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A convenient method for the conversion of the three thieno-fused quinoline *N*-oxides to the corresponding 4-oxo-4,5-dihydrothienoquinolines is described. They have been alkylated with dimethylaminoethyl and dimethylaminopropyl chlorides. The reaction of the three thieno-fused quinolines with dimethyl acetylenedicarboxylate has been studied, as well as their reactions with butyllithium and LDA.

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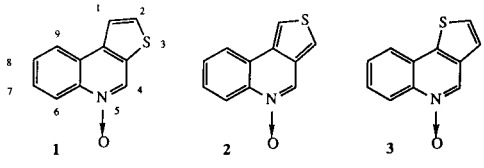
Introduction.

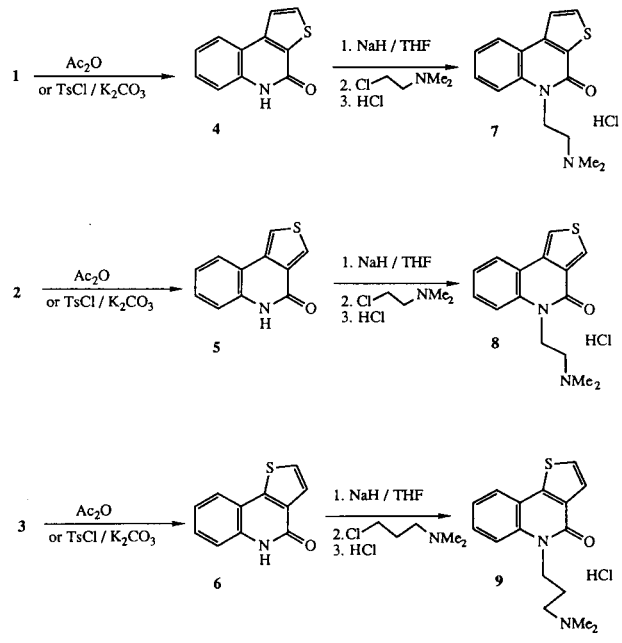
Convenient methods for the preparation of the three isomeric thieno-fused quinoline *N*-oxides **1-3** have recently been described [1,2]. Aromatic nitration [3] and bromination [4] have been investigated. The orientation obtained in the nitration reaction was in accordance with MNDO calculation [5]. We have now investigated some other reactions of compounds **1-3**. It is well known [6] that pyridine *N*-oxides can be converted to pyridones [6a]. Klemm *et al.* found [6b] that refluxing of thieno[2,3-*b*]pyridine 7-oxide with acetic anhydride, followed by hydrolysis, produced a mixture of thieno[2,3-*b*]pyrid-6(7*H*)-one and 5-hydroxythieno[2,3-*b*]pyridine in 13% and 4% yield, respectively. We found that treatment of **1-3** with tosyl chloride and aqueous potassium carbonate in chloroform at room temperature gave higher yields than refluxing with acetic anhydride. In this way, 4-oxo-4,5-dihydrothieno[2,3-*c*]-quinoline (**4**), 4-oxo-4,5-dihydrothieno[3,4-*c*]quinoline (**5**) and 4-oxo-4,5-dihydrothieno[3,2-*c*]quinoline (**6**) were obtained in about 80% yield. The anions of **4-6** generated *in situ* using sodium hydride in THF were alkylated with 2-dimethylaminoethyl chloride and 3-dimethylaminopropyl chloride to obtain compounds with potential psycho-pharmacological properties. The infrared spectrum (C=O, 1650-1665 cm^{-1}) revealed exclusive formation of *N*-alkylated products (Scheme 1).



1 **2** **3**

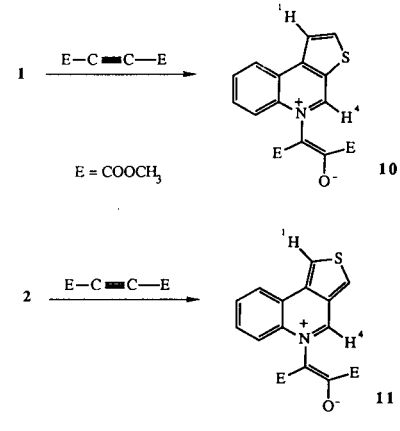
We reacted the c-fused system **2** with dimethyl acetylenedicarboxylate, expecting 1,4-addition over the thiophene ring, which after elimination of sulfur should give a phenanthridine derivative. However this reaction did not occur. Instead, **2** as well as **1** reacted analogously to isoquinoline *N*-oxide and phenanthridine *N*-oxide. Acheson and co-workers [7] and Huisgen *et al.* [8] found the latter compound to give phenanthridinium-5-vinyl oxide. Thus, thieno[3,4-*c*]quinolinium-5-(1,2-dimethoxycarbonylvinyl 2-oxide) (**11**) and thieno[2,3-*c*]quinolinium-5-(1,2-dimeth-

Scheme 1



oxycarbonylvinyl 2-oxide) (**10**) were obtained in good yields. The infrared spectrum of **11** showed two ester carbonyl absorptions (1730 and 1670 cm^{-1}), and a strong band at 1550 cm^{-1} associated with the carbon-oxygen stretching in enolate anions. Its mass spectrum showed a parent peak (M = 343), the stepwise loss of two ester groups, and the

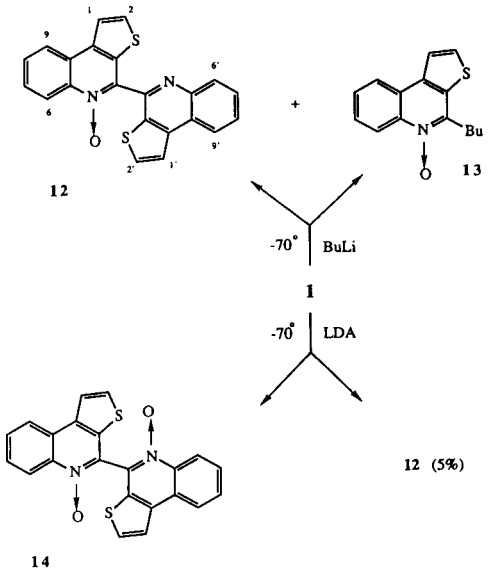
Scheme 2



base peak at M-158, corresponding to the loss of the 5-substituent. The ^{1}H nmr spectrum showed two 3-proton singlets, at 3.97 and 3.64 ppm, and the characteristic long-range coupling between H1 and H4 (J_{14} = 0.4 Hz) also confirmed the structure (Scheme 2). The mechanism of this interesting reaction is not known, although Huisgen [8] assumes that the first step is a 1,3-dipolar addition, followed by rapid rearrangement.

Attempts to functionalize the thiophenic α-position by metallation with butyllithium or LDA, followed by reaction with electrophiles, were unsuccessful. With butyllithium at −70°, compound **1** gave 50% of 4,4′-dithieno[2,3-*c*]quinolyl 5-oxide (**12**) and 16% of 4-*n*-butylthieno[2,3-*c*]quinoline *N*-oxide (**13**). In order to avoid the addition of butyllithium across the azomethine bond, LDA was used. This gave now 4,4′-dithieno[2,3-*c*]quinolyl 5,5′-dioxide (**14**). The structures of the dithienoquinolyl *N*-oxide and dithienoquinolyl *N,N*′-dioxide were revealed by their mass and nmr spectra. The mass spectrum of **12** showed a parent peak (M = 384), the loss of one oxygen atom (M-16), and the base peak at (M-16)/2 = 184, corresponding to the breakdown of the dimer. In contrast, the fragmentation pattern of the dioxide **14** showed a small parent peak (M = 400), the stepwise loss of two oxygen atoms, and the same base peak at 184 (Scheme 3).

Scheme 3



The symmetrical compound **14**, showed only six proton signals in the ^{1}H nmr, while the ^{1}H nmr spectrum of the unsymmetrical compound **12** showed twelve different proton signals, one of which (H_6) was more deshielded than the other protons, owing to the neighbouring oxygen atom. In addition, a Hetcor experiment (twelve proton-bearing carbon atoms) also confirmed the structure. The behavior of **1** is different from that of pyridine *N*-oxides which react with butyllithium at low temperatures to give the 2-lithiopyridine *N*-oxides, which react with carbon dioxide to give acids and with esters to give ketones [9,10]. However, with slower-reacting electrophiles, such as *N,N*-dimethylacetamide and benzonitrile, dimeric products were obtained in low yields. The formation of **12** might be similarly explained by the addition of the 4-lithium derivative of **1** to another molecule of **1**, followed by elimination of lithium hydroxide. The formation of **14** is more difficult to explain. However, it brings to mind the reactions of quinoline and of isoquinoline with LDA, in the presence of HMPA, which give 2,2′-diquinolyl and 1,1′-diisoquinolyl in good yield [11]. It is interesting to note that under similar reaction conditions, phenanthridine *N*-oxide reacted with butyllithium to give only the butyl-substituted product. However, using LDA, the starting *N*-oxide was recovered, indicating restricted formation of the dimer compounds probably due to steric hindrance between the oxygen atoms and the neighbouring (*peri*) hydrogens [12].

EXPERIMENTAL

Melting points are uncorrected. The ^{1}H nmr spectra were recorded on a Varian XL-300 spectrometer. The mass spectra were recorded on a Finnigan 4021 spectrometer. The glc analyses were carried out on a Varian 3700 gas chromatograph using an OV-17, 3%, 2m column.

General Procedure for the Reaction of Thieno[*c*]quinoline *N*-oxides **1-3** with Acetic Anhydride.

A mixture of 0.2 g (1 mmole) of **1-3**, 0.5 ml of acetic anhydride and 0.4 ml of glacial acetic acid was heated for two hours at 130°. At the end of the reaction period, the acetic anhydride and acid were removed under reduced pressure and the residue was treated with 5 ml of 5% sodium hydroxide solution. The resulting precipitate was filtered off and washed with water. After recrystallization from ethanol, **4**, **5** and **6** were obtained in 43%, 56% and 42% yield, respectively.

General Procedure for the Reaction of Thieno[*c*]quinoline *N*-oxides **1-3** with Tosyl Chloride.

A heterogeneous reaction mixture consisting of 0.2 g (1 mmole) of **1-3**, 0.21 g (1.1 mmoles) of tosyl chloride in 6 ml of chloroform and 6 ml of 10% potassium carbonate was shaken at room temperature for 30 minutes. The resulting precipitate was separated by filtration, washed with water, dried and then triturated thoroughly with ether to remove unreacted tosyl chloride. After recrystallization from ethanol, **4**, **5** and **6** were obtained in 84%, 80% and 82% yield, respectively.

4-Oxo-4,5-dihydrothieno[2,3-*c*]quinoline (**4**).

This compound was obtained as colorless needles (ethanol), mp 236-237°; ir: NH 3440, CO 1640 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 7.88 (m, 1H, H_6), 7.78 (d, 1H, H_1), 7.71 (d, 1H, H_2), 7.41 (m, 1H, H_9), 7.18-7.35 (m, 2H, H_7H_8), $J_{1,2}$ = 5.1 Hz.

Anal. Calcd. for $C_{11}H_7NOS$: C, 65.6; H, 3.48; N, 6.96. Found: C, 65.1; H, 3.65; N, 7.12.

4-Oxo-4,5-dihydrothieno[3,4-*c*]quinoline (**5**).

This compound was obtained as colorless needles (ethanol), mp 232-233°; ir: NH 3450, CO 1650 cm^{-1}; ^1H nmr (DMSO-d_6): δ 8.31 (d, 1H, H_3), 7.91 (d, 1H, H_1), 7.85 (m, 1H, H_6), 7.25 (m, 1H, H_9), 7.08-7.23 (m, 2H, H_7H_8), $J_{1,3}$ = 3.2 Hz.

Anal. Calcd. for $C_{11}H_7NOS$: C, 65.6; H, 3.48; N, 6.96. Found: C, 65.3; H, 3.57; N, 7.18.

4-Oxo-4,5-dihydrothieno[3,2-*c*]quinoline (**6**).

This compound was obtained as colorless needles (ethanol), mp 228-230°; ir: NH 3450, CO 1650 cm^{-1}; ^1H nmr (DMSO-d_6): δ 7.57 (d, 1H, H_3), 7.44 (d, 1H, H_2), 7.70 (m, 1H, H_6), 7.36 (m, 1H, H_9), 7.1-7.28 (m, 2H, H_7H_8), $J_{2,3}$ = 5.2 Hz.

Anal. Calcd. for $C_{11}H_7NOS$: C, 65.6; H, 3.48; N, 6.96. Found: C, 65.1; H, 3.61; N, 7.21.

General Procedure for the Reaction of Thieno[*c*]quinolones **4-6** with 2-Dimethylaminoethyl Chloride and with 3-Dimethylaminopropyl Chloride.

To a cold solution of 0.2 g (1 mmole) of **4-6** in 4 ml of anhydrous THF, 0.03 g (1.25 mmoles) of sodium hydride was added in three portions. After being stirred under nitrogen for 10 minutes, 0.2 g (2 mmoles) of 2-dimethylaminoethyl chloride (or 3-dimethylaminopropyl chloride in the preparation of **9**) was added to the solution and the reaction mixture was refluxed for 6 hours. The solid (sodium chloride) was separated by filtration and the solvent was removed under reduced pressure. The oily residue was dissolved in 10 ml of ether. To the ethereal solution saturated ether-hydrogen chloride solution was added and the resulting precipitate was filtered off. After recrystallization from ethanol, **7**, **8** and **9** were obtained in 52%, 48% and 54% yield, respectively.

5-(2-Dimethylaminoethyl)-4-oxo-4,5-dihydro[2,3-*c*]quinoline Hydrochloride (**7**).

This compound was obtained as colorless needles (ethanol), mp 257-258°; ir: CO 1650-1655 cm^{-1}; ^1H nmr (DMSO-d_6): δ 8.32 (m, 1H, H_6), 8.24 (d, 1H, H_1), 8.13 (d, 1H, H_2), 7.85 (m, 1H, H_9), 7.42-7.69 (m, 2H, H_7H_8), 4.72 (t, 2H, N-CH_2), 2.91 (s, 6H, N-Me_2), 2.60 (m, 2H, CH_2-N), $J_{1,2}$ = 5.2 Hz.

Anal. Calcd. for $C_{15}H_{16}N_2SO{\cdot}HCl$: C, 58.3; H, 5.25; N, 9.08. Found: C, 58.24; H, 5.50; N, 9.08.

5-(2-Dimethylaminoethyl)-4-oxo-4,5-dihydro[3,4-*c*]quinoline Hydrochloride (**8**).

This compound was obtained as colorless needles (ethanol), mp 248-250°; ir: CO 1650-1660 cm^{-1}; ^1H nmr (DMSO-d_6): δ 8.73 (d, 1H, H_3), 8.38 (d, 1H, H_1), 8.10 (m, 1H, H_6), 7.93 (m, 1H, H_9), 7.5-7.7 (m, 2H, H_7H_8), 4.58 (t, 2H, N-CH_2), 2.83 (s, 6H, N-Me_2), 2.58 (m, 2H, CH_2-N), $J_{1,3}$ = 3.1 Hz.

Anal. Calcd. for $C_{15}H_{16}N_2SO{\cdot}HCl$: C, 58.3; H, 5.25; N, 9.08. Found: C, 58.2; H, 5.25; N, 9.08.

5-(3-Dimethylaminopropyl)-4-oxo-4,5-dihydro[3,2-*c*]quinoline Hydrochloride (**9**).

This compound was obtained as colorless needles (ethanol), mp 228-231°; ir: CO 1645-1660 cm^{-1}; ^1H nmr (DMSO-d_6): δ 8.12 (d, 1H, H_3), 7.87 (d, 1H, H_2), 8.05 (m, 1H, H_6), 7.75 (m, 1H, H_9), 7.45-7.62 (m, 2H, H_7H_8), 4.62 (t, 2H, N-CH_2), 2.98 (s, 6H, N-Me_2), 2.42 (m, 2H, CH_2-N), 1.85 (m, 2H, -CH_2-), $J_{2,3}$ = 5.1 Hz.

Anal. Calcd. for $C_{16}H_{18}N_2SO{\cdot}HCl$: C, 59.5; H, 5.57; N, 8.67. Found: C, 59.3; H, 5.77; N, 8.47.

Reaction of Thieno[*c*]quinoline *N*-Oxides **1** and **2** with Dimethyl Acetylenedicarboxylate.

To a benzene solution (8 ml) of 0.2 g (1 mmole) of **1** or **2**, 0.16 g (1.2 mmoles) of dimethyl acetylenedicarboxylate was added. The reaction mixture was stirred at room temperature for 24 hours, whereupon the resulting precipitate was filtered off. The residual yellow solids were recrystallized from DMF to give **10** and **11** in 92% and 90% yield, respectively.

Thieno[2,3-*c*]quinolinium-5-(1,2-dimethoxycarbonylvinyl 2-Oxide) (**10**).

This compound was obtained as yellow needles, mp 253-254°; ir: esters 1730, 1670, enolate 1550 cm^{-1}; ^1H nmr (deuteriochloroform): δ 9.32 (d, 1H, H_4), 8.48 (d, 1H, H_2), 8.43 (m, 1H, H_6), 8.40 (m, 1H, H_9), 8.21 (dd, 1H, H_1), 7.88-7.98 (m, 2H, H_7H_8), 3.97 (s, 3H, CH_3), 3.64 (s, 3H, CH_3), $J_{1,2}$ = 5.3 Hz, $J_{1,4}$ = 0.4 Hz.

Anal. Calcd. for $C_{17}H_{13}NO_5S$: C, 59.5; H, 3.79; N, 4.08. Found: C, 59.6; H, 3.80; N, 4.06.

Thieno[3,4-*c*]quinolinium-5-(1,2-dimethoxycarbonyl 2-Oxide) (**11**).

This compound was obtained as yellow needles, mp 250° dec; ir: esters 1730, 1660, enolate 1550 cm^{-1}; ^1H nmr (deuteriochloroform): δ 9.27 (d, 1H, H_4), 8.85 (d, 1H, H_3), 8.28 (dd, 1H, H_1), 8.18 (m, 1H, H_6), 7.93 (m, 1H, H_9), 7.46-7.58 (m, 2H, H_7H_8), $J_{1,3}$ = 3.2 Hz, $J_{1,4}$ = 0.4 Hz.

Anal. Calcd. for $C_{17}H_{13}NO_5S$: C, 59.5; H, 3.79; N, 4.08. Found: C, 59.1; H, 3.92; N, 4.06.

Reaction of Thieno[2,3-*c*]quinoline *N*-Oxide (**1**) with Butyllithium.

To a stirred solution of butyllithium (0.73 ml of hexane solution, 1.5*N*, 1.1 mmoles) in 2 ml of anhydrous THF, a solution of 0.2 g (1 mmole) of **1** in 5 ml of THF was added dropwise under nitrogen at −70°. The reaction mixture was stirred at this temperature for two hours; at this point, the starting *N*-oxide could no longer be detected. After removing the cooling bath, the mixture was warmed to room temperature and the solvent was evaporated. The oily residue was treated with water and extracted with chloroform. After drying (magnesium sulfate) the solvent was evaporated. The residue was separated by column chromatography (silica gel-chloroform) to give **12** and **13** in 50% and 16% yield, respectively.

4,4'-Dithieno[2,3-*c*]quinolyl 5-Oxide (**12**).

This compound was obtained as yellow needles (acetonitrile), mp 255-256°; ms: (50 eV) m/e 384 (M^+), 368 (M^+-16), 184 ((M^+-16)/2); ^1H nmr (deuteriochloroform): δ 9.04 (m, 1H, H_6), 8.41 (m, 1H, $H_{6'}$), 8.35 (m, 1H, $H_{9'}$), 8.33 (m, 1H, H_9), 8.05 (d, 1H, $H_{1'}$), 7.91 (d, 1H, H_2), 7.89 (d, 1H, H_1), 7.76 (d, 1H, $H_{2'}$), 7.74-7.85 (m, 4H, $H_7H_8H_7H_8$), $J_{1,2}$ = 5.3 Hz; $J_{1',2'}$ = 5.4 Hz.

Anal. Calcd. for $C_{22}H_{12}N_2OS_2$: C, 68.8; H, 3.12; N, 7.29. Found: C, 68.3; H, 3.05; N, 7.18.

4-Butylthieno[2,3-*c*]quinoline *N*-Oxide (**13**).

This compound was obtained as colorless needles (cyclohexane), mp 88-89°; ms: (50 eV) m/e 257 (M^+), 241 (M-16); ^1H nmr (deuteriochloroform): δ 8.89 (m, 1H, H_6), 8.24 (m, 1H, H_9), 7.91 (d, 1H, H_1), 7.79 (d, 1H, H_2), 7.70-7.82 (m, 2H, H_7H_8), 3.4 (t, 2H, Ar-CH_2), 1.55-1.95 (m, 4H, -CH_2-CH_2-), 1.01 (t, 3H, CH_3), $J_{1,2}$ = 5.4 Hz.

Anal. Calcd. for $C_{15}H_{15}NOS$: C, 70.03; H, 5.83; N, 5.50. Found: C, 69.7; H, 5.94; N, 5.38.

Reaction of Thieno[2,3-*c*]quinoline *N*-Oxide with LDA.

A dried 25 ml flask was equipped with magnetic stirrer, nitrogen inlet, a reflux condenser with a drying tube, and a rubber septum for the injection of samples. The flask was charged with anhydrous THF (2 ml) and *n*-butyllithium (0.73 ml hexane solution 1.5 *N*, 1.1 mmoles). To this mixture diisopropylamine (0.166 ml, 1.1 mmoles) in 1 ml of anhydrous THF was added dropwise at room temperature with stirring. After stirring for 10 minutes, the flask was immersed in a dry-ice bath and the temperature kept at −70°. Thieno[2,3-*c*]quinoline *N*-oxide (**1**) was dissolved in 5 ml of THF and was injected dropwise into the lithium diisopropylamide (LDA) mixture. After two hours the cooling bath was removed, the temperature was raised to room temperature, and the mixture was then evaporated. The solid residue was treated with water and extracted with chloroform. After drying (magnesium sulfate) the solvent was removed by evaporation. The solid yellow residue was separated by column chromatography (silica gel-chloroform) to give **12** and **14** in 5% and 60% yield, respectively.

4,4'-Dithieno[2,3-*c*]quinolyl 5,5'-Dioxide (**14**).

This compound was obtained as pale yellow needles (acetonitrile), mp 298-299°; ms: (50 eV), m/e 400 (M^+), 384 (M-16), 368 (M-32), 184 ((M-32)/2); ^1H nmr (deuteriochloroform): δ 8.94 (m, 2H, $H_6H_{6'}$), 8.30 (m, 2H, $H_9H_{9'}$), 7.91 (d, 2H, $H_1H_{1'}$), 7.74-7.81 (m, 4H, $H_7H_8H_{7'}H_{8'}$), 7.68 (d, 2H, $H_2H_{2'}$), $J_{1,2}$ = 5.2 Hz.

Anal. Calcd. for $C_{22}H_{12}N_2O_2S_2$: C, 66.0; H, 3.0; N, 7.0. Found: C, 65.8; H, 3.12; N, 7.05.

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