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Reactions of Thioquinanthrene with Alcoholates

Sulfuration of Azines, IV.

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Reactions of thioquinanthrene (**1**) with primary and secondary sodium alcoholates yielded sodium 4-[1-alkyl-4(1*H*)-quinolon-3-ylthio]-3-quinolinethiolates (**2**), which were characterized by their *S*-methyl derivatives (total yields 70-90%).

[Keywords: O—N Alkylrearrangement; 1,4-Dithiinodiquinoline; Nucleophilic aromatic substitution; 4(1H)-Quinolones; Quinolyl-quinolonyl sulfides]

Die Reaktionen von Thiochinantren mit Alkoholaten. Sulfurierung von Azinen, 4. Mitt.

Die Reaktionen von Thiochinantren (**1**) mit primären und sekundären Natrium-Alkoholaten führten zu Natrium-4-[1-Alkyl-4(1*H*)-chinolon-3-ylthio]-3-chinolinthiolaten (**2**), die als *S*-Methylderivate charakterisiert wurden (Gesamtausbeute 70—90%).

Introduction

In previous paper[1] we reported on cleavage reactions of the 4-quinolyl-sulfur bond in a 1,4-dithiin ring of thioquinanthrene (**1**) with sulfide ions. It prompted us to study the reactions of thioquinanthrene (the main product of quinoline sulfuration[2]) with other nucleophilic agents. For purposes of comparison with the previously applied soft S^{-2} base we now used the hard oxygen bases: HO^-, RO^-, AcO^- and PhO^-. In the case of hydroxyl and alcoholate ions, the reactions proceeded with a 100% dithiin—**1** conversion, but no reaction with phenolate and acetate ions was observed. The reactions with KOH or NaOH yielded

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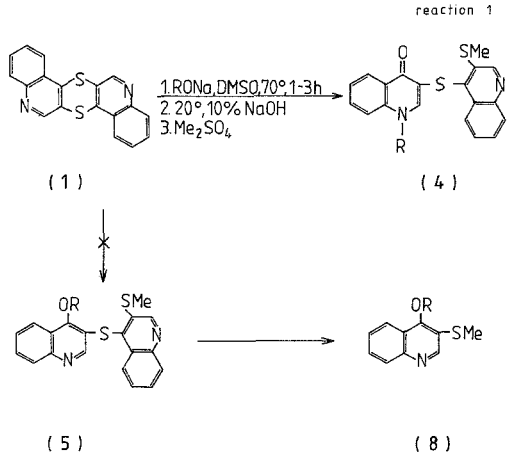
several products (cf. Table 1), whereas those with alcoholates gave high yields quinolyl-quinolonyl sulfides (**4**) instead of the expected diquinolyl sulfides (**5**) or products of a complete cleavage of 1,4-dithiin ring (**8**) (see Scheme 1).

Scheme 1



The unexpected results of thioquinanthrene reactions with alcoholates encouraged us to perform the present study.

Results and Discussion

Structure and Spectroscopic Data of the Products

It was to be expected that reactions of dithiin (**1**) with alcoholates would proceed with the formation of sodium 4-[3-(4-alkoxyquinolyl)-thio]-3-quinolinethiolate, and then sodium 4-alkoxy-3-quinolinethiolate (**6**), whereas methylation of thiolates would yield their corresponding *S*-methyl derivatives **5** or **8** (see Scheme 1 and Scheme 2). In fact, elementary analysis data as well as molecular weight of the products obtained corresponded to structure **5**; however, their ^{1}H NMR spectra revealed a signal of only one "quinoline" H-2 proton at $\delta = 8.80$–8.85 ppm. A signal of the second H-2 proton occurs at 8.05–8.11, i.e. within the region of occurrence of H-2 proton signals in 1-alkyl-4(1*H*)-quinolones[3,4]. Thus molecules of the products obtained in reaction 1 contained quinoline as well as quinolonyl units and their structures are shown by formula **4**. Differences in the spectral position of signals of groups $-OCH_n$ and $>NCH_n$ have little identificational value, and cannot serve as a direct distinction between structures **4** and **5**.

IR spectra ($CHCl_3$ solution) of reaction **1** products reveal a medium intensive band of valence vibration of the CO—C=C group (for sulfides **4a** and **4b** $\nu C=O = 1610\,cm^{-1}$), similar to those found in the case of *N*-substituted-4-(1*H*)-quinolones; for 1-methyl-3-methylthio-4-(1*H*)-quinolone (**9a**) $\nu C=O = 1620\,cm^{-1}$ (Ref.[4]). No similar band was observed for 4-methoxy-3-methylthioquinolines (**8a**). (Sulfides **4a** and **4b** recyclize to dithin **1** on pressing pellets with KBr.)

A comparison of UV spectra of products of reaction 1 with model compounds indicates the *N*-alkyl-4-(1*H*)-quinolone form of these products e.g. sulfide **4a**, because for 4-methoxy-3-methylthioquinoline (**8a**) $\lambda_{max} = 332\,nm$ (1310), but for *N*-methyl-3-methylthio-4-(1*H*)-quinolone (**9a**) $\lambda_{max} = 338$ (8820), 378 (2200), and for sulfide **4a** $\lambda_{max} = 337{,}5$ (19600), 370 (11820).

Conditions of the Reaction

It was found that the reaction of cleaving the 4-quinolyl-sulfide bond in the thioquinanthrene molecule with oxygen nucleophilic agents proceeds easily (room temp., 1 h) in aprotic solvents *DMSO* and *DMF*. No reactions were observed in boiling water but in alcohol solutions they occured at 180-200°, yielding a complex mixture of products. It can be seen from the data listed in Table 1 that thioquinanthrene (**1**) in *DMSO* solutions reacts easily (100% conversion) with primary and secondary alcoholates, and with little difficulty with sodium or

Table 1. *Experimental data of the reaction of thioquinanthrene with oxygen nucleophilic agents*

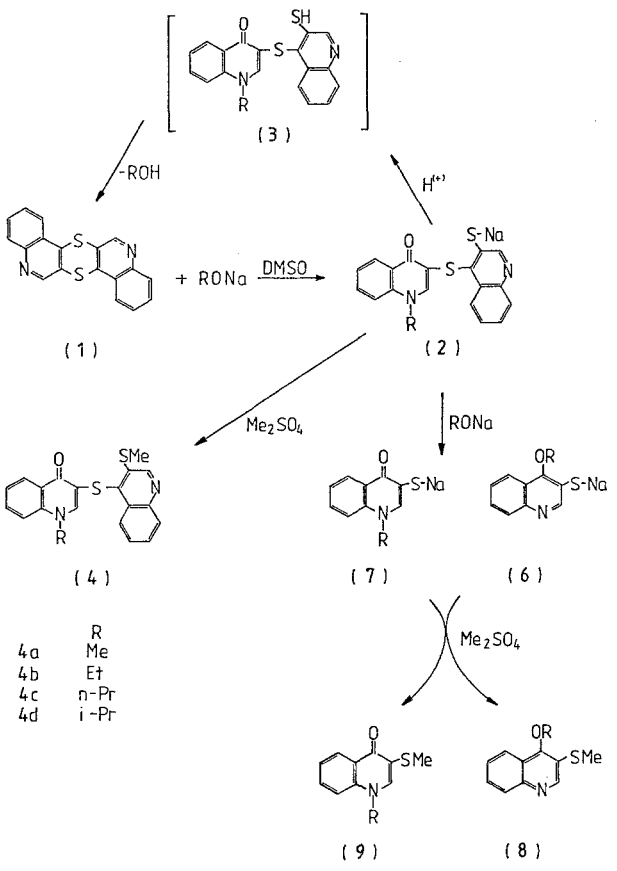
No.	Nucleophilic agent	Temperature °C	Time h	Conversion %	Main product	Yield %
1	CH_3O^-	70	0.5	100	**4a**	91.5
2	CH_3O^-	20	1	100	**4a**	76.5
3	CH_3O^-	70	3	100	**4a**	56.0
4	$C_2H_5O^-$	70	0.5	100	**4b**	91.5
5	$CH_3CH_2CH_2O^-$	70	0.5	100	**4c**	79.0
6	$(CH_3)_2CHO^-$	70	0.5	100	**4d**	70.0
7	OH^-	70	3	31.5	**4a**, **8a**, **9a** and 5 other compounds	—
8	OH^-	95	24	100	**9a**	58.5
9	$C_6H_5O^-$	70	3	—	—	—
10	CH_3COO^-	70	3	—	—	—

potassium hydroxides; however, it does not react with sodium phenolate and sodium acetate. On the other hand, the conversion of thioquinanthrene in reactions with sodium *t*-butanolate reached 72%, but these reactions yielded products different from sulfides **4**. [Similar products were observed in reactions of thioquinanthrene with dimsyl ion $CH_3S(O)CH_2^{(-)}$ formed from sodium hydride and *DMSO*; a study of these reactions is now in progress].

We could not isolate pure free thiols of type **3** which recyclized again to thioquinanthrene after aqueous *DMSO* solutions of thiolates **2** were acidized ($pH \sim 5$). Recyclization also occurs on oxidizing thiolates **2** with such oxidants as I_2 in KI water solution or H_2O_2 in aqueous ethanol. That is why we characterized the products **2**, **6**, and **7** as their *S*-methyl derivatives **4**, **8**, and **9**.

Scheme 2 illustrates the reactions and isolation of the products.

Scheme 2

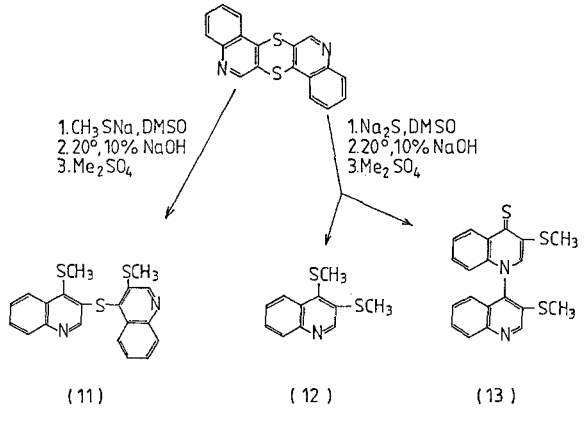


In contrast to the results obtained in the reaction of cyclic 3,4-dithioquinolines (such as thioquinanthrene) with alcoholates the same reaction of non-cyclic 3,4-dithioquinolines [3,4-dimethylthioquinoline (**12**) and 3′,4-dimethylthio-3,4′-diquinolyl sulfide (**11**)] gave 4-alkoxy-3-methylthioquinolines but corresponding 1-alkyl-4(1*H*)-quinolones were found with lower yields.

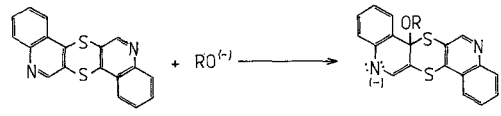
The instability of sulfide **4** in the presence of nucleophilic agents in *DMSO* solutions was tested in the reaction of sulfide **4a** with sodium methanolate, which gave 4-methoxy-3-methylthioquinoline (**8a**) (83%) (a product formed from the "quinoline" part) and 1-methyl-3-methylthio-4(1*H*)-quinoline (**9a**) (32%) (a product formed from the "quinolonyl" part). It seems that the instability of sulfides **4** and probably also that of thiolates **2** is connected with the reactivity of the quinolonyl ring caused by nucleophilic oxygen reactants.

Reaction of thioquinanthrene with sulfur nucleophilic agents methanethiolate ion and sulfide ion gave analogously products to expected oxygen ones: **11** (90%) and **12** (12%) and an unexpected one: **13** (65%) (see Scheme 3).

Scheme 3



We assume, that the reaction of thioquinanthrene with alcoholates proceeds through an additive intermediate complex A (Ref.[5]).



complex A

Unusual steric and electronic structure (amide-type anion) of complex A would cause its O—N-rearrangement with formation of thiolate **2**.

We have found no *N*-alkylation of thioquinanthrene in *DMSO* solutions using ethyl bromide or methyl iodide at 40-70° for 4 or 24 hours. Therefore, we believe that the formation of sulfide **2** does not proceed through the stage of *N*-alkylthioquinanthrenium salts occurrence.

Experimental

Melting points were determined on a Boetius heated table and were not corrected. ^{1}H NMR spectra were recorded on a Varian Anaspect EM 360 spectrometer at 60 MHz in $CDCl_3$ or *DMSO-d*$_6$ solutions using *TMS* or *HMDSO* as internal standards. Mass spectra were determined on a LKB S spectrometer at 15 and 70 eV, and at temp. 80-100°. IR spectra were taken on an UR-10 (Carl Zeiss) in KBr pellets and chloroform solutions. UV-Vis spectra were obtained in 95% ethanol solutions by means of a Carry 118 C spectrometer. TLC analyses were performed employing Merck's silica gel G and solution of CCl_4: isopropanol/150: 7 (*v/v*) as developing system or Merck's aluminium oxide neutral (typ E) and methylene chloride or solution of CCl_4: isopropanol/320: **1** (*v/v*) as developing systems.

Sodium alcoholates were prepared from sodium and anhydrous boiling alcohols. The excess of alcohol was removed using a water bath with rotatory evaporator at vacuum.

Sodium phenolate was obtained according to[6]. Commercial (p.a.) potassium and sodium hydroxides and fresh prepared anhydrous sodium acetate were used.

Thioquinanthrene (**1**) was isolated from quinoline exhaustive sulfuration products and crystallized from dimethylformamide; m.p. 314-315° (lit.[7] m.p. 314-315°); TLC analyses revealed one spot only.

3,4-Dimethylthioquinoline (**12**) was isolated from quinoline sulfuration reaction products[2].

3',4-Dimethylthio-3,4'-diquinolyl sulfide (**11**) was prepared from thioquinanthrene and sodium methanethiolate (see experimental procedure 1 below) with 90% yield, m.p. 142-143° (acetone, hexane). NMR: H-2: 8.75 s, 2 H; $H_{arom.}$: 7.75-8.85 m, 8 H; CH_3S: 2.60 s, 6 H. MS (70 eV): *m/e* = 380 (*M*$^+$, 36.3%); 333 (*M*—CH_3S, 74.9), 318 (*M*—CH_3S and —CH_3, 100). $C_{20}H_{16}N_2S_3$ (380).

1-[3-methylthio-4-quinolyl]-3-methylthio-4(1H)-thioquinolone (**13**) was obtained from anhydrous sodium sulfide and thioquinanthrene (see below, procedure 1). After crystallization from ethanol pale yellow plates were obtained (65%). NMR: H-2: 8.96 s, 1 H; H-2': 7.94 s, 1 H; $H_{arom.}$: 7.50-8.62 m, 8 H; CH_3S: 2.57 s, 3 H; CH_3S: 2.61 s, 3 H. MS (70 eV): *m/e* = 380 (*M*$^+$, 26.0), 333 (*M*—CH_3S, 55.8), 318 (*M*—CH_3S and CH_3, 100%). $C_{20}H_{16}N_2S_3$ (380).

3,4-Dimethylthioquinoline (**12**) (yield ca. 12%) was detected in the thioquinolone **13** crystallization filtrate.

4-Methoxy-3-methylthioquinoline (**8a**) was obtained in reaction of sulfide **4a** with sodium methanolate (see below, procedure 2). M.p. 26-27°. NMR: H-2: 8.80 s, 1 H; CH_3O: 3.96 s, 3 H; CH_3S: 2.38 s, 3 H; $H_{arom.}$: 7.40-8.20 m, 4 H. MS (70 eV): *m/e* = 205 (*M*$^+$, 100%), 190 (*M*—CH_3, 41.7%). $C_{11}H_{11}NSO$ (205).

1-Methyl-3-methylthio-4(1H)quinolone (**9a**) was prepared by thermal rearrangement of ether **8a** (1 mmol, 200°, 30 min; 95% yield). M. p. 118–121° (Ref.[3] 123–124°). NMR: H-2: 7.75 s, 1 H; CH_3S: 2.41 s, 3 H; NCH_3: 3.80 s, 3 H; $H_{arom.}$: 7.15–8.45 m, 4 H. MS (70 eV): $m/e = 205$ (M^+, 51.9%), 172 (M—SH, 100). $C_{11}H_{11}NSO$ (205).

1. *General procedure of the thioquinanthrene reactions with sodium alcoholates*

Thioquinanthrene **1** (3.18 g, 10 mmol), freshly prepared sodium alcoholate (usually 60 mmol) and dimethyl sulfoxide (70 ccm) were stirred for 1 h at 70°. The cool reaction mixture was poured into a solution of 24 g sodium hydroxide in 150 ccm of water. Residual unreacted thioquinanthrene was filtered off and the filtrate was methylated on stirring with dimethyl sulfate (2.4 ccm) or methyl iodide (0.8 ccm). Stirring was continued for 0.5 h and then the mixture was cooled to 10°. Yellow-brown sulfide **4** was filtered off, dried on air and crystallized from methanol, ethanol, acetone or hexane. The reaction parameters and results are given in Table 1.

A water filtrate was extracted several times with chloroform. The chloroform extracts were combined, washed with water and dried over anhydrous sodium sulfate. Stripping of chloroform left a mixture (ca. 5% per weight of products) of alkoxyquinoline **8** and 4(1*H*)-quinolone **9** type compounds.

Sulfides:

4a: M. p. 131–132°. NMR: H-2: 8.85, s, 1 H; H-2′: 8.11 s, 1 H; CH_3S: 2.50 s, 3 H; NCH_3: 4.10 s, 3 H; $H_{arom.}$: 7.40–8.50 m, 8 H. MS (70 eV): $m/e = 364$ (M^+, 100%), 349 (M—CH_3, 8), 302 [M—(N)—CH_3 and CH_3S 45.0]. $C_{20}H_{16}N_2S_8O$ (364).

4b: M. p. 105–106°. NMR: H-2: 8.85 s, 1 H; H-2′: 8.10 s, 1 H; CH_3S: 2.50 s, 3 H; NCH_2: 4.15–4.55 q, 2 H, $J = 6$ Hz; CH_3—C: 1.30–1.60 t, 3 H, $J = 6$ Hz; $H_{arom.}$: 7.30–8.50 m, 8 H. MS (70 eV): $m/e = 378$ (M^+, 100%), 350 (M—C_2H_4, 9.5), 303 (M—C_2H_4 and CH_3S, 39.3), 302 (M—C_2H_5 and CH_3S, 63.1), $C_{21}H_{18}N_2S_2O$ (378).

4c: M. p. 83–84°. NMR: H-2: 8.80 s, 1 H; H-2′: 8.05 s, 1 H; CH_3S: 2.43 s, 3 H; NCH_2: 4.05–4.30 t, 2 H, $J = 7$ Hz; C—CH_2—C: 1.60–2.00 m, 2 H, $J = 6$ Hz, $J = 7$ Hz; CH_3—C: 0.90–1.15 t, $J = 6$ Hz; $H_{arom.}$: 7.30–8.45 m, 8 H. MS (70 eV): $m/e = 392$ (M^+, 100%), 350 (M—C_3H_6, 19.4), 303 (M—C_3H_6 and CH_3S, 63.4), 302 (M—C_3H_7 and CH_3S, 35.8). $C_{22}H_{20}N_2S_2O$ (392).

4d: M. p. 84–85°. NMR: M-2: 8.85 s, 1 H, H-2′: 8.05 s, 1 H; CH_3S: 2.60 s, 3 H; NCH: 4.80–5.25 q, 1 H, $J = 6$ Hz; CH_3C 1.45–1.55 d, 6 H, $J = 6$ Hz; $H_{arom.}$: 7.40–8.40 m, 8 H. MS (70 eV): $m/e = 392$ (M^+, 87.2%), 350 (M—C_3H_6, 86.3), 303 (M—C_3H_6 and CH_3S, 91.5), 302 (M—C_3H_7 and CH_3S, 48.3). $C_{22}H_{20}N_2S_2O$ (392).

2. *Reactions of 4-substituted-3-methylthioquinolines* (**4**), (**11**) *and* (**12**) *with sodium methanolate*

5 mmol of sulfides **4** or **11** or **12**, 40 ccm of dimethylsulfoxide and 1.62 g (30 mmol) of sodium methanolate were stirred at 70° for 1 h. A cooled reaction mixture was poured in 90 ccm of 10% sodium hydroxide water solution and extracted several times with chloroform. Chloroform extract (marked as CE I) were washed 3 times with water and dried over anhydrous sodium sulfate. Chloroform was distilled off yielding mainly 4-methoxy-3-methylthioquinoline (**8a**) and some amounts of 1-methyl-3-methylthio-4(1*H*)-quinolone (**9a**). Water solution of thiolate was methylated on stirring with 0.6 ccm of dimethyl sulfate.

The methylated product was isolated from chloroform extracts (marked as CE II) as above.

Results:

Substrate	Products	
	from extract CE I	from extract CE II
4a	**8a** 83%, **9a** 3%	**9a** 29%
11	**8a** 57%, **9a** 4%	**9a** 8%, **12** 72%
12	**8a** 30%, **9a** 3%	

3. *Attempts on oxidation of thiolates* **2** (in analogy to[8,9])

The reaction mixture resulting from the reaction of thioquinanthrene (10 mmol) and sodium methanolate according to exper. procedure **1** was poured:

a) into the solution of sodium hydroxide (6 g) in 250 ccm of water or 60% ethanol. Then an excess of 30% hydrogen peroxide was added dropwise on stirring up to the end of yellow-orange solid formation. The solid was filtered off, washed with water and identified as thioquinanthrene (45-52%). The same results were obtained using an iodine-potassium iodide solution as oxidant.

b) into 200 ccm of water and then cautiously acidified (to *pH*-5) with 2% HCl solution. Orange-red solid of thiol **3** was quickly separated by centrifugation, washed with water and suspended in 2% NaOH solution (100 ccm). Yellow solid was then filtered off and identified as thioquinanthrene (9%). The filtrate was oxidized with an iodine-potassium iodide solution, but only thioquinanthrene was obtained (44%).

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