Monatshefte für Chemie 129, 1199–1205 (1998)

Monatshefte für Chemie
Chemical Monthly

Printed in Austria

Reaction of 4-Hydroxyacridin-9(10*H*)-one and 4-Hydroxyacridine-9(10*H*)-thione with α,ω-Alkyl Dibromides

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Summary. Starting from 4-hydroxyacridin-9(10*H*)-one (**1**) and 4-hydroxyacridine-9(10*H*)-thione (**2**), a series of *bis*-derivatives was prepared, among them the bridged *bis*-acridin-(10*H*)-ones **9–14** and the *bis*-mercapto-(9*H*)-acridines **15–18**. The reactivity of the 2- and 4-hydroxy series was compared; it was found that it is harder to demethylate 4-methoxy derivatives than their 2-methoxy analogues.

Keywords. 4-Hydroxyacridinone; 4-Hydroxyacridine thione; 4-Methoxyacridinone; 4-Methoxyacridine thione; Alkylation.

Reaktion von 4-Hydroxyacridin-9(10*H*)-on und 4-Hydroxyacridin-9(10*H*)-thion mit α,ω-Alkyldibromiden

Zusammenfassung. Ausgehend von 4-Hydroxyacridin-9(10*H*)-on (**1**) und 4-Hydroxyacridin-9(10*H*)-thion (**2**) wurde eine Serie von *bis*-Derivaten, unter ihnen die verbrückten *bis*-Acridin-9(10*H*)-one **9–14** und die *bis*-Mercapto-(9*H*)-acridine **15–18**, hergestellt. Die Reaktivität der 2- und 4-Hydroxyderivate wurde verglichen; es wurde festgestellt, daß die 4-Methoxyderivate schwerer zu demethylieren sind als die 2-Methoxyderivate.

Introduction

Compounds like 4-hydroxyacridin-9(10*H*)-one (**1**) [1] and 4-hydroxyacridine-9(10*H*)-thione (**2**) present an interesting case of ambident reactivity since they can be alkylated or acylated at the oxygen (or sulfur) and nitrogen atoms of the ring as well as at the 4-hydroxy group [2–4]. Moreover, the resulting derivatives are important from biological and supramolecular points of view, particularly in the case of compounds containing several acridine units (Scheme 1) [5–8]. In this paper we will report on the reactivity of compounds **1** and **2** and some of their N- and O-methyl derivatives towards alkylating and acylating agents.

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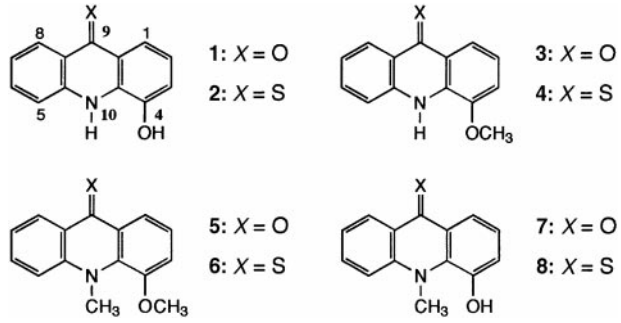


Scheme 1

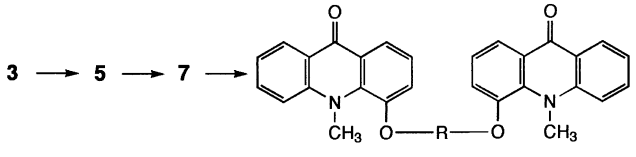
Results and Discussion

When the acridinone is N-substituted, further substitution can only take place at the 4-hydroxy group. We studied the case of 4-hydroxy-10-methylacridin-9-one (**7**). This compound was obtained by demethylation of 4-methoxy-10-methylacridin-9-one (**5**) [9] by means of HBr (Scheme 2). **5** was prepared by N-methylation of 4-methoxyacridin-9(10*H*)-one (**3**) [1] under phase transfer catalysis (PTC) conditions.

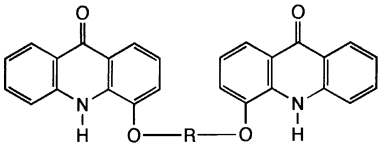
Alkylation of **7** with alkyldihalides under PTC conditions afforded the *bis*-acridinone diethers **10** and **11**. An attempt to prepare the corresponding acridinone diesters using thallium salts [10] and acylating agents failed; however, this reaction gave good yields in the 2-hydroxy series [4] (Scheme 1). Compounds **9**, **10**, and **11** were characterized by their ^{13}C NMR spectra (cf. Experimental).

A similar study with the corresponding thione **8** was not possible since it could not be prepared. Two approaches were attempted: treatment of **7** with either *Lawesson* reagent [11, 12] or P_4S_{10} (note that **6** was obtained from **5** using P_4S_{10}) [13, 14] and demethylation of **6** with HBr (only **7** was obtained) or with $C_2H_5SH/AlCl_3$ [15, 16] (no reaction was observed).

Alkylation of **1** with several dialkylhalides under PTC conditions afforded a mixture of isomers from which the 4,4′-bridged *bis*-acridines **12**, **13**, and **14** were isolated by crystallization from ethanol. Proof for the 4,4′-symmetrical acridinone structure of **12**, **13**, and **14** was derived from their ^{13}C NMR spectra which display only one group of signals for the heterocycle together with a signal at 171 ppm



Scheme 2

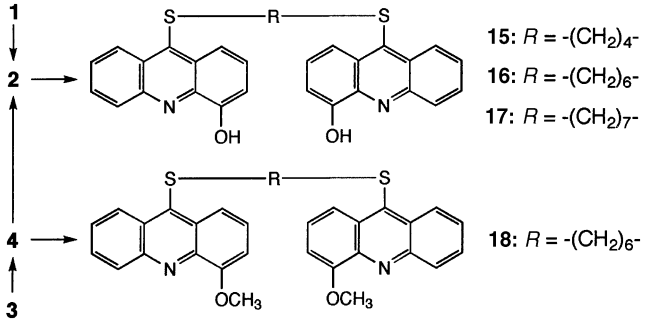


12: $R = -(CH_2)_4-$

13: $R = -(CH_2)_2-O-(CH_2)_2-$

14: $R = -(CH_2)_2-O-(CH_2)_2-O-(CH_2)_2-$

Scheme 3



15: $R = -(CH_2)_4-$

16: $R = -(CH_2)_6-$

17: $R = -(CH_2)_7-$

18: $R = -(CH_2)_6-$

Scheme 4

(C-9) and one at 70–72 ppm for the two -O-CH_2- groups. The other regioisomers, if present, could not be identified (Scheme 3).

The results obtained in the case of acridinethiones **2** and **4** are summarized in Scheme 4. The only practical procedure to prepare **2** was treating **1** with P_4S_{10} since demethylation of **4** by means of HBr led to complex mixtures. For instance, treating **4** with HBr for 4 days led to a mixture of **1** (40%), **2** (40%), **3** (10%), and **4** (10%); after 8 days, only **1** was obtained. The reaction of **2** and **4** with alkyldihalides afforded the 9,9′-bridged *bis*-mercaptoacridines **15**, **16**, **17**, and **18** (only, 1,6-dibromohexane was used). The demethylation of **18** to **15** failed, whereas 2-methoxy dimers resulted in 2-hydroxy derivatives [4] (Scheme 4).

The S-substitution and the symmetry pattern of compounds **15**, **16**, **17**, and **18** was established from their ^{13}C NMR Spectra. The signal of C-9 is shifted from 194–195 ppm in thiones to 134.5 ppm in thioethers; moreover, the terminal methylene groups appear at 36 ppm which is characteristic for -S-CH_2-moieties.

Conclusions

This study has established two facts:
i) 2-OCH_3 and 4-OCH_3 derivatives of the title compounds behave quite differently; the former (48 h in all cases) [4] are much easier to demethylate than the latter (5 days for **3**, 8 days for **5**).
ii) Concerning the regioselectivity, 4-hydroxy derivatives behave similarly to 2-hydroxy derivatives [4], although the yields differ (Table 1).

Table 1. Alkylation yields of hydroxy derivatives (%)

	2-OH derivatives	4-OH derivatives [4]
9	86	60
10	95	60
11	90	70
12	64	50
13	41	33
14	28	20
15	86	80
16	49	90
17	46	70

Experimental

Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker AMX-200 spectrometer. ^{1}H and ^{13}C chemical shifts (δ, ppm) were measured relative to internal Me_4Si. Elemental analyses (C, H, N) agreed with the calculated values.

4-Hydroxyacridine-9(10H)-thione (**2**; $C_{13}H_9NOS$)

A mixture of 1.5 g 4-hydroxyacridin-9(10*H*)-one (**1** [1]: 7 mmol), 2 g tetraphosphorus decasulfide (4.5 mmol), and 20 ml hexamethylphosphorotriamide was refluxed for 48 h. After cooling, the solution was poured into cold water. A red precipitate was obtained, filtered, and dried before crystallization from methanol. Yield: 55%; m.p.: 213°C; ^{1}H NMR (200 MHz, δ, *DMSO*-d_6): 9.1–7.1 (m, 7H) ppm.

4-Hydroxy-10-methylacridin-9-one (**7**; $C_{14}H_{11}NO_2$)

A mixture of 3.7 g 4-methoxy-10-methylacridin-9-one (**5** [9]; 15 mmol) and 165 ml hydrobromic acid (48%) was refluxed for 24 h. After cooling, the solution was poured into cold water. The precipitate obtained by addition of diluted ammonia was filtered and crystallized from ethanol.

Yield: 80%; m.p.: >260°C; ^{1}H-NMR (200 MHz, δ, *DMSO*-d_6): 8.3–7.0 (m, 7H), 4.0 (s, 3H) ppm).

General procedure for the preparation of 4,4′-(α″,ω″-dioxaalkyl)-bis-(10-methylacridin-9-ones) **9**, **10**, and **11**

A mixture of 2.25 g 4-hydroxy-10-methylacridin-9-one (**7**, 10 mmol), 1.14 g triethylbenzylammonium chloride (*TEBAC*) (5 mmol), 50 ml 50% aqueous potassium hydroxide, 100 ml toluene, and 6 mmol α,ω dibromoalkane was refluxed for 4 h. The precipitate was separated, the organic layer evaporated, and another crop was obtained. The solids (identical by ^{1}H NMR) were mixed and crystallized from ethanol.

4,4′-(1″,6″-dioxahexyl)-bis-(10-methylacridin-9-one) (**9**; $C_{32}H_{28}N_2O_4$)

Yield: 60%; m.p.: >260°C; ^{1}H NMR (200 MHz, δ, CF_3CO_2D): 8.9–7.6 (m, 14H), 4.8 (s, 6H), 4.5 (m, 4H), 2.5 (m, 4H) ppm; ^{13}C NMR (50 MHz, δ, CF_3CO_2D): 117.99 (C-1), 128.54 (C-2), 119.32

(C-3), 152.28 (C-4), 120.94 (C-5), 140.81 (C-6), 126.63 (C-7), 128.85 (C-8), 171.00 (C-9), 44.84 (C-10), 120.53 (C-9a), 138.58 (C-4a), 147.15 (C-10a), 117.99 (C-8a), 72.32 (CH_2-α), 27.80 (CH_2-β) ppm.

4,4′-(1″,8″-Dioxaoctyl)-bis-(10-methylacridin-9-one) (**10**; $C_{34}H_{32}O_2N_4$)

Yield: 60%; m.p.: >260°C; ^{1}H NMR (200 MHz, δ, CF_3CO_2D): 8.9–7.6 (m, 14H), 4.8 (s, 6H), 4.45 (m, 4H), 2.5–1.7 (m, 8H) ppm; ^{13}C NMR (50 MHz, δ, CF_3CO_2D): 117.85 (C-1), 128.35 (C-2), 119.29 (C-3), 152.41 (C-4), 120.96 (C-5), 140.59 (C-6), 126.52 (C-7), 128.93 (C-8), 170.93 (C-9), 44.89 (C-10), 120.47 (C-9a), 138.66 (C-4a), 147.10 (C-10a), 117.93 (C-8a), 72.65 (CH_2-α), 30.69 (CH_2-β) ppm.

4,4′-(1″,10″-Dioxadecyl)-bis-(10-methylacridin-9-one) (**11**; $C_{36}H_{36}N_2O_4$)

Yield: 70%; m.p.: >260°C; ^{1}H NMR (200 MHz, δ, CF_3CO_2D):P 8.9–7.6 (m, 14H), 4.8 (s, 6H), 4.35 (m, 4H), 2.5–1.5 (m, 12H) ppm; ^{13}C NMR (50 MHz, δ, CF_3CO_2D): 117.34 (C-1), 128.10 (C-2), 119.25 (C-3), 152.33 (C-4), 120.70 (C-5), 140.33 (C-6), 126.36 (C-7), 128.77 (C-8), 170.63 (C-9), 44.74 (C-10), 120.30 (C-9a), 138.48 (C-4a), 146.86 (C-10a), 117.75 (C-8a), 72.84 (CH_2-α), 30.79 (CH_2-β), 30.56 (CH_2-γ), 27.78 (CH_2-δ) ppm.

General procedure for the preparation of 4,4′-(a″,ω″-dioxaalkyl)-bis-(acridin-9(10H)-ones) **12**, **13**, and **14**

A mixture of 2.11 g 4-hydroxyacridin-9(10*H*)-one (**1**, 10 mmol), 1.14 g *TEBAC* (5 mmol), 50 ml 50% aqueous potassium hydroxide, 100 ml toluene, and 6 mmol α,ω-dibromoalkane was refluxed for 4 h. The resulting viscous product solidifies when poured into water. The precipitate was filtered, dried, and crystallized from ethanol.

4,4′-(1″,6″-Dioxahexyl)-bis-(acridin-9(10H)-one) (**12**; $C_{30}H_{24}N_2O_4$)

Yield: 50%; m.p.: >260°C; ^{1}H NMR (200 MHz, δ, CF_3CO_2D): 8.9–7.3 (m, 14H), 4.5 (m, 4H), 2.4 (m, 4H) ppm; ^{13}C NMR (50 MHz, δ, CF_3CO_2D): 116.54 (C-1), 129.06 (C-2), 117.00 (C-3), 149.31 (C-4), 120.93 (C-5), 140.05 (C-6), 125.88 (C-7), 128.60 (C-8), 171.31 (C-9), 117.83 (C-9a), 135.22 (C-4a), 142.41 (C-10a), 117.58 (C-8a), 71.72 (CH_2-α), 27.12 (CH_2-β) ppm.

4,4′-(1,4,7-Trioxaheptyl)-bis-(acridin-9(10H)-one) (**13**; $C_{30}H_{24}N_2O_5$)

Yield: 33%; m.p.: >260°C; ^{1}H NMR (200 MHz, δ, CF_3CO_2D): 8.9–7.3 (m, 14H), 4.6 (m, 8H) ppm; ^{13}C NMR (50 MHz, δ, CF_3CO_2D): 117.08 (C-1), 128.80 (C-2), 117.33 (C-3), 148.67 (C-4), 120.70 (C-5), 139.76 (C-6), 125.85 (C-7), 128.11 (C-8), 171.40 (C-9), 117.33 (C-9a), 134.75 (C-4a), 142.18 (C-10a), 117.33 (C-8a), 70.94 (CH_2-α), 69.62 (CH_2-β) ppm.

4,4′-(1,4,7,10-Tetraoxadecyl)-bis-(acridin-9(10H)-one) (**14**; $C_{32}H_{28}N_2O_6$)

Yield: 20%; m.p.: 170°C; ^{1}H NMR (200 MHz, δ, CF_3CO_2D): 9.0–7.5 (m, 14H), 4.6 (m, 12H) ppm; ^{13}C NMR (50 MHz, δ, CF_3CO_2D): 117.00 (C-1), 128.75 (C-2), 117.30 (C-3), 148.61 (C-4), 120.70 (C-5), 139.83 (C-6), 125.82 (C-7), 128.05 (C-8), 171.15 (C-9), 117.76 (C-9a), 134.70 (C-4a), 142.05 (C-10a), 117.30 (C-8a), 71.70 (CH_2-α), 69.80 (CH_2-β), 71.20 (CH_2-γ) ppm.

General procedure for the preparation of 9,9′-(α″,ω″-dithiaalkyl)-bis-(4-hydroxyacridines) **15**, **16**, and **17**

A mixture of 1.9 g 4-hydroxyacridine-9(10H)-thione (**2**, 8.3 mmol), 0.8 g *TEBAC* (3.5 mmol), 85 ml 50% aqueous potassium hydroxide, 165 ml toluene, and 5 mmol α,ω-dibromoalkane was refluxed for 5 h. The resulting viscous product solidifies when poured into water. The precipitate was filtered, dried, and washed with hot methanol.

9,9′-(1″,6″-Dithiahexyl)-bis-(4-hydroxyacridine) (**15**; $C_{32}H_{28}N_2O_2S_2$)

Yield: 80%; m.p.: 167°C; ^{1}H NMR (200 MHz, δ, CF_3CO_2D): 9.3–7.7 (m, 14H), 3.6–3.1 (m, 4H), 2.0–1.2 (m, 8H) ppm; ^{13}C NMR (50 MHz, δ, CF_3CO_2D): 120.73 (C-1), 130.85 (C-2), 122.13 (C-3), 147.65 (C-4), 121.53 (C-5), 140.12 (C-6), 130.15 (C-7), 130.85 (C-8), 167.19 (C-9), 132.75 (C-9a), 133.88 (C-4a), 139.77 (C-10a), 131.52 (C-8a), 42.13 (CH_2-α), 32.17 (CH_2-β), 29.69 (CH_2-γ) ppm.

9,9′-(1″,8″-Dithiaoctyl)-bis-(4-hydroxyacridine) (**16**; $C_{34}H_{32}N_2O_2S_2$)

Yield: 90%; m.p.: >300°C; ^{1}H NMR (200 MHz, δ, CF_3CO_2D): 9.3–7.4 (m, 14H), 3.6–3.1 (m, 4H), 2.0–1.1 (m, 12H) ppm; ^{13}C NMR (50 MHz, δ, CF_3CO_2D): 120.38 (C-1), 130.51 (C-2), 121.80 (C-3), 147.44 (C-4), 120.94 (C-5), 139.75 (C-6), 130.00 (C-7), 130.51 (C-8), 166.83 (C-9), 131.75 (C-9a), 133.37 (C-4a), 140.50 (C-10a), 131.42 (C-8a), 42.21 (CH_2-α), 31.76 (CH_2-β), 29.98 (CH_2-γ), 29.65 (CH_2-δ) ppm.

9,9′-(1″,9″-Dithianonyl)-bis-(4-hydroxyacridine) (**17**; $C_{35}H_{34}N_2O_2S_2$)

Yield: 70%; m.p.: >300°C; ^{1}H NMR (200 MHz, δ, CF_3CO_2D): 9.3–7.4 (m, 14H), 3.6–3.1 (m, 4H), 2.0–1.0 (m, 14H) ppm; ^{13}C NMR (50 MHz, δ, CF_3CO_2D): 120.53 (C-1), 130.58 (C-2), 121.82 (C-3), 147.39 (C-4), 121.47 (C-5), 139.98 (C-6), 130.15 (C-7), 130.58 (C-8), 167.75 (C-9), 132.01 (C-9a), 133.48 (C-4a), 139.48 (C-10a), 131.34 (C-8a), 42.47 (CH_2-α), 32.17 (CH_2-β), 30.62 (CH_2-γ), 30.31 (CH_2-δ), 29.94 (CH_2-ε) ppm.

9,9′-(1″,6″-dithiahexyl)-bis-(4-methoxyacridine) (**18**; $C_{34}H_{32}N_2O_2S_2$)

A mixture of 1.14 g 4-methoxy-10-acridine-9(10H)-thione (**4**,5 mmol), 50 ml 50% aqueous potassium hydroxide, 100 ml toluene, and 0.77 ml 1,6-dibromohexane (1.22 g, 6 mmol) was refluxed for 3 h. The residual viscous product was separated, and the organic layer was evaporated *in vacuo*. The residue from evaporation was poured into water. The precipitate thus obtained and the viscous residue (identical by ^{1}H NMR) were mixed, washed with warm ether, and dried.

Yield: 70%; m.p.: 138°C; ^{1}H NMR (200 MHz, δ, CF_3CO_2D): 8.9–7.4 (m, 14H), 2.85 (s, 6H), 2.8 (m, 4H) 1.50 (m, 2H), 1.35 (m, 6H) ppm; ^{13}C NMR (50 MHz, δ, CF_3CO_2D): 119.86 (C-1), 130.93 (C-2), 120.44 (C-3), 152.08 (-C4), 121.25 (C-5), 140.23 (C-6), 130.09 (C-7), 130.77 (C-8), 166.88 (C-9), 132.04 (C-9a), 132.67 (C-4a), 139.56 (C-10a), 131.48 (C-8a), 42.15 (CH_2-α), 32.18 (CH_2-β), 29.70 (CH_2-γ), 57.58 (OCH_3) ppm.

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Received April 15, 1998. Accepted (revised) June 22, 1998