New and Facile Synthesis of Mono- and Bifunctional *N*-Substituted 4-Alkylidenequinolines by an Eschenmoser Approach

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A new methodology based on the Eschenmoser coupling reaction has been developed for the preparation of quinoline anhydro bases. Its application has allowed the synthesis of 4-alkylidene-*N*-methylquinolines in two steps from *N*-methyl-4-quinolinethione **(1)** via appropriately 4-thiosubstituted quinolinium salts. Starting from 4(1*H*)-quinolinethione **(6)** itself, this process, combined with the Menschutkin reaction, is further demonstrated by the preparation of variously *N*-substituted 4-alkylidenequinolines. It is believed this route should provide access to pyridine and other quinoline anhydro bases.

Pyridine anhydro bases, having the general structures I and II, and formed upon deprotonation of appropriately substituted azinium cations, have traditionally played an important role in the synthesis of cyanine dyes.[1] More recently, their participation in the construction of polyfunctionalized heterocyclic systems such as indolizines[2] and pyridazines[3] and in recyclization reactions[4] has been documented. The fundamental chemical interest in nitrogen analogs of sesquifulvalene[5] and azafulvenes[6] is further enhanced by the fact that many natural alkaloids possess the pyridinium anhydro base molecular framework.[7]

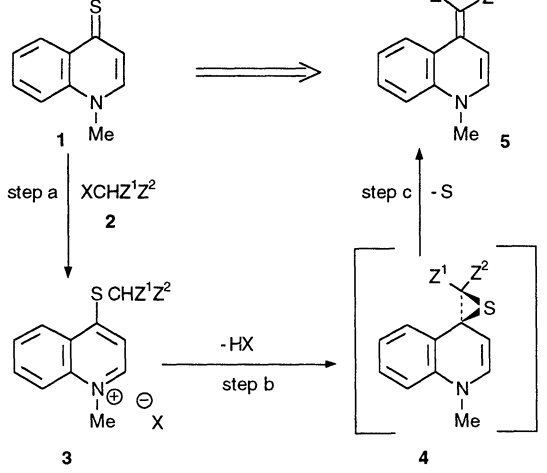
I

II

Deprotonation reactions apart, structurally specific syntheses of stable species I and II having electron-withdrawing substituents at the exocyclic double bond rely basically on the reactions of the quaternary salts with soft carbon nucleophiles. For example, the 4-exo alkylidene linkage can be achieved by condensation of azinium cations with carbanions derived from nitromethane, methyl ketones, 1,3-diketones and malonic acid derivatives under oxidizing conditions.[8] Stabilized azinium anhydro bases can also be conveniently prepared by nucleophilic substitution[9] of halogens or other nucleofugal groups located at the α- or γ-site of a salt precursor. Other syntheses are most often related to ring transformations of γ-pyrones[6] or require less common starting materials.[10]

With regard to carbonyl alkylidenation methods that proceed from amides (lactams), the Eschenmoser coupling reaction and its Knoevenagel-based variant have been extensively studied[11] and have proven valuable in natural product synthesis owing to their high efficiency. Very little, however, has been published about similar reactions with vinylogous compounds. Although Knoevenagel-based condensation of preformed α- or γ-methylthiopyridinium and quinolinium salts has been studied by Fujita et al.,[12] no synthetically useful method has yet been reported based on the Eschenmoser-type reaction with suitable azinium salts. During studies aimed at exploring further versatility of pyridine- and quinoline-4-thiones,[13] we had occasion to perform the sulfide contraction procedure developed by the Eschenmoser group.[14] The details of our investigation are described herein.

The conversions of *N*-methyl-4-quinoline-thione **(1)** to 4-alkylidene-*N*-methylquinolines **5** were examined first. The process we have investigated can be divided into three stages (see Scheme 1): *S*-alkylation of quinolinethione **1** with activated halides **2** (step a), dehydrohalogenation to yield thiiranes **4** (step b), and sulfur extrusion from **4** (step c). To obtain satisfactory yields of **5**, the Eschenmoser sulfide contraction method requires, in most cases, a base to abstract an α-proton in the appended side chain of a γ-thioquinolinium salt **3** and a phosphine thiophile to assist the sulfur extrusion of an unisolable episulfide intermediate **4**.



step a : $XCHZ^1Z^2$, CH_3CN, 20-50 °C, 0.5-1 h, 85-93 %

steps b/c : $(MeO)_3P$, Et_3N (slight excess), CH_3CN, 25-90 °C, 2-6 h, 62-88 %

2-5	X	Z^1	Z^2
a	Br	CO_2Et	CO_2Et
b	Br	H	CO_2Et
c	Cl	H	CN
d	Cl	H	COMe
e	Br	H	COPh

Scheme 1

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Table 1. 4-Thiosubstituted Quinolinium Salts **3a–e** and **8aa–ce** Prepared

Salt	Yield[a] (%)	mp (°C) (solvent)	Molecular Formula[b]	IR (KBr) ν (cm^{-1})
3a	93	51–55 (EtOAc/$CHCl_3$)	$C_{17}H_{20}BrNO_4S$	2922–2850, 1720, 1604, 1564, 1532, 1370, 1304
3b	86	184–185 (EtOAc/MeCN)	$C_{14}H_{16}BrNO_2S$	3070–2876, 1728, 1604, 1560, 1528, 1380, 1312
3c	85	216–220[c]	$C_{12}H_{11}ClN_2S$	3074–2874, 2254, 1602, 1566, 1526, 1380
3d	91	157–160 (EtOAc/EtOH)	$C_{13}H_{14}ClNOS$	3070–2932, 1718, 1610, 1600, 1556, 1526, 1366
3e	92	199–201 (EtOH)	$C_{18}H_{16}BrNOS$	3042–2892, 1662, 1612, 1596, 1558, 1528
8aa	80	105 (EtOAc/$CHCl_3$)	$C_{19}H_{22}BrNO_4S$	3086–2856, 1726, 1598, 1560, 1526, 1392, 1308
8ab	81	122 (EtOAc/MeCN)	$C_{16}H_{18}BrNO_2S$	3082–2874, 1726, 1598, 1560, 1530, 1392, 1316
8ac	85	189–191[c]	$C_{14}H_{13}BrN_2S$	3080–2932, 2258, 1614, 1604, 1566, 1526, 1382
8ad	87	177–178 (EtOAc/MeCN)	$C_{15}H_{16}BrNOS$	3070–2842, 1712, 1606, 1594, 1556, 1528, 1394
8bd	92	163 (EtOAc/MeCN)	$C_{16}H_{18}BrNO_3S$	3018–2860, 1748, 1734, 1602, 1558, 1532, 1392
8ce	83	186 (EtOH)	$C_{24}H_{20}BrNOS$	3064–2860, 1684, 1596, 1558, 1528, 1392, 1198

[a] Yield based on isolated product.
[b] Satisfactory microanalyses obtained for **3b,d**: C ± 0.30, H ± 0.15, O ± 0.25, N ± 0.20, S ± 0.30, Br/Cl ± 0.40; all other compounds gave S ± 0.45, except **3c** and **8ac**.
[c] These salts were not recrystallized.

Table 2. *N*-Substituted-4-alkylidenequinolines Prepared[a]

Product	Conditions Time (h)/ Temp (°C)	Yield[b] (%)	mp (°C)	Molecular Formula[c]	MS *m/z* (%)	IR (KBr) ν (cm^{-1})
5a	[d]	77	146	$C_{17}H_{19}NO_4$	301 (M^+, 19), 256 (18), 228 (11), 157 (100)	2974–2898, 1684, 1654, 1614, 1602
5b	2/60	79	118	$C_{14}H_{15}NO_2$	229 (M^+, 8), 184 (35), 157 (42), 43 (100)	2958–2924, 1734, 1666, 1622, 1504
5c	3/70	62[e] (75)	106	$C_{12}H_{10}N_2$	182 (M^+, 100), 167 (30), 140 (23), 75 (11), 63 (11)	3072–2934, 2180, 1638, 1608, 1540
5d	6/25	88	149–150	$C_{13}H_{13}NO$	199 (M^+, 25), 184 (100), 154 (46), 86 (25), 75 (17)	3042–2820, 1636, 1590, 1496, 1474
5e	3/90	74	90–96	$C_{18}H_{16}NO$	232 (4), 184 (100), 77 (23)	3010–2920, 1625, 1515, 1490, 1470
9aa	[d]	79	101	$C_{19}H_{21}NO_4$	327 (M^+, 11), 283 (92), 129 (24)	2978–2898, 1698, 1666, 1614, 1602, 1522, 1464
9ab	3/40	71	88	$C_{16}H_{17}NO_2$	255 (M^+, 52), 210 (26), 183 (42), 142 (13), 115 (20), 41 (100)	3060–2890, 1666, 1620, 1546
9ac	4/25	< 10[f] (57)	126	$C_{14}H_{12}N_2$	208 (M^+, 14), 185 (21), 184 (13), 167 (8), 156 (13), 41 (100)	2980–2842, 2166, 1642, 1630, 1610
9ad	3/25	87	109	$C_{15}H_{15}NO$	226 (M + 1, 18), 225 (M^+, 100), 210 (40)	3060–2890, 1666, 1620, 1606, 1546
9bd	3/80	91	169	$C_{16}H_{17}NO_3$	271 (M^+, 13), 256 (34), 228 (55), 43 (100)	2922, 1734, 1636, 1596, 1522, 1456
9ce	2/25	86	175	$C_{24}H_{19}NO$	337 (M^+, 47), 260 (6), 246 (7), 91 (100), 77 (41)	3050–2924, 1632, 1522, 1502, 1482

[a] Recrystallization in EtOAc/pentane.
[b] Isolated yield after plate chromatography. Yield in parentheses refers to the crude perchlorate salts.
[c] Satisfactory microanalyses were obtained for **5a,d,e** and **9ab**, **ac**: C, H, N, O ± 0.15 except for **9bd**: N ± 0.6. For other compounds, HRMS: ± 0.006.
[d] By chromatography on alumina.
[e] **7c** was also isolated in 28% yield.
[f] **7c**: 43% yield; 1-allyl-4-quinolinethione: 16% yield.

The syntheses (and properties) of thiosubstituted quinolinium salts are mainly related to the penicillin and cephalosporin series, as judged by the number of patents mentioned in the literature.[15] Far less work has been reported on more simple systems. It was also known from earlier work on the development of the sulfide contraction step with tertiary thiolactams as substrates that the contraction is problematic due, in part, to the reversibility of the thioamide alkylation reaction. In search of efficient experimental conditions to carry out both steps outlined in Scheme 1, we made great use of results obtained in the field of tertiary thiolactams.

The condensation reactions between *N*-methylquinolinethione **1** and the commercially available α-activated halides **2a–e** were performed in dry acetonitrile at room temperature over a short period of time. The resulting pale coloured quinolinium salts **3a–e** precipitated from the solution and these compounds were separated and purified (Table 1). However, in most cases, the reaction mixture was evaporated to dryness and the residue was triturated in anhydrous diethyl ether affording the salts in sufficient purity for further reaction. To drive the reaction to completion, an excess of halide can then be used.

At this stage, the reagents and reaction conditions necessary to conduct the sulfide contraction process were briefly examined. As a dehydrohalogenating reagent, Et_3N was a better choice than piperidine or K_2CO_3, the most noticeable drawbacks of the latter bases being the

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Table 3. 4-Thiosubstituted Quinolines **7a–e** Prepared

Starting halide	Product	Yield[a] (%)	mp (°C) (solvent)	Molecular[b] Formula	MS (70 eV) *m/z* (%)	IR (KBr) ν (cm^{-1})
2a	**7a**	74	oil	$C_{16}H_{17}NO_4S$	319 (M^+, 64), 200 (24), 174 (43), 173 (43), 172 (100)	3064–2872, 1732, 1562, 1496, 1376
2b	**7b**	95	oil[23]	$C_{13}H_{13}NO_2S$	247 (M^+, 27), 219 (21), 174 (100), 77 (11)	3050–2850, 1730, 1560, 1495, 1375
2c	**7c**	93	139 (EtOAc/Pentane)	$C_{11}H_8N_2S$	200 (M^+, 27), 160 (16), 89 (10), 69 (38), 60 (51), 57 (78), 41 (100)	3160–2880, 2238, 1564, 1498, 1378
2d	**7d**	98	87 (EtOAc/light petroleum)	$C_{12}H_{11}NOS$	217 (M^+, 22), 174 (41), 160 (4), 43 (100)	3080–2985, 1705, 1560, 1490, 1370
2e	**7e**	87	125 (EtOAc/light petroleum)	$C_{17}H_{13}NOS$	279 (M^+, 27), 167 (21), 149 (100), 81 (25), 69 (46)	3080, 1684, 1560, 1496, 1374

[a] All yields were based on isolated product.
[b] Satisfactory microanalyses were obtained for **7c–e**: C, H, N, O, S ± 0.2; for **7a,b**: S ± 0.25.

Table 4. ^1H NMR and ^{13}C NMR Spectral Data of 4-Thiosubstituted Quinolines **7a–e** ($CDCl_3$/TMS)

Product	^1H NMR δ, *J* (Hz)	^{13}C NMR δ
7a	1.23 (6H, t, *J* = 7.0), 4.2 (4H, q, *J* = 7.0), 4.8 (1H, s), 7.47 (1H, d, *J* = 4.7), 7.62 (1H, ddd, *J* = 7.7, 7.0, 1.4), 7.77 (1H, ddd, *J* = 8.3, 7.0, 1.4), 8.10 (1H, dd, *J* = 7.7, 1.4), 8.29 (1H, dd, *J* = 8.3, 1.4), 8.78 (1H, d, *J* = 4.7)	s: 126.4, 145.7, 147.5, 167.3 d: 53.9, 121.6, 122.8, 127.4, 129.5, 130.7, 150.2 t: 62.4 q: 14.1
7b	1.26 (3H, t, *J* = 7.1), 3.87 (2H, s), 4.23 (2H, q, *J* = 7.1), 7.26 (1H, d, *J* = 4.8), 7.56 (1H, ddd, *J* = 8.4, 7.2, 1.0), 7.72 (1H, ddd, *J* = 8.0, 7.2, 1.4), 8.08 (1H, dd, *J* = 8.4, 1.4), 8.12 (1H, dd, *J* = 8.0, 1.0), 8.73 (1H, d, *J* = 4.8)	s: 126.4, 145.8, 147.5, 168.8 d: 116.7, 123.5, 126.7, 130.0, 130.2, 149.4 t: 33.9, 62.2 q: 14.2
7c	3.85 (2H, s), 7.40 (1H, d, *J* = 4.6), 7.60 (1H, ddd, *J* = 7.2, 7.0, 1.2), 7.80 (1H, ddd, *J* = 7.2, 7.0, 1.5), 8.10 (1H, dd, *J* = 7.2, 1.2), 8.14 (1H, dd, *J* = 7.2, 1.5), 8.86 (1H, d, *J* = 4.6)	s: 115.3, 126.6, 142.3, 148.0 d: 118.9, 123.4, 127.4, 130.4, 130.5, 149.6 t: 17.9
7d	2.34 (3H, s), 3.91 (2H, s), 7.14 (1H, d, *J* = 4.8), 7.57 (1H, ddd, *J* = 8.2, 7.0, 1.2), 7.73 (1H, ddd, *J* = 8.4, 7.0, 1.3), 8.08 (1H, dd, *J* = 8.2, 1.3), 8.12 (1H, dd, *J* = 8.4, 1.2), 8.7 (1H, d, *J* = 4.8)	s: 126.3, 145.6, 147.4, 202.2 d: 116.6, 123.4, 126.8, 130.1, 130.1, 149.9 t: 42.0 q: 28.2
7e	4.56 (2H, s), 7.30 (1H, d, *J* = 4.7), 7.4–7.7 (5H, m), 8.1 (3H, m), 8.17 (1H, d, *J* = 8.4), 8.72 (1H, d, *J* = 4.7)	s: 126.6, 135.2, 145.7, 147.6, 192.9 d: 117.3, 123.7, 126.7, 128.8, 129.0, 129.9, 130.2, 134.1, 149.5 t: 38.7

low conversion and the formation of a substantial amount of the *S*-dealkylation product. On the other hand, when a thiophile reagent such as Ph_3P or $(MeO)_3P$ was used in combination with Et_3N, yields of quinoline anhydro bases were generally lower with the former. This was mainly ascribable to a required aqueous (acid–base) workup.[16] Incidentally, it was also found that the present Eschenmoser sulfide contraction of the diethyl bromomalonate derivative **3a** proceeded readily upon chromatography on alumina. However, attempts to extend this procedure to primary α-keto halides were not satisfactory. As summarized in Table 2, application of the appropriate conditions allowed the synthesis of the quinoline anhydro bases **5a–e** in yields of at least 60%, based on starting *N*-methylquinolinethione **1**. These yellow-orange compounds, first free from the insoluble material in diethyl ether, were isolated by chromatography on silica gel plates. $(MeO)_3PS$ and small amounts of starting quinolinethione **1** were occasionally separated.

In order to vary the *N*-substituent of the 4-alkylidenequinolines synthesized so far, we made use of the mild conditions of the Menschutkin reaction.[17] For this purpose, the reactions outlined in Scheme 2 were developed, starting from the readily available 4(1*H*)-quinolinethione **6**. The results of these experiments are also listed in Tables 1 and 2. The quinoline bases **7a–e** were obtained in high yield by *S*-alkylation of **6** with α-activated halides **2a–e** in ethanol followed by K_2CO_3 treatment of the resulting protonated quinolinium salts according to a slightly modified literature procedure[18] (Tables 3 and 4). Further quaternization of compounds **7** with reactive bromides in dry acetonitrile gave new quinolinium salts **8aa–ce** (Table 5). No reaction with bromonitromethane or chloroacetone was observed. The combination of the Menschutkin reaction with allyl bromide and diethyl (4-quinolylthio)malonate **(7a)** and subsequent sulfide contraction involving direct chromatography on alumina was quite effective for the synthesis of the unsaturated diester **9aa**. As in other cases where only one electron-withdrawing group was present, the use of the $(MeO)_3P$–Et_3N system to extrude sulfur was found to be essential. In this manner, the unsaturated ketones **9ad, 9bd** and **9ce** were isolated in high yields, and the somewhat lower yield of the monoester **9ab** was mainly due to a compe-

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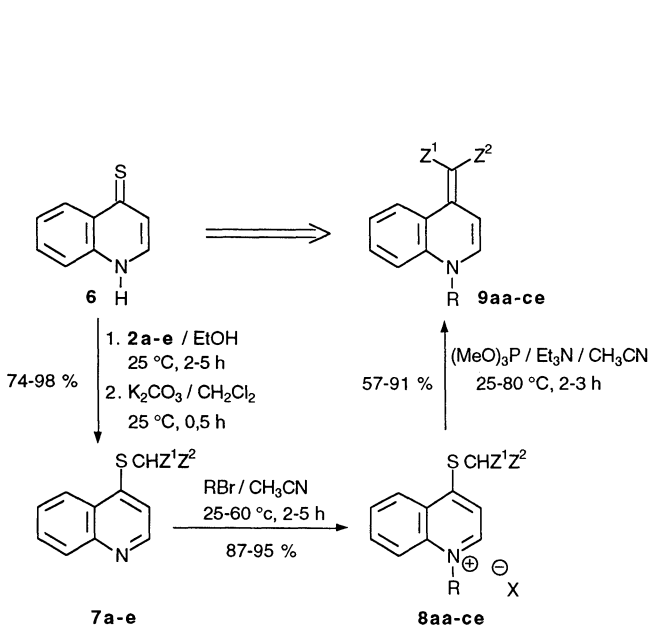
Table 5. ^1H NMR and ^{13}C NMR Spectral Data of Selected 4-Thiosubstituted Quinolinium Salts ($CDCl_3$ or DMSO/TMS)

Salt	^1H NMR δ, J (Hz)	^{13}C NMR δ
3a[a]	1.32 (6H, t, J= 7.0), 4.33 (4H, q, J= 7.0), 4.81 (3H, s), 5.27 (1H, s), 7.8–8.0 (2H, m), 8.18 (1H, dd, J= 7.3, 8.4), 8.25 (1H, d J= 8.4), 8.42 (1H, d, J= 8.5), 10.35 (1H, d, J= 6.4)	s: 126.3, 136.9, 159.7, 164.2 d: 52.6, 116.8, 119.1, 125.5, 130.0, 136.0, 148.8 t: 64.2 q: 14.1, 45.1
3b[a]	1.34 (3H, t, J= 7.0), 4.26 (3H, s), 4.30 (2H, q, J= 7.0), 4.82 (2H, s), 7.92 (1H, d, J= 6.4), 7.92 (1H, ddd, J= 7.3, 7.0, 1.2), 8.18 (1H, ddd, J= 8.0, 7.0, 1.2), 8.32 (1H, dd, J= 7.3, 1.2), 8.41 (1H, dd, J= 8.0, 1.2), 10.25 (1H, d, J= 6.4)	s: 126.3, 136.8, 161.6, 166.8 d: 116.5, 119.4, 125.3, 129.8, 135.9, 148.1 t: 34.2, 63.1 q: 14.2, 45.2
3c[b]	4.57 (3H, s), 4.94 (2H, s), 8.06 (1H, t, J= 7.7), 8.15 (1H, d, J= 6.5), 8.30 (1H, dd, J= 8.4, 7.6), 8.42 (1H, d, J= 8.4), 8.51 (1H, d, J= 8.8), 9.45 (1H, d, J= 6.5)	s: 116.3, 125.5, 136.8, 157.8 d: 116.1, 120.3, 124.7, 130.9, 135.7, 147.7 t: 44.8 q: 16.6
3d[b]	2.35 (3H, s), 4.51 (5H, s), 7.75 (1H, t, J= 7.5), 7.9–8.07 (3H, m), 8.28 (1H, d, J= 8.3), 9.78 (1H, d, J= 6.7)	s: 125.6, 136.6, 161.3, 200.6 d: 116.3, 120.0, 124.8, 129.8, 135.3, 146.9 t: 42.1 q: 29.2, 44.3
3e[b]	4.48 (3H, s), 5.48 (2H, s), 7.63 (2H, t, J= 7.3), 7.73 (1H, dd, J= 8.3, 7.3), 7.9–8.1 (2H, m), 8.18 (2H, d, J= 7.3), 8.27 (1H, t, J= 7.3), 8.45 (1H, d, J= 8.3), 8.57 (1H, d, J= 8.1), 9.16 (1H, d, J= 6.7)	s: 125.7, 135.1, 136.6, 161.3, 192.3 d: 116.6, 120.1, 124.9, 128.8, 128.9, 129.9, 134.3, 135.3, 146.9 t: 79.2 q: 44.3
8ab[a]	1.36 (3H, t, J= 7.1), 4.23 (2H, s), 4.35 (2H, q, J= 7.1), 5.42 (1H, d, J= 17.1), 5.45 (1H, d, J= 10.4), 5.93 (2H, d, J= 5.2), 6.18 (1H, m), 7.94 (1H, d, J= 6.4), 7.9 (1H, ddd, J= 8.5, 8.2, 0.9), 8.13 (1H, ddd, J= 8.2, 7.6, 1.2), 8.24 (1H, dd, J= 8.5, 1.2), 8.42 (1H, dd, J= 7.6, 0.9), 10.32 (1H, d, J= 6.4)	s: 126.5, 136.1, 162.2, 166.7 d: 116.7, 119.6, 125.5, 129.6, 130.0, 135.6, 147.9 t: 34.3, 59.0, 63.2, 121.7 q: 14.2
8ad[a]	2.57 (3H, s), 4.82 (2H, s), 4.36 (1H, d, J= 17.0), 5.43 (1H, d, J= 10.2), 5.81 (2H, d, J= 5.4), 6.14 (1H, m), 7.86 (1H, ddd, J= 8.5, 7.0, 1.2), 8.08 (1H, ddd, J= 8.5, 7.0, 1.6), 8.20 (1H, dd, J= 8.5, 1.2), 8.32 (1H, d, J= 6.7), 8.44 (1H, dd, J= 8.5, 1.6), 9.55 (1H, d, J= 6.7)	s: 126.8, 136.0, 163.4, 199.8 d: 118.1, 119.4, 125.9, 129.4, 129.8, 135.4, 147.1 t: 42.2, 59.0, 121.6 q: 30.1
8bd[a]	1.29 (3H, t, J= 7.2), 2.55 (3H, s), 4.27 (2H, q, J= 7.2), 4.77 (2H, s), 6.24 (2H, s), 7.85 (1H, t, J= 8.1), 7.96 (1H, d, J= 8.9), 8.06 (1H, d, J= 6.9), 8.15 (1H, m), 8.44 (1H, d, J= 8.5), 9.35 (1H, d, J= 6.9)	s: 126.15, 136.2, 164.6, 165.6, 199.5 d: 116.7, 118.5, 125.5, 129.5, 135.8, 147.4 t: 43.1, 56.5, 62.9 q: 13.9, 29.4

[a] In $CDCl_3$.

[b] In DMSO.

titive nucleophilic attack at the α-carbon of the sulfur side chain. The very low yield for the nitrile **9ac** was due to both *S*- and *N*-dealkylation (16 and 43%, respectively). The occurrence of the reverse Menschutkin reaction was not surprising in view of the work of Metzger.[19] Deady and co-workers[20] postulated that the halide counterion rather than the thiophile was the dealkylating agent of quaternary salts of nitrogen heterocycles. Although no serious attempts to optimize the conditions of anhydro base formation have been made, one experiment exchanging the bromide for a less nucleophilic anion[21] by the addition of silver perchlorate in CH_2Cl_2 shows that the yield of nitrile **9ac** may be substantially increased (to 57%). It should also be noted that the sulfide contraction process produced here the corresponding *N*-substituted quinolinethiones, and sometimes quinolones, albeit in very low yield. We plan to make this the subject of a separate publication. As a general trend, quinoline anhydro bases **5** and **9** do not suffer decomposition upon recrystallization from hot solvents except nitrile derivatives **5c** and **9ac**.



Scheme 2

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Table 6. ^{1}H NMR Data [δ, J (Hz)] of *N*-Substituted 4-Alkylidenequinolines (250 MHz, $CDCl_3$/TMS)

Product	H^2 (d)	H^3 (d)	$\Delta\delta$	$J_{2,3}$	H-5 (dd)	H-6 (ddd)	H-7 (ddd)	H-8 (dd)	H-9 (s)	N–R	Others
5a	6.92	7.66	−0.74	7.9	7.71	7.2	7.54	7.2	–	3.55	1.2 (6H, t, J = 7.1), 4.2 (4H, t, J = 7.1)
5b	7.17	7.75	−0.58	7.9	7.97	7.2	7.49	6.84	5.69	3.57	1.2 (3H, q, J = 7.1), 4.2 (2H, q, J = 7.1)
5c	7.20	6.43	0.77	7.7	7.73	7.2	7.52	6.8	4.8	3.56	–
5d	7.27	8.27	−1.00	7.77	8.06	7.3	7.55	7.0	6.18	3.65	2.24 (1H, s)
5e	7.33	8.59	−1.26	7.94	8.22	7.34	7.59	7.14	6.9	3.72	7.4–7.5 (3H, m), 7.9–7.8 (2H, m)
9aa	6.94	7.78	−0.84	8.0	7.79	7.09	7.47	7.22	–	[a]	1.2 (6H, t, J = 7.1), 4.2 (4H, q, J = 7.1)
9ab	7.14	7.77	−0.63	7.9	7.96	7.16	7.42	6.85	5.70	[a]	1.2 (3H, t, J = 7.1), 4.2 (2H, q, J = 7.1)
9ac	7.13	6.46	0.67	7.7	7.72	7.2	7.46	6.83	4.83	[a]	–
9ad	7.25	8.29	−1.04	7.8	8.05	7.25	7.48	7.0	6.19	[a]	2.24 (3H, s)
9bd	7.03	8.25	−1.22	7.8	8.05	7.27	7.50	6.94	6.24	[b]	2.26 (3H, s)
9ce	[7.3][c]	8.65	−1.4	7.6	8.20	[7.2–7.5]			6.94	[d]	7.2–7.5 (3H, m), 8.0–8.1 (2H, m)

[a] 4.5 (2H, d, J = 4.7), 5.1 (1H, d, J = 17.2), 5.2 (1H, d, J = 10.5), 5.9 (1H, m).
[b] 1.25 (3H, t, J = 7.1), 4.23 (2H, q, J = 7.1), 4.63 (2H, s).
[c] This proton signal is masked by aromatic protons.
[d] 5.4 (2H, s), 7.2–7.5 (5H, m).

Table 7. ^{13}C NMR Data of Selected 4-Alkylidenequinolines ($CDCl_3$/TMS)

5a	s: 100.0, 121.1, 138.3, 147.7, 168.0 d: 106.2, 113.5, 122.0, 127.3, 130.1, 136.4 t: 59.1 q: 13.1, 39.2
5c	s: 121.5, 122.1, 138.4, 149.6 d: 67.4, 105.4, 115.0, 123.6, 124.1, 131.4, 137.0 q: 40.1
5d	s: 123.5, 132.4, 146.0, 195.5 d: 99.7, 106.8, 115.0, 123.8, 124.5, 130.8, 138.8 q: 31.9, 40.5
5e	s: 123.5, 139.1, 143.2, 147.7, 188.2 d: 96.7, 107.6, 115.3, 124.1, 124.6, 127.4, 128.2, 130.4, 131.1, 139.3 q: 40.7
9ab	s: 122.6, 138.2, 146.5, 168.8 d: 90.7, 105.6, 115.4, 123.3, 124.6, 130.5, 131.6, 136.6 t: 54.3, 58.1, 118.1 q: 14.8
9ac	s: 121.5, 121.9, 137.6, 149.4 d: 68.0, 105.7, 115.6, 123.5, 124.2, 131.2, 131.5, 136.4 t: 54.4, 118.3
9ad	s: 122.9, 138.8, 145.7, 195.7 d: 100.1, 107.1, 115.7, 123.7, 124.6, 130.8, 131.6, 138.2 t: 54.8, 118.4 q: 31.9
9bd	s: 136.0, 138.8, 144.8, 167.7, 195.8 d: 101.4, 107.1, 114.4, 123.9, 124.6, 131.0, 138.1 t: 54.0, 62.3 q: 14.2, 32.0

The most notable feature of Schemes 1 and 2 is the stereoselective production of monofunctional 4-alkylidenequinolines. An examination of steric interactions in **5b–e** and **9ab–ce** suggests that these compounds with the *E* geometry should be the thermodynamically more stable configurational isomers. In others words, the functional group remaining in the plane of the quinoline nucleus should lie away from the aromatic ring. Further evidence was gathered from spectral data.

To confirm the quinoline anhydro base structures, ^{1}H and ^{13}C NMR spectra were measured in $CDCl_3$ (Tables 6 and 7). Data for a few bifunctional compounds are known,[12] but in general are incomplete or have been measured in a variety of solvents. While data for monofunctional derivatives in the pyridine series, prepared from the oxygen analogs by N–O exchange, have also been reported,[6] data of benzoanalogs are much rarer. ^{1}H NMR spectra of quinoline anhydro bases are summarized in Table 6. Protons H-2 and H-3 in the unsaturated diester **5a** resonate at comparable δ values to those of H-2 and H-3 in the monoester **5b**. Such a situation also occurs for the corresponding *N*-allyl derivatives **9aa** and **9ab**. This observation supports rather than disproves the assignment of the *E* geometry to the exocyclic double bond. Clearly, it is only in the *E*-isomer where the methine proton at C-3 falls into the deshielding region of the carbonyl group that this observed insensitivity is readily explainable. On the other hand, inspection of the chemical shift data for the monofunctional quinoline anhydro bases shows that the positions of the H-2 and H-3 signals shift by about 0.15 and 2.2 ppm, respectively, upon changing Z from COPh to CN. The relative order of the chemical shifts for the H-3 proton is $\delta_H(COPh) > \delta_H(CO_2Et) > \delta_H(CN)$. These conclusions are closely related to findings disclosed by Shvo et al. on monocyclic heterofulvenes.[6] It is also worth mentioning that the vinylic proton at the exocyclic double bond, H-9 in Table 6, exhibits a sharp singlet at relatively high field but, once again, in the same order as above. The assignments of the aromatic protons were based on their chemical shifts values and their multiplicities.

In conclusion, we have found that mono- and bifunctional *N*-substituted 4-alkylidenequinolines can be synthesized by the sulfide contraction process. Considering that the Eschenmoser reaction, first described by Knott,[22] tolerates a variety of functional groups, this synthetic procedure can be of substantial value in the preparation of highly functionalized quinoline and pyridine anhydro bases as useful intermediates in organic synthesis.

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Mps were determined with a Gallenkamp apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AC 250 instrument operating at 250.13 MHz for ^{1}H, 62.89 for ^{13}C. IR spectra were recorded with a Perkin–Elmer 16 PC FT-IR spectrophotometer. Mass spectra were recorded with a Nermag Riber R10 spectrometer (70 eV). HRMS were recorded on a DM 300 JEOL (70 eV) spectrometer. Microanalyses were obtained from the "Laboratoire Central de Microanalyse du CNRS" (Lyon). Analyses of sulfur were performed at Caen following Debal and Levy's method (*Bull. Chem. Soc. Fr.* **1968**, 426). TLC plastic sheets silica gel 60 F_{254} (0.2 mm layer thickness) and PLC plates silica gel F_{254} (1 mm layer thickness) were used for chromatography.

All commercially available halides were used as received from the suppliers. All other chemicals were distilled before use. Et_3N was freshly distilled over CaH_2. The quinolinethiones **1** and **6** were prepared from the commercially available 4(1*H*)-quinolone according to known procedures.[24,25]

S-Alkylation of *N*-Methyl-4-quinolinethione (1); General Procedure:
A mixture of N-methyl-4-quinolinethione (**1**; 175 mg, 1 mmol) and the appropriate α-activated halide (**2**; 1.2 mmol) in MeCN (5 mL) was stirred at r.t. for 30–60 min. After the reaction was complete (TLC, eluent: $CHCl_3$/MeOH, 95:5), the solvent was evaporated and the solid residue was triturated with Et_2O several times to give quinolinium compounds **3a,b,d,e** as slightly yellow, crystalline powders. These salts were pure enough for use in the next step or were recrystallized as needles (Table 1). Salt **3c** was obtained as a brown-green solid.

Diethyl (4-Quinolylthio)malonate 7a; Typical Procedure:
4(1*H*)-quinolinethione (**6**; 176 mg, 1.5 mmol) was dissolved in boiling EtOH (5 mL) and when the temp. had fallen to 50 °C, diethyl bromomalonate (**2a**; 0.29 mL, 1.7 mmoles) in EtOH (2 mL) was added. After being stirred for 1 h, a quantitative yield of the corresponding 4-thiosubstituted pyridine hydrobromide separated. The solvent was evaporated and the residue was diluted with fresh Et_2O (10 mL) and filtered. The filter cake was washed with Et_2O. The remaining solid was treated with K_2CO_3 (345 mg, 2.5 mmol) in CH_2Cl_2 (10 mL) with stirring at r.t. for 1 h. The reaction mixture was filtered, the filter cake was washed with Et_2O and the combined filtrate was dried and concentrated in vacuo to give the title compound in high purity as a pale yellow oil. Quinoline bases **7c–e** were recrystallized as light-cream-coloured crystals (Table 3).

***N*-Alkylation of 4-Thiosubstituted Quinolines 7; General Procedure:**
A mixture of 4-thiosubstituted quinoline **7** (1 mmol) and the bromide (1.2 mmol) in MeCN (5 mL) was stirred at 25–60 °C. After complete conversion of the quinoline base (2–5 h; TLC as above), the precipitated solid was filtered and washed well with Et_2O. Quinolinium salts **8aa–ce** were obtained in sufficient purity for further reactions. Except **8ac**, salts were recrystallized as pale cream needles (Table 1).

Anion Exchange from Chloride or Bromide to Perchlorate:
To a suspension of quinolinium chloride or bromide (**3c** or **8ac**) (0.5 mmol) in CH_2Cl_2 (5 mL) was added silver perchlorate (103 mg, 0.5 mmol) and the resulting mixture stirred overnight at r.t. The solvent was evaporated and the residue solid was used without purification.

***N*-Substituted 4-Alkylidenequinolines 5 and 9; General Procedure:**
To a suspension of 4-thiosubstituted *N*-alkylquinolinium salt **3** or **8** (0.5–0.8 mmol) in MeCN (5–8 mL) was added Et_3N (1.5 equiv) and $(MeO)_3P$ (1 equiv) in sequence via a syringe. After stirring for the temp. and time indicated in Table 2, the solvent was removed and the residue dried with an oil pump. The remaining solid was triturated with Et_2O, filtered and washed twice with Et_2O. The filtrate was evaporated to dryness and further purified by plate chromatography using EtOAc/light petroleum (40:60 or 60:40) as eluent. Quinoline anhydro bases **5** and **9** were isolated as yellow-red crystals. By recrystallization most of them became purple coloured needles.

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