 H 3.6 N 27.3.

*1,3-Thiazin-3-[3,2–a]pyridoimidazol-3(2H)-one* **(8)**

The same procedure described for cyanoethylation of **1** with acrylonitrile was used for the reaction of **1** with ethylacrylate to give **8**. Colourless crystals from ethanol, m.p. 140°C, yield 55 %. $C_9H_7N_3OS$ (205) Calcd.: C 52.7 H 3.4 N 20.5; Found C 52.4 H 3.2 N 20.1.

*Conversion of* **7** *to* **8**

A suspension of 0.1 mole **7** in 20 ml glacial acetic acid and 5 ml hydrochloric acid was boiled under reflux for 4 h. The solvent was removed i. vac. and the reaction mixture was triturated with water. The resulting solid product was crystallized from ethanol.

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# Anticoagulante 3-Aralkyl-4-hydroxy-2-pyrone

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Die Synthese und gerinnungsphysiologische Wirkung von 9 Titelverbindungen wird beschrieben. Nach einmaliger oraler Verabreichung von 330 mg/kg an Ratten wurden bei 6 Substanzen Prothrombinspiegel von weniger als 15 % gefunden. Bei zwei Substanzen war dies auch noch bei einer Dosis von 165 mg/kg der Fall. Bei der aktivsten Verbindung **8** war Vollwirkung bereits nach 12 h gegeben. Nach 48 h lag der Prothrombinspiegel noch unter 25 %. Die Tautomerie mit der 2-Hydroxy-4-pyronform wird diskutiert.

**Anticoagulant 3-Aralkyl-4-hydroxy-2-pyrones**

Nine title compounds were synthesized and tested for their anticoagulant activity. After oral administration of a single dose of 330 mg/kg to rats, prothrombin levels below 15 % were seen with 6 compounds. With two compounds the same result was obtained when the dose was reduced to 165 mg/kg. With the most active compound **8**, the maximum effect was reached after 12 h and maintained up to 48 h. The existence of tautomeric 2-hydroxy-4-pyrones is discussed.

Vor einiger Zeit haben wir über anticoagulante 3-Cinnamoyl-4-hydroxy-2-pyrone berichtet[1]. Hieraus ergab sich die Schlußfolgerung, daß das Auftreten anticoagulanter Wirkungen nicht an benzokondensierte Stammverbindungen wie 4-Hydroxycumarine oder 1,3-Indandione gebunden ist. Unter pharmakokinetischer Sicht war der rasche Einsatz der indirekten anticoagulanten Wirkung bemerkenswert.

Um zu wirkungsstärkeren Substanzen zu gelangen, haben wir nun einige 3-Aralkyl-4-hydroxy-2-pyrone dargestellt und geprüft. Die Auswahl der Substituenten erfolgte in Anlehnung an potente Vertreter aus der Reihe der o. g. klassischen Anticoagulantien. Das Syntheseschema ist in Abb. 1 zusammengefaßt. Ausgangspunkt aller Synthesen war Triacetsäurelacton **(1)**. Analog *Enders*[2] wurden durch Umsetzung mit Benzhydrol bzw. 4,4'-Dichlorbenzhydrol **2a** bzw. **2b** erhalten. Diese liegen zumindest im Festzustand als 4-Pyrone vor, wie die charakteristische IR-Bande [3,4] bei 1660 bzw. 1655 $cm^{-1}$ zeigt. In

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