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Antitumor pyrido[3,2-*d*][1]benzazepines: Synthesis and *in vitro* activity of thiophene analogs

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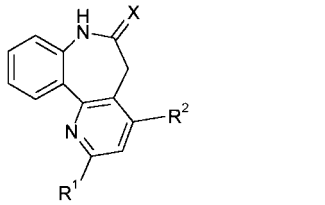
Dedicated to the memory of Dr. Kenneth D. Paull, 1942–1998

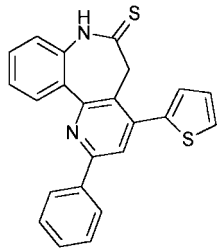
The bioisosteric replacement of benzene elements in the antitumor lead structures **2** and **3** led to the thienyl substituted 5*H*-pyrido[3,2-*d*][1]benzazepin-6(7*H*)-ones **8a** and **8b**, the analogous thiolactams **4a** and **4b**, and the 4*H*-pyrido[2,3-*d*]-thieno[3,2-*b*]azepines **11** and **12** which represent a novel heterocyclic scaffold. The *in vitro* evaluation of **4a** in a cell line based screening revealed a noteworthy antitumor activity and a remarkable selectivity for renal tumor cell lines. The cell line selectivity pattern of **4a** differs distinctly from the pattern displayed by standard antitumor agents.

1. Introduction

In the course of studies directed to the design of anticancer compounds structurally based on the [1]benzazepine skeleton, a series of pyrido[3,2-*d*][1]benzazepines of the type **1** was recently reported to exhibit *in vitro* antitumor activity in the NCl (National Cancer Institute) cell line screenig [1]. A remarkable selectivity pattern with respect to the organ-specific subpanels of the NCI tumor cell screen was observed for several members of this series. For instance, the thiolactam **2** analog of the basic structure **1** exhibited a selectivity for renal cancer cells. The bromo substituted thiolactam **3** exhibited increased potency with retained renal selectivity [1]. However, when **3** was studied *in vivo* in the hollow fiber assay in mice, it did not meet the criteria for further development [2]. One of the classical approaches in the concept of bioisosterism is the replacement of benzene for thiophene [3–5]. In an effort to design derivatives with comparable potency and selectivity pattern with respect to **3**, the analogs **4a**, **b** and **8a**, **b** were synthesized, in which the phenyl rings of **1** and **2** are replaced by thiophene. Another structural modification led to the synthesis of the pyrido[2,3-*d*]thieno[3,2-*b*]azepines **11** and **12**, which are representatives of a novel heterocyclic system. Of the compounds prepared in the course of this project, namely the thiolactam **4a** proved to exhibit equivalent activity on renal cell lines with respect to **3**, and therefore it is currently being evaluated *in vivo* by the NCl.



1 (R^1, R^2 = Ph, X = O)
2 (R^1, R^2 = Ph, X = S)
3 (R^1 = Ph, R^2 = 4-Br-Ph, X = S)



4a

2. Investigations, results and discussion

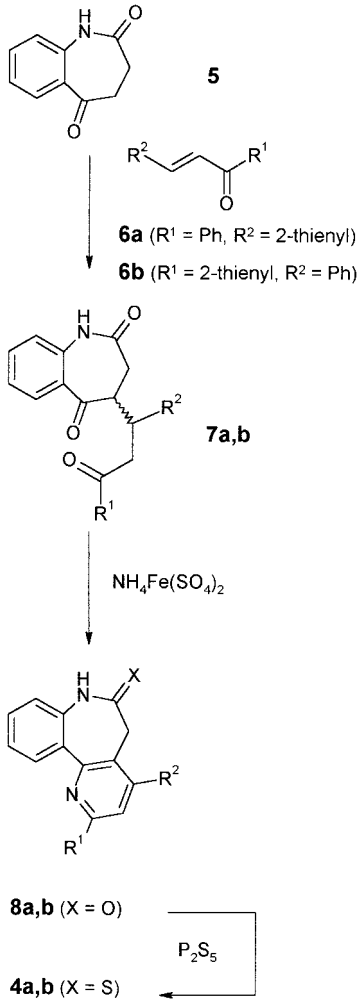
2.1. Synthesis of the compounds

The preparation of the target structures followed established procedures [6], which are outlined in Schemes 1 and 2. The 1*H*-[1]benzazepine-2,5(3*H*, 4*H*)-dione **5** [7] was reacted with an appropriate α, β-unsaturated ketone **6** in the presence of potassium hydroxide to furnish the Michael-adducts **7** as mixtures of diastereomers. Without separation of the single diastereomers, the mixtures were cyclized by means of ammonium ferric sulfate in glacial acetic acid, yielding the 2,4-diaryl-5*H*-pyrido[3,2-*d*][1] benzazepin-6(7*H*)-ones **8a** and **8b**. The conversion to the thiolactams **4** was performed with phosphorus pentasulfide. The pyrido[2,3-*d*]thieno[3,2-*b*]azepines **11** and **12** were prepared in a similar procedure, starting from 4*H*-thieno[3,2-*b*]azepine-5,8(6*H*, 7*H*)-dione **9** [7] and chalcone **6c**.

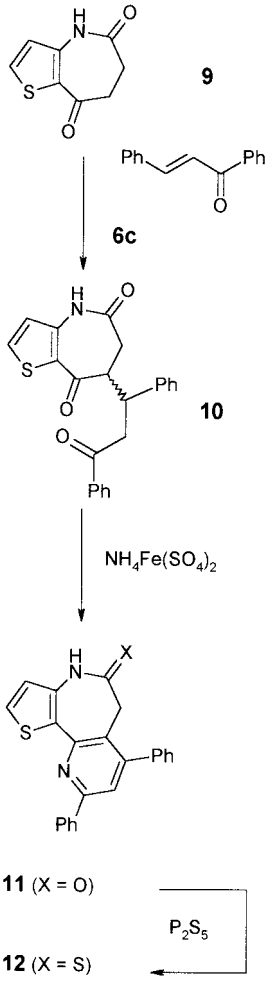
2.2. Antitumor screening

Compounds **4a**, **4b**, **8a**, **8b**, and **11** were investigated in the cell line disease oriented antitumor screening of the NCI. Reports on rationale [8–10], experimental details and reproducibility [11–13] and the manifold methods for the extraction of data from this screening program [14–16] have been published. Each compound that is submitted to the antitumor cell line screening is tested against an array of 60 tumor cell lines originating from the following sources: leukemia, non-small cell lung cancer, colon cancer, cancer of the central nervous system, melanoma, ovarian cancer, renal cancer, prostate cancer, and breast cancer. For each cell line, three parameters are calculated and provided by the NCI: log GI_{50} (GI_{50}: molar concentration inhibiting 50% net cell growth), log TGI (TGI: molar concentration for total inhibition of net cell growth), and log LC_{50} (LC_{50}: molar concentration leading to 50% net cell death). From the parameters of the distinct cell lines, averaged values are calculated for each test compound, giving a mean activity over all the tested cancer cells (MG_MID-value, see ref. [14] for details). The cell line screen is designed to discover antitumor compounds with selectivity for subpanels of the screen or with unique selectivity patterns over all cell lines. The selectivity pattern enables a prediction of the molecular target

Scheme 1



Scheme 2



of a test compound, because compounds with similar mechanisms of activity share similar activity patterns [14–17]. To illustrate the selectivity for renal cancer cell lines exhibited by the derivatives that are objectives of this report, an averaged GI_{50} value for renal cell lines was calculated, using the available results of the eight renal cancer cell lines that are included in the screen (786-0, A498, ACHN, CAKI-1, RXF-393, SN12C, TK-10, UO-31). These averaged renal antitumor activities are compared in the Fig. with the MG_MID GI_{50} values over all cell lines. The lactams **8a**, **8b** and **11** are less active and less selective with respect to the lead compound **3**. On the other hand, the thiolactams **4a** and **4b** displayed a renal selectivity comparable to **3**, but only **4a** was equipotent to **3**. Based on these preliminary *in vitro* results, **4a** is currently being evaluated *in vivo* in the programs of the NCI. Test results for thiolactam **12** are not yet available.

The molecular target of the compounds discussed in this report is hitherto unknown. The computer program COMPARE is a tool that enables the prediction of molecular mechanisms by comparing activity patterns of antitumor agents in the NCI cancer cell line screen. If COMPARE discloses a significant similarity of selectivity patterns for two different compounds in the cell line screen, these compounds probably share a common mode of action [14, 15]. Valid predictions based on this tool have been published, establishing for instance the mode of action of topoisomerase II inhibitors [18], tubulin binders [19], and dihydroorotate dehydrogenase inhibitors [20]. When **4a** was used as seed for a COMPARE analysis in a database of 171 standard antitumor agents [21], no significant correlations were found. The ten best correlations of **4a** with standard agents are given in the Table. The highest Pearson correlation coefficient (PCC) to be observed was 0.400 with bleomycin, whereas all other compounds from the standard agent database had PCCs below 0.300. These

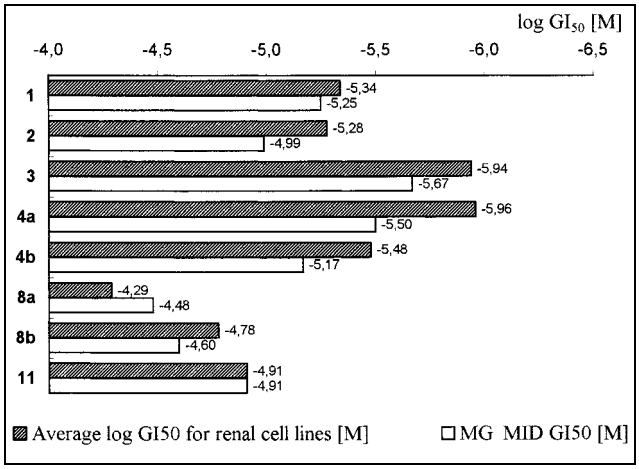


Fig.: *In vitro* antitumor activity of compounds **1**, **2**, **3**, **4a**, **4b**, **8a**, **8b**, and **11**. Given is the log of the molar concentration leading to 50% net cell growth inhibition (log GI_{50}). MG_MID: Averaged growth inhibition for all cell lines tested. Renal cell lines: 786-0, A498, ACHN, CAKI-1, RXF-393, SN12C, TK-10, UO-31. For **11** the log GI_{50} value for cell line TK-10 was not available and is therefore not included in the calculation

Table: COMPARE analysis of 4a in the standard agent database of the NCI

Rank [a]	Compound [b]	NCI identification number [b]	Pearson correlation coefficient with **4a**
1	bleomycin	NSC 125066	0.400
2	N,N-bis(2-hydroxyethyl)-2-nitro-1 *H*-imidazole-1-acetamide	NSC 314055	0.295
3	DHAD (mitoxantrone)	NSC 301739	0.283
4	chlorozotocin	NSC 178248	0.251
5	pyrazoloacridine	NSC 366140	0.249
6	O6-methylguanine	NSC 37364	0.241
7	chloroquinoxaline sulfonamide	NSC 339004	0.236
8	AZQ (diaziquone)	NSC 182986	0.229
9	penclomedine	NSC 338720	0.223
10	anthrapyrazole	NSC 355644	0.215

[a] Compounds of the NCI standard agent database are ranked by their correlation coefficient (PCC) with **4a**. [b] Structures and selectivity pattern of the standard agents are accessible from ref. [21].

correlations are much lower than the correlations usually seen between compounds with similar mechanisms of action [15, 19]. Therefore, it seems likely that the molecular mechanism by which **4a** inhibits cell growth is different from the mechanism of growth inhibition associated with any standard antitumor agent. Further investigations are underway to evaluate the mode of action of **4a** and its congeners from the pyrido[3,2-*d*][1]benzazepine series.

3. Experimental

3.1. Apparatus

Melting points were determined on an electric variable heater (Gallenkamp) and evaluated on a Mettler FP 62 automatic m.p. instrument. Elemental analyses were performed in the analytical department of the Institut für Pharmazie, Universität Hamburg. Results obtained were within ±0.4% of the calculated values (C, H, N, S). IR spectra were recorded using KBr pellets on a Pye-Unicam SP 3-200 S, a Philips PU 9712, or a Perkin Elmer 1660 FTIR spectrometer, respectively. NMR spectra were recorded on a Bruker AMX 400, using tetramethylsilane as internal standard. TLC analyses were carried out on fluorescent Polygram Sil G/UV$_{254}$ silica gel plates, using CH_2Cl_2/ethyl acetate 8 : 2 as eluent. Spots were visualized under 254 nm UV illumination. Compounds **5** and **9** were prepared by literature methods [7].

3.2. Synthesis

3.2.1. General Procedure A for the synthesis of the 2,4-diaryl-5 H-pyrido[3,2-d][1]benzazepin-6(7 H)-ones **8a**, **8b** *and 7,9-diphenyl-4 H-pyrido[2,3-d]thieno[3,2-b]azepin-5(6 H)-one* (**11**)

A slurry of 1 *H*-[1]benzazepine-2,5(3 *H*, 4*H*)-dione (**5**) [7] (352 mg, 2 mmol) or 4 *H*-thieno[3,2-*b*]azepine-5,8(6 *H*, 7*H*)-dione (**9**) [7] (362 mg, 2 mmol), the appropriate 1,3-diarylpropen-1-one **6** (2 mmol) and KOH (11 mg; 0.2 mmol) in ethanol (7 ml) was stirred at room temperature. The reaction was monitored by TLC analyses. After the starting material **5** or **9** had disappeared (5–20 h), the pH of the mixture was adjusted to 5 by dropwise addition of glacial acetic acid. A precipitate was formed, which was filtered off with suction and recrystallized once from ethanol or toluene to furnish the diastereomeric mixtures **7a**, **b** or **10**, respectively. For subsequent cyclization, a mixture of the appropriate Michael adduct **7a**, **b** or **10** (1 mmol), ammonium ferric sulfate dodecahydrate (1 g, 2.07 mmol) and ammonium acetate (1.2 g, 15.67 mmol) was refluxed under nitrogen in glacial acetic acid (7.5 ml) for 3 h. The mixture was then cooled to room temperature, poured onto crushed ice (10 g) and stirred until the ice had melted. A solid was formed, which was filtered off with suction, washed with water, and purified by recrystallization from ethanol/toluene.

3.2.1.1. 2-Phenyl-4-(2-thienyl)-5 *H*-pyrido[3,2-*d*][1]benzazepin-6(7 *H*)-one (**8a**)

Compound **8a** was prepared following general procedure A starting from **5** (352 mg, 2 mmol) and 1-phenyl-3-(2-thienyl)-2-propen-1-one (**6a**) (429 mg, 2 mmol) to furnish 37% cream-colored crystals, m.p. >270 °C (dec.); IR 3190 cm^{-1} (NH), 1680 cm^{-1}(C=O); ^{1}H NMR (400 MHz, [D$_6$]-DMSO) δ (ppm) = 3.37 (br. s, 1 H, azepine-CH$_2$, overlapping the H$_2$O-signal), 3.74 (br. s, 1 H, azepine-CH$_2$), 7.25–7.40 (m, 3 H, H arom.), 7.45–7.57 (m, 4 H, H arom.), 7.74 (dd, 1 H, J = 3.6/1.0 Hz, H arom.), 7.86 (dd, 1 H, J = 5.1/1.0 Hz, H arom.), 8.00 (s, 1 H, pyridine-H), 8.20–8.27 (m, 3 H, H arom.), 10.46 (s. 1 H, NH); ^{13}C NMR (100.6 MHz, [D$_6$]-DMSO) δ (ppm) = 35.2 (azepine-CH$_2$), 119.8, 121.5, 123.8, 125.0, 126.7, 128.3, 128.6, 128.7, 129.3, 129.9, 130.0, 130.8, 131.0, 137.5, 138.0, 138.5, 141.7, 154.60, 154.64, 171.1 (C=O).
$C_{23}H_{16}N_2OS$ (368.5)

3.2.1.2. 4-Phenyl-2-(2-thienyl)-5 *H*-pyrido[3,2-*d*][1]benzazepin-6(7 *H*)-one (**8b**)

Compound **8b** was prepared following general procedure A starting from **5** (352 mg, 2 mmol) and 3-phenyl-1-(2-thienyl)-2-propen-1-one (**6b**) (429 mg, 2 mmol) to furnish 35% gray crystals, m.p. 230 °C; IR 3180 cm^{-1} (NH), 1660 cm^{-1} (C=O); ^{1}H NMR (400 MHz, [D$_6$]-DMSO) δ (ppm) = 3.36 (br. s, 2 H, azepine-CH$_2$, overlapping the H$_2$O-signal), 7.15–7.20 (m, 1 H, H arom.), 7.22–7.28 (m, 2 H, H arom.), 7.37 (d″t″, 1 H, J = 7.6/7.6/1.0 Hz, H arom.), 7.50–7.78 (m, 6 H, H arom.), 7.96–7.97 (m, 2 H, H arom.), 8.09 (dd, 1 H, J = 8.1/1.5 Hz, H arom.), 10.40 (s, 1 H, NH); ^{13}C NMR (100.6 MHz, [D$_6$]-DMSO) δ (ppm) = 35.4 (azepine-CH$_2$), 118.6, 121.5, 123.8, 125.2, 125.9, 128.0, 128.4, 128.47, 128.53, 129.5, 129.9, 130.5, 130.8, 137.39, 137.43, 144.1, 149.3, 150.4, 153.8, 171.1 (C=O).
$C_{23}H_{16}N_2OS$ (368.5)

3.2.1.3. 7,9-Diphenyl-4 *H*-pyrido[2,3-*d*]thieno[3,2-*b*]azepin-5(6 *H*)-one (**11**)

Compound **11** was prepared following general procedure A starting from **9** (362 mg, 2 mmol) [7] and benzalacetophenone (**6c**) (416 mg, 2 mmol) to furnish 15% cream colored crystals, m.p.: 299 °C; IR 3106 cm^{-1} (NH), 1680 cm^{-1} (C=O); ^{1}H NMR (400 MHz, [D$_6$]-DMSO) δ (ppm) = 3.43 (br, s, 2 H, azepine-CH$_2$, overlapping the H$_2$O-signal), 6.96 (d, 1 H, J = 5.1 Hz, H arom.), 7.44–7.57 (m, 4 H, H arom.), 7.60 (″t″, 2 H, J = 7.1/7.1 Hz, H arom.), 7.65 (d, 2 H, J = 7.1 Hz, H arom.), 7.77 (d, 1 H, J = 5.1 Hz, H arom.), 7.92 (s, 1 H, pyridine-H), 8.21 (d, 2 H, J = 8.1 Hz, H arom.), 10.83 (s, 1 H, NH); ^{13}C NMR (100.6 MHz, [D$_6$]-DMSO) δ (ppm) = 36.6 (azepine-CH$_2$), 119.7, 121.3, 122.6, 126.6, 126.8, 128.5, 128.7, 129.3, 129.6, 137.1, 137.5, 137.8, 150.2, 150.9, 154.3, 171.1 (C=O) (two signals are not detected due to peak overlapping).
$C_{23}H_{16}N_2OS$ (368.5)

3.2.2. General Procedure B for the synthesis of the thiolactams **4a**, **4b**, *and* **12**

A solution of the appropriate lactam **8a**, **8b** or **11** in THF or 1,4-dioxane was stirred at 50 °C under nitrogen. Phosphorus pentasulfide and after one minute $NaHCO_3$ were added to the mixture, which was then refluxed under nitrogen. The reaction was monitored by TLC. If the reaction was not complete after 3 h, addition of the indicated amounts of phosphorus pentasulfide and $NaHCO_3$ was repeated and refluxing was continued for 3 h. After cooling to room temperature, the mixture was poured onto crushed ice (50 ml) and stirred until the ice had melted. The precipitate was filtered, washed with water and recrystallized from ethanol/toluene.

3.2.2.1. 2-Phenyl-4-(2-thienyl)-5 H-pyrido[3,2-*d*][1]benzazepin-6(7 *H*)-thione (**4a**)

Compound **4a** was prepared following general procedure B starting from **8a** (230 mg, 0.62 mmol) in THF (20 ml) employing phosphorus pentasulfide (224 mg, 1.0 mmol) and $NaHCO_3$ (319 mg, 3.8 mmol) to yield 45% colorless crystals, m.p.: 282 °C (dec.); IR 3170 cm^{-1} (NH); ^{1}H NMR (400 MHz, [D$_6$]-DMSO) δ (ppm) = 3.60 (br. s, 1 H, azepine-CH$_2$), 4.27 (br. s, 1 H, azepine-CH$_2$), 7.34 (dd, 1 H, J = 5.0/3.2 Hz, H arom.), 7.39 (dd, 1 H, J = 8.0/0.9 Hz, H arom.), 7.45–7.56 (m, 4 H, H arom.), 7.59 (d″t″, 1 H, J =7.6/7.6/1.6 Hz, H arom.), 7.86 (dd, 1 H, J = 5.1/1.0 Hz, H arom.), 8.01 (s, 1 H, pyridine-H), 8.18–8.25 (m, 4 H, H arom.), 12.44 (s, 1 H, NH); ^{13}C NMR (100.6 MHz, [D$_6$]-DMSO) δ (ppm) = 42.4 (azepine-CH$_2$), 120.7, 121.8, 125.6, 126.77, 126.84, 128.1, 128.7, 129.4, 130.0,

131.2, 132.1, 137.6, 137.8, 138.2, 141.9, 154.0, 155.0, 200.3 (C=S) (two signals are missing due to peak overlapping).
$C_{23}H_{16}N_2OS$ (384.5)

3.2.2.2. 4-Phenyl-2-(2-thienyl)-5 *H*-pyrido[3,2-*d*][1]benzazepine-6(7 *H*)-thione (**4b**)

Compound **4b** was prepared following general procedure B starting from **8b** (350 mg, 0.95 mmol) in 1,4-dioxane (30 ml) employing phosphorus pentasulfide (400 mg, 1.8 mmol) and $NaHCO_3$ (585 mg, 7.0 mmol) to yield 44% colorless crystals, m.p. 281 °C (dec.); IR 3130 cm^{-1} (NH); ^1H NMR (400 MHz, [D_6]-DMSO) δ (ppm) = 3.60 (br. s, 1 H, azepine-CH_2), 4.67 (br. s, 1 H, azepine-CH_2), 7.32–7.35 (m, 1 H, H arom.), 7.40 (d, 1 H, J = 7.6 Hz, H arom.), 7.45–7.56 (m, 4 H, H arom.), 7.60 (d″t″, 1 H, J = 7.6/7.6/1.0 Hz, H arom.), 7.86 (d, 1 H, J = 5.1 Hz, H arom.), 8.01 (s, 1 H, pyridine-H), 8.18–8.25 (m, 4 H, H arom.), 12.44 (s, 1 H, NH); ^{13}C NMR (100.6 MHz, [D_6]-DMSO) δ (ppm) = 43.4 (azepine-CH_2), 121.7, 122.8, 126.5, 127.7, 129.1, 129.7, 130.0, 131.0, 132.2, 127.8, 133.1, 138.5, 138.8, 139.1, 142.9, 154.9, 156.0, 201.3 (C=S) (two signals are not detectable because of peak overlapping).
$C_{23}H_{16}N_2OS$ (384.5)

3.2.2.3. 7,9-Diphenyl-4 *H*-pyrido[2,3-*d*]thieno[3,2-*b*]azepine-5(6 *H*)-thione (**12**)

Compound **12** was prepared following general procedure B starting from **11** (70 mg, 0.19 mmol) in THF (10 ml) employing phosphorus pentasulfide (150 mg, 0.68 mmol) and $NaHCO_3$ (215 mg, 2.5 mmol) to yield 73% colorless crystals, m.p.: 292 °C (dec.); IR 3140 cm^{-1} (NH); ^1H NMR (400 MHz, [D_6]-DMSO) δ (ppm) = 3.92 (s, 2 H, azepine-CH_2), 7.10 (d, 1 H, J = 5.6 Hz, H arom.), 7.45–7.61 (m, 6 H, H arom.), 7.76–7.81 (m, 3 H, H arom.), 7.93 (s, 1 H, pyridine-H), 8.20 (d, 2 H, J = 6.6 Hz, H arom.), 12.74 (s, 1 H, NH); ^{13}C NMR (100.6 MHz, [D_6]-DMSO) δ (ppm) = 44.0 (azepine-CH_2), 120.7, 122.7, 126.7, 128.2, 128.4, 128.5, 128.7, 129.4, 129.8, 122.6, 130.7, 137.2, 137.6, 150.4, 150.6, 154.7, 196.4 (C=S) (one signal missing due to peak overlapping).
$C_{23}H_{16}N_2OS$ (384.5)

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4-Dialkylamino-1,2-anthrachinon-1/2-arylhydrazone

H.-J. KALLMAYER und U. BOCK

Herrn Prof. Dr. C. H. Brieskorn mit allen guten Wünschen zum 85. Geburtstag gewidmet

4-Dialkylamino-1,2-anthrachinone **3** kondensieren in salzsaurem DMSO mit dem Arylhydrazinen **4** zu roten 4-Dialkylamino-1,2-anthrachinon-1-arylhydrazonen **5** und zu blauen 4-Dialkylamino-1,2-anthrachinon-2-arylhydrazonen **6**, deren Farbigkeit im Hinblick auf die ähnlich farbigen 4-Dialkylamino-1,2-naphthochinon-1/2-arylhydrazone diskutiert wird.

4-Dialkylamino-1,2-anthraquinone-1/2-arylhydrazones

4-Dialkylamino-1,2-anthraquinones **3** condense in hydrochloric DMSO with arylhydrazines **4** to give the red 4-dialkylamino-1,2-anthraquinone-1-arylhydrazones **5** and the blue 4-dialkylamino-1,2-anthraquinone-2-arylhydrazones **6**. The colours of these are discussed with regard to the similar coloured 4-dialkylamino-1,2-naphthoquinone-1/2-arylhydrazones.