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N-Quaternary Compounds. Part LVI.*
3-Hydroxyquinoline-2(1*H*)-thiones and Their *N*-Vinylation

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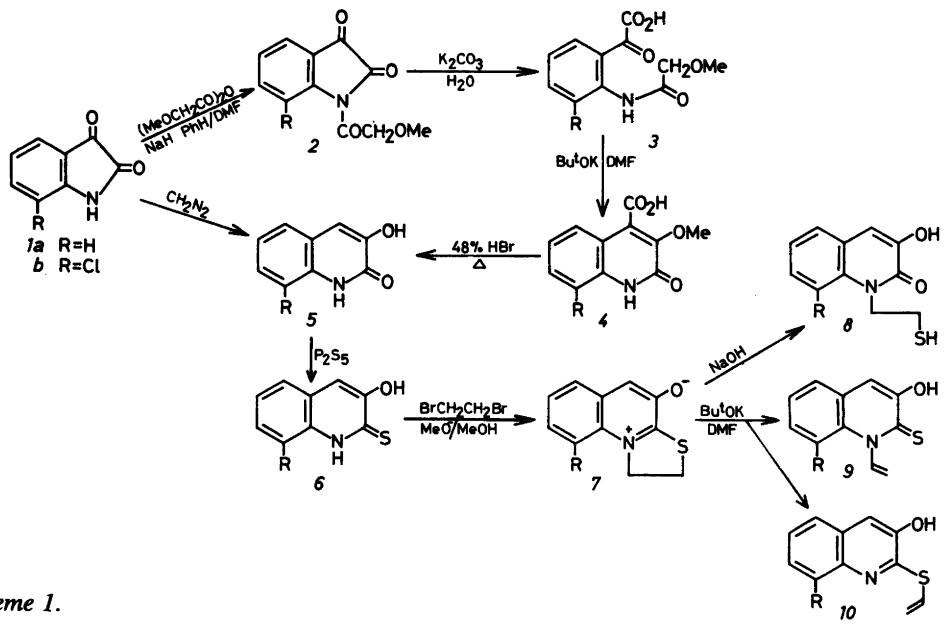
A convenient method for the synthesis of 2,3-dihydroxyquinolines is described. These intermediates are converted to 1,2-dihydrothiazolo[3,2-*a*]quinolinium-4-olates. Ring opening reactions of the latter to the isomeric *N*- and *S*-vinylquinolines are affected by steric and electronic factors. Mass spectrometry data show that the quinoline betaines are volatilized without any change in structure.

The dihydrothiazolo ring in 2,3-dihydrothiazolo[3,2-*a*]-pyridinium-8-olates can be opened by base treatment whereby *N*-vinyl-and *S*-vinylpyridines are formed.[2] Important factors for preferential *N*- or *S*-vinyl derivative formation are high electron deficiency in the azine ring which favours *N*-vinylation, whereas a 5-substituent increases the relative amount of the *S*-vinyl isomer.[2] In this report syntheses and properties of quinoline analogues are described.

2,3-Dihydroxyquinolines *5* are the key intermediates in the syntheses. The parent compound *5a* as a mixture with its 3-methoxy analogue can be prepared from isatin by diazomethane ring expansion.[3] Using this method for the ring expansion of 7-chloroisatin, however,

*Part LV. See Ref. 1.



Scheme 1.

0302-4369/84 $2.50

gave unsatisfactory yields of the chloroquinoline *5b*. 2,3-Dihydroxyquinolines have also been prepared by a number of steps *via* adducts between acetylenedicarboxylic esters and hydrazobenzenes.[4] We have developed a preparation which is based on the reports that base treatment of *N*-acetylisatin results in formation of 4-carboxyquinolin-2(1*H*)-one[5] and that *N*-(chloroacetyl)-isatin gives a mixture of 2,3- and 2,4-dihydroxyquinoline.[6] It was reasoned that the use of a suitably protected hydroxyacetyl group should furnish a 4-carboxyquinoline which can be converted further into a 2,3-dihydroxyquinoline. The methoxyacetyl derivatives *2* were explored for this purpose. Methoxyacetic anhydride[7] was preferable to methoxyacetyl chloride[8] in the *N*-acylation of the sodium salt of the isatin; heating the reaction mixture results in partial deacylation, especially in the chloro derivative *2b*. The isatins are ring opened to isatoic acids *3* in aqueous sodium carbonate and the acids *3* are cyclized to the 4-carboxyquinolines *4* by the use of potassium *tert*-butoxide in DMF. The ring opening and recyclization can also be effected in one operation by heating *2* in aqueous carbonate; the yield of *4a* but not of *4b* was satisfactory by this direct procedure. Cleavage of the methoxy group and decarboxylation of *4* were effected in one operation by heating with 48 % HBr.

1,2-Dihydrothiazolo[3,2-*a*]quinolinium-4-olate *7a* has previously been prepared by the reaction of 3-hydroxyquinoline-2(1*H*)-thione with 1,2-ethanedibromide.[3a] The 9-chloro derivative *7b* was prepared in the same way from the thione *6b*; the latter was available by thiation of *5b* using phosphorus pentasulfide.

Fusion of a phenyl ring to pyridine, which constitutes the quinoline system, activates substituents in the pyridine ring towards nucleophilic substitution. Thus the thioether bond (S–C3a) of the betaines *7* is cleaved in aqueous alkali under conditions were the pyridine analogues are largely unaffected. The products are the *N*-mercaptoethylquinolin-2(1*H*)-ones *8*; IR absorption at 1620–1630 cm^{-1} (CO) and UV maxima in methanolic alkali at *ca.* 340, 330 and 260 nm corresponding closely to the absorption of the parent quinolin-2(1*H*)-ones *5*.

With potassium *tert*-butoxide in DMF the parent betaine *7a* gives the *N*-vinylquinoline-2(1*H*)-thione *9a*. The 9-chloro betaine *7b*, however, yields the *S*-vinyl derivative *10b* as the major product, the ratio between the *N*- and *S*-vinyl derivatives *9b* and *10b* being 1:5. This observation is rationalized by repulsion of the large anion base required for proton abstraction at C-1 by the bulkiness of the chloro substituent and probably also by the dipolar effects from the lone pairs on the chlorine.

The UV absorption spectra are used to identify the vinyl isomers. Thus, the *N*-vinyl isomer *9b* exhibits maxima in methanolic potassium hydroxide at 406, 385 and 260 nm, the *S*-vinyl isomer *10b* at 366, 351 and 268 nm; the latter compares well with the maxima at 363, 349 and 259 nm found for 3-hydroxy-2-methylthioquinoline.[3a]

M–*H* is the base peak in the mass spectrum from the *N*-vinyl derivative *9a*. Both *N*- and *S*-vinyl pyridine analogues are characterized by *M*–*H* being the base peak.

The high intensity of the *M*–*H* signal is rationalized by hydrogen expulsion from the β-vinyl carbon and cyclization to the fully conjugated thiazolo[3,2-*a*]quinolinium cation. The *S*-vinyl chloro derivative *10b* also falls into this pattern but the *N*-vinyl chloro derivative *9b* preferentially cleaves the vinyl group by expulsion of C_2H_2. The isomeric betaines *7*, however, behave differently; the molecular ion is the base peak whereas the intensities of the *M*–*H* signals are low. Hence the betaines *7* are volatilized in the mass spectrometer without any structural rearrangement which corresponds to the behaviour of pyridine betaines.[9]

EXPERIMENTAL

The mass spectra are given as MS [70 eV; *m/z* (% rel.int.)].

N-*(Methoxyacetyl)isatin* 2a. 55 % sodium hydride in oil (3.50 g, 0.07 mol) was gradually added to a solution of isatin (7.35 g, 0.05 mol) in DMF (10 ml) and benzene (200 ml) and the mixture stirred at room temperature for 60 min. Methoxyacetic anhydride[7] (8.10 g, 0.05 mol) was added dropwise to the mixture with stirring and ice-cooling, and the mixture stirred for an additional 3 h at room temperature. The precipitate was then removed by filtration and washed with benzene. Concentration of the combined benzene solutions led to precipitation of the product; yield 8.45 g (77 %), m.p. 126 °C (Et_2O). Anal. $C_{11}H_9NO_4$:C,H. ^1H NMR (DMSO-d_6): δ 3.46 (MeO), 4.62 (CH_2), 7.3–8.4 (arom.). IR (KBr): 1800 and 1735 (3,2-CO), 1760 cm^{-1} (α-CO). MS:

219(6,M), 191(13), 163(3), 147(10), 146(100), 90(19).

7-Chloro-N-*(methoxyacetyl)isatin* 2b was prepared as above from 7-chloroisatin[10] in 71 % yield, m.p. 160 °C (benzene). Anal. $C_{11}H_8ClNO_4$: C,H. ^{1}H NMR (DMSO-d_6): δ 3.42 (OMe) 4.60 (CH_2), 7.3–8.0 (arom.). IR (KBr): 1785 and 1730 (3,2-CO), 1750 (α-CO). MS: 253(l,M), 228(6), 226(17), 195(11), 182(35), 180(87), 45(100).

N-*(Methoxyacetyl)isatoic acid* 3a. *N*-(Methoxyacetyl)isatin (58,0 g, 0.28 mol) was added to a solution of potassium carbonate (58,0 g, 0.42 mol) in water (700 ml) and the mixture heated under reflux for 1 h. Acidification of the cold reaction mixture to pH *ca.* 2 precipitated the product which was well washed with water; yield 55.0 (87 %), m.p. 196 °C (MeOH). Anal.$C_{11}H_{11}NO_3$: C,H. ^{1}H NMR (DMSO-d_6): δ 3.41 (OMe), 4.06 (CH_2), 4.8 (NH,OH), 7.1=8.7 (arom). MS: 237 (2,M), 192(29), 161(6), 148(12), 147(48), 146(67), 132(24), 119(100).

3-Chloro-N-*(methoxyacetyl)isatoic acid* 3b. 7-Chloro-*N*-(methoxyacetyl)isatin (3.9 g, 0.015 mol) was added to a solution of potassium carbonate (3.5 g, 0.025 mol) in water (50 ml), the mixture stirred at room temperature for 2 h and then heated under reflux for 30 min, the cold mixture acidified to pH *ca.* 2 with HCl, the mixture extracted with ethyl acetate and the dried ($MgSO_4$) ethyl acetate solution concentrated when the product crystallized out; yield 74 %, m.p. 128–130 °C. Anal. $C_{11}H_{10}ClNO_5$: C,H, ^{1}H NMR (DMSO-d_6): δ 3.40 (OMe), 4.01 (CH_2), 4.7 (NH,OH), 7.3–7.9 (arom). IR (KBr): 1745 and 1685 (3,2-CO), 1635 (α-CO). MS: 271 (0.1,M), 228(11), 226(36), 195(5), 182(12), 180(19), 166(19), 45(100).

*4-Carboxy-3-methoxyquinolin-2(1*H*)-one* 4a. *N*-(Methoxyacetyl)isatoic acid (23,7 g, 0.1 mol) was added to potassium *tert*-butoxide (33.6 g, 0.3 mol) in DMF (700 ml) and the mixture heated at 100 °C for 5 h. The solvent was then removed at reduced pressure, the residue dissolved in water (400 ml), the solution acidified with HCl to pH *ca.* 2 and the precipitate washed well with water; yield 16.5 g (75 %), m.p. 268 °C (H_2O). Anal: $C_{11}H_9NO_4$: C,H. ^{1}H NMR (DMSO-d_6): 3.97 (OMe), 7.0–7.6 (arom). IR (KBr): 1700 (4-CO), 1660 cm^{-1} (2-CO). MS: 219 (76,M), 190(41), 173(100), 161(43), 159(16), 148(21), 146(31), 145(96).

*4-Carboxy-8-chloro-3-methoxyquinolin-2(1*H*)-one* 4b was prepared as above from 3-chloro-*N*-(methoxyacetyl)isatoic acid in 76 % yield, m.p. 225 °C (decomp: H_2O). Anal. $C_{11}H_8ClNO_4$: C,H. ^{1}H NMR (DMSO-d_6) δ 3.92 (OMe), 7.2–7.7 (arom). IR (KBr): 1700 (4-CO), 1640 (2-CO). MS: 255/253(17/53,M). 226/224(10/31), 211(8), 210(12) 209(45), 208(28), 207(76), 195(12), 182(22), 181(32), 180(80), 179(100), 153(23), 151(34).

*3-Hydroxyquinolin-2(1*H*)-one* 5a. A mixture from 4-carboxy-3-methoxyquinolin-2(1*H*)-one (35.0 g 0.16 mol), 48 % aq. HBr (100 ml) and acetic anhydride (100 ml) was heated under reflux for 5 d. The title compound as HBr salt was precipitated from the cold solution. The free base was obtained by dissolution of this salt in 1 M NaOH followed by neutralization with HCl, which led to precipitation; yield 22.2 g (84 %), m.p. 266 °C.[3]

*8-Chloro-3-hydroxyquinolin-2(1*H*)-one* 5b was prepared as above from 4-carboxy-8-chloro-3-methoxyquinolin-2(1*H*)-one in 73 % yield, m.p. 210 °C (MeOH). Anal. $C_9H_6ClNO_2$: C,H. ^{1}H NMR (DMSO-d_6) δ 7.0–7.5 (arom).KBr: 1660 cm^{-1} (CO). UV (1 M KOH/MeOH): 341 (logε 3.88), 329(3.84), 260 mm (4.16). MS: 197/195(31/100,M), 179/177(5/15), 169/167(15/50), 151/149(6/17), 138(20).

*8-Chloro-3-hydroxyquinoline-2(1*H*)-thione* 6b. A mixture from 8-chloro-3-hydroxyquinolin-2(1*H*)-one (8.0 g, 0.04 mol) and phosphorus pentasulfide (10.0 g, 0.045 mol) in pyridine (100 ml) was heated under reflux for 48 h. The pyridine was then distilled off, 2 M HCl (120 ml) added to the residue and the mixture heated to boiling. The title compound was precipitated on cooling: yield 8.0 g (92 %), m.p. 150 °C (EtOAc). Anal. C_9H_6ClNOS: C,H. ^{1}H NMR (DMSO-d_6): δ 7.2–7.8 (m). UV (1 M KOH in MeOH): 376 (logε 4.05), 263 nm (4.51). MS: 213(35), 211(100), 185(2), 183(8), 148(21), 114(6).

*9-Chloro-1,2-dihydrothiazolo[3,2-*a*]quinolinium-4-olate* 7b. A mixture from 8-chloro-3-hydroxyquinoline-2(1*H*)-thione (3.0 g, 0.015 mol) and 1,2-dibromoethane (5.6 g, 0.03 mol) in methanolic sodium methoxide (NaOMe, 0.03 mol; 200 ml) was heated at 60 °C for 24 h. The mixture was then concentrated to a small volume and the precipitate which separated from the cold mixture was crystallized from water; yield 2.5 g (70 %), m.p. 232 °C. Anal. $C_{11}H_8ClNOS$: C,H. ^{1}H NMR (DMSO-d_6): 3.58 (2H-3), 5.80 (2H-2), 6.68 (H-5), 7.0–7.5. MS: 239/237 (37/100,M), 213(3), 211(24), 209(48), 197(3), 196(9), 195(11), 194(23), 183(3), 181(8), 173(8).

*3-Hydroxy-1-(2-mercaptoethyl)quinolin-2(1*H*)-one* 8a. 1,2-Dihydrothiazolo[3,2-*a*]quinolinium-4-olate[3a] (1.0 g, 5 mmol) was added to l M NaOH (25 ml) and the mixture heated under reflux for 2 h. The cold reaction mixture was neutralized with aqueous HCl, the mixture extracted with chloroform, the dried ($MgSO_4$) solution concentrated

to a small volume when the title compound was precipitated; yield 0.8 g (72 %), m.p. 128 °C ($CHCl_3$). Anal. $C_{11}H_{11}NO_2S$: C,H. ^1H NMR (DMSO-d_6): δ 2.62 (N-CH_2), 4.45 (S-CH_2), 7.0–7.7 (arom). IR (KBr): 1620 cm^{-1} (CO). UV (1 M KOH in MeOH): 341 (logε 4.07), 328 (4.06), 310 (sh.; 3.82), 251 nm (4.14). MS: 221 (19, M), 204 (2), 192(2), 182(2), 177(3), 175(3), 174(8), 162(34), 161(100).

*8-Chloro-*N*-(2-mercaptoethyl)quinolin-2(1*H*)-one* 8b was prepared as above from 9-chloro-1,2-dihydrothiazolo[3,2-*a*]quinolinium-4-olate in 77 % yield, m.p. 111 °C (MeOH). Anal. $C_{11}H_{10}ClNO_2S$: C,H. ^1H NMR (DMSO-d_6): 2.88 (N-CH_2), 4.60 (S-CH_2), 6.8–7.5 (arom). IR (KBr): 1630 cm^{-1} (CO). UV (1 M KOH in MeOH): 342 (log ε 4.05), 328 (4.02), 316 nm (sh.; 3.97), 257 (4.21). MS: 255 (0.2, M), 220(35), 219(13), 204(16), 197(32), 195(100), 177(18), 169(9), 167(27), 149(15).

*3-Hydroxy-*N*-vinylquinoline-2(1*H*)-thione* 9a. A solution of 1,2-dihydrothiazolo[3,2-*a*]quinolinium-4-olate[3a] (1.0 g, 5 mmol) in dry DMF (100 ml) was stirred at room temperature while a solution of 1 M potassium *tert*-butoxide (10 ml, 0.01 mol) was added dropwise. The mixture was stirred for another 30 min before neutralization with acetic acid. The residue after evaporation at reduced pressure was shaken with water (20 ml), the mixture extracted with chloroform, the dried ($MgSO_4$) chloroform solution filtered through a short silica gel column and the chloroform distilled off; yield 0.6 g (63 %), m.p. 111 °C (MeOH). Anal. $C_{11}H_9NOS$: C,H. ^1H NMR (DMSO-d_6): δ 5.5 (H-β, *J* 16 Hz), 5.9 (H-β, J 8 Hz), 6.7–8 (H-α, 5H-arom.). UV (1 M KOH in MeOH): 400 (logε 4.43), 390 (sh., 4.38), 282 (4.11), 248 (4.37). MS: 203 (50,M), 202(100), 177(1), 174(2), 173(3), 117(3), 116(6), 115(5).

*8-Chloro-3-hydroxy-*N*-vinylquinoline-2(1*H*)-thione* 9b and *8-chloro-3-hydroxy-2-vinylthioquinoline* 10b were prepared from 9-chloro-1,2-dihydrothiazolo[3,2-*a*]quinolinium-4-olate by treatment with potassium *tert*-butoxide as above. The vinyl isomers were separated by chromatography on a column of silica gel using chloroform for elution. The *N*-vinyl isomer *9b* was obtained in 10 % yield, m.p. 139 °C (MeOH/$CHCl_3$). Anal. $C_{11}H_8ClNOS$: C,H. ^1H NMR (DMSO-d_6): δ 4.97 (H-β, *J* 16 Hz), 5.56 (H-β, *J* 8 Hz), 7.0–7.8 (H-α, 4H-arom.). UV (1 M KOH in MeOH): 406 (logε 3.75), 385 (3.85), 260 nm (4.47). MS: 239 (10,M), 238 (17), 237 (27), 236 (42), 213 (36), 211 (100), 183 (17), 151 (14).

The *S*-vinyl isomer *10b* was obtained in 52 % yield, m.p. 124 °C (MeOH). Anal. $C_{11}H_8ClNOS$: C,H. ^1H NMR (DMSO-d_6): δ 5.62 (H-β, *J* 10 Hz), 5.67 (H-β, *J* 17 Hz), 7.0–8.0 (H-α, 4H-arom.). UV (1 M KOH in MeOH): 366 (logε 3.96), 351 (3.88), 268 nm (4.44). MS: 239 (25,M), 238(38), 237(70), 236(100), 213(24), 211(75), 181(20), 169(22), 151(25), 148(26).

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