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N-Quaternary Compounds. Part XLVI.¹ Contrasting Regioselectivities in Bromination and Chlorination of the Dihydrothiazolo[3,2-*a*]pyridinium- 8-olate Systems

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Simple pyridinium systems resist electrophilic substitution. A 6- or 8-amino substituent in dihydrothiazolo[3,2-*a*]pyridinium derivatives does not introduce sufficient activation for such substitution.² A hydroxy substituent in the 8-position, however, activates the system for ready substitution in the 7-position.³ With a strong electron withdrawing substituent attached to the pyridine ring, the dihydrothiazolo[3,2-*a*]pyridinium ion undergoes electrophilic substitution as a pseudo-base in which case the new substituent enters a pyridine *beta* position, *viz.* at C-6 or at C-8.²

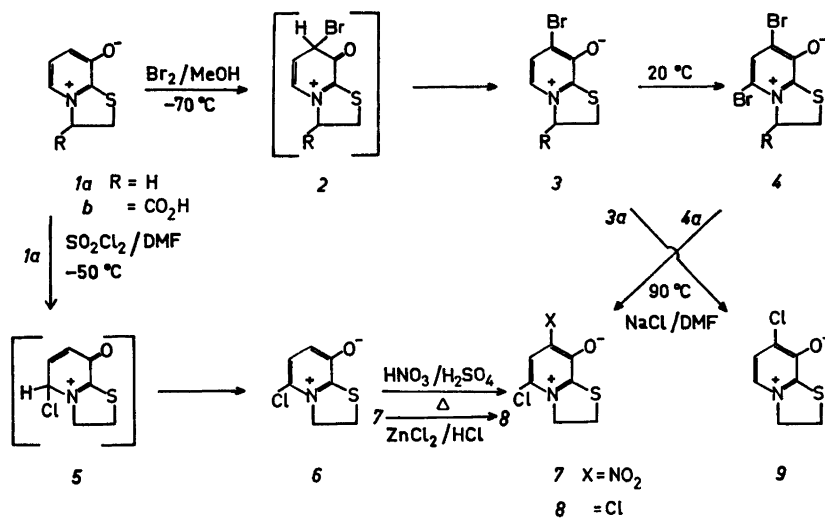
Without a 5-substituent in the 8-hydroxy derivative, which presumably reacts as the olate *I*, electrophilic substitution may occur in either the 5- or the 7-position and finally in both positions. Bromination with one equivalent of bromine reagent gave at room temperature mixtures of mono- and dibromo products. Preparatively, the dibromo derivative *4a* is available by the use of two equivalents of bromine in methanol. A 3-carboxy group does not interfere with the bromination at C-5 and *Ib* gives *4b*. At -70°C in methanol, however, the 7-bromo derivative *3a* was selectively formed on very slow addition of one equivalent of bromine. The assignment of the 7-bromo structure to the regioisomer formed, rests on the ^1H NMR coupling J 6.5 Hz which corresponds to coupling between vicinal α,β -protons in the pyridine ring. The monochloro derivative obtained by direct substitution, on the other hand, has coupling J 8.5 Hz which corresponds

to coupling between vicinal β,γ -protons in pyridines, and hence this isomer is assigned the 5-chloro structure *6*. Further confirmation for the structural assignments follows from the nucleophilic displacement of the bromine in *3a* with chlorine, as discussed below, in which case the coupling J 6.5 Hz is less than for the monochloro product from the direct substitution, and hence the product after bromine displacement must be the 7-chloro derivative *9*.

Chlorinating agents such as *N*-chlorosuccinimide or chlorine led to oxidation of *I* and sulfoxide formation.⁴ A good reagent for selective chlorination in the pyridine ring, however, was found to be sulfuryl chloride in dimethylformamide (DMF) at low temperature (-40 to -50°C). Once the 5-chloro derivative *6* had been formed, further chlorination was difficult to effect without oxidation of the sulfur atom. Nitration of *6* in the 7-position, however, readily occurs using a combination of nitric acid and sulfuric acid. A nitro group situated in an activated position in an electron deficient system can be displaced by nucleophiles.⁵ In this case it was found that the nucleophilic substitution to yield the dichloro derivative *8* could be achieved by heating *7* with zinc chloride in 3 *N* HCl. Alternatively, *8* can be obtained by nucleophilic displacement of both bromine atoms in *4a* with chlorine atoms by heating *4a* with sodium chloride in DMF. In a similar manner the 7-chloro derivative *9* was prepared from its bromo analogue *3a*.

The regioselective bromination in the 7-position is not unexpected in view of numerous literature reports which rationalise preferential vicinal substitution to a strong electron donating substituent, by initial coordination with the electrophile. Rationalisation of the regioselective chlorination in the 5-position, seems less obvious. The chlorine is introduced as an electrophile, and not as a nucleophile by addition to an intermediate pyridinium species, since no bromine was incorporated when the reaction was run in the presence of lithium bromide. The actual chlorinating reagent may well be a relatively bulky complex between sulfuryl chloride and DMF which may for steric reasons prefer the *para* position to the oxygen function.

Experimental. 7-Bromodihydrothiazolo[3,2-*a*]pyridinium-8-olate HBr-salt *3a*. Bromine (4.8 g, 0.03 mol) in methanol (70 ml) at -70°C was added dropwise over 10 h to a solution of dihydrothiazolo[3,2-*a*]pyridinium-8-olate HBr-salt (7.0 g, 0.03 mol) in methanol (600 ml) at -70°C . The solution was then allowed to reach room temperature. The residual material after evaporation of the solvent was recrystallised thrice from small volumes of water; yield 3.0 g (32%), m.p. 245°C (decomp). Anal. $\text{C}_7\text{H}_8\text{BrNOS}\cdot\text{HBr}$: C, H. ^1H NMR (60 MHz, TFA): δ 3.9 ($\text{CH}_2\text{-S}$), 5.2 ($\text{CH}_2\text{-S}$), 7.7 and 8.1 (Pyr., J 6.5 Hz).



5,7-Dibromodihydrothiazolo[3,2-a]pyridinium-8-olate HBr-salt 4a. Bromine (16.0 g, 0.10 mol) in methanol (100 ml) was added dropwise at room temperature to a solution of dihydrothiazolo[3,2-a]pyridinium-8-olate HBr-salt (11.9 g, 0.05 mol) in methanol (200 ml). The precipitated product was collected the next day; yield 12.0 g (66%), m.p. 280°C (decomp.) (aq. HBr). Anal. $\text{C}_7\text{H}_5\text{Br}_2\text{NOS}\cdot\text{HBr}$: C, H. ^1H NMR (60 MHz, TFA): δ 4.0 ($\text{CH}_2\text{-S}$), 5.4 ($\text{CH}_2\text{-N}$), 8.0 (H-6).

5,7-Dibromo-8-hydroxydihydrothiazolo[3,2-a]pyridinium-3-carboxylate 4b. Bromine (5.6 g, 0.04 mol) was added dropwise to a solution of 8-hydroxydihydrothiazolo[3,2-a]pyridinium-3-carboxylate (4.2 g, 0.015 mol) in water (300 ml). The decolourised solution was concentrated to a small volume and the solid precipitate recrystallised from water; yield 2.5 g (47%), m.p. 220°C (decomp.). Anal. $\text{C}_7\text{H}_5\text{Br}_2\text{NO}_3\text{S}$: C, H. ^1H NMR (60 MHz, TFA): δ 4.3 (CH_2 , m.), 6.5 (H-3), 8.0 (H-6).

5-Chlorodihydrothiazolo[3,2-a]pyridinium-8-olate HCl-salt 6. Dihydrothiazolo[3,2-a]pyridinium-8-olate (7.6 g, 0.05 mol) was dissolved in DMF (500 ml) and the solution cooled to -50°C . Sulfuryl chloride (6 ml, 0.07 mol) was then added dropwise to this solution at -40 to -50°C with stirring. When the addition was completed, the reaction mixture was slowly allowed to reach room temperature. The reaction mixture was then evaporated at reduced pressure and the residue triturated with a little ethanol before recrystallisation from a small volume of water; yield 7.4 g (75%), m.p. 270°C (decomp.). Anal. $\text{C}_7\text{H}_5\text{ClNOS}\cdot\text{HCl}$: C, H. ^1H NMR (60 MHz, TFA): δ 3.9 ($\text{CH}_2\text{-S}$), 5.3 ($\text{CH}_2\text{-N}$) 7.4 and 7.7 (Pyr., J 8.5 Hz).

The betaine can be obtained by passage of an aqueous solution over a strong cation exchanger (Amberlite. IR-120, H^+), washing

with water until the washings no longer contain Cl^- and finally elution with 0.6 N aq. NH_3 .

5-Chloro-7-nitrodihydrothiazolo[3,2-a]pyridinium-8-olate 7. 5-Chlorodihydrothiazolo[3,2-a]pyridinium-8-olate (5.9 g, 0.03 mol) was dissolved in acetic acid (100 ml) and a solution of fuming nitric acid (5 ml) and concentrated sulfuric acid (4 ml) in acetic acid (50 ml) added dropwise with stirring at room temperature. The reddish precipitate of the title compound was collected and recrystallised from ethanol; yield 4.3 g (60%), m.p. 180–190°C (decomp.). Anal. $\text{C}_7\text{H}_5\text{ClN}_2\text{O}_3\text{S}$: C, H. ^1H NMR (60 MHz, TFA): δ 4.1 ($\text{CH}_2\text{-S}$), 5.5 ($\text{CH}_2\text{-N}$), 1.9 (H-6).

5,7-Dichlorodihydrothiazolo[3,2-a]pyridinium-8-olate 8. (a) 5,7-Dibromodihydrothiazolo[3,2-a]pyridinium-8-olate HBr-salt in DMF was heated as below with sodium chloride at 90°C for 4 h and the product worked up in the same way; yield 55%, m.p. 275°C (decomp.) (H_2O). Anal. for HBr-salt $\text{C}_7\text{H}_5\text{Cl}_2\text{NOS}\cdot\text{HBr}$: C, H. ^1H NMR (60 MHz, TFA): δ 4.0 ($\text{CH}_2\text{-S}$), 5.3 ($\text{CH}_2\text{-N}$), 7.6 (H-6).

(b) A solution of 5-chloro-7-nitrodihydrothiazolo[3,2-a]pyridinium-8-olate (1.1 g, 0.005 mol) and zinc chloride (2.0 g) in 3 N HCl (50 ml) was heated under reflux for 3 days. The solution was then evaporated, the residue dissolved in water and the solution passed through a cation exchange column (IR-120 Amberlite, H^+). Elution with water removed the chloride ions before the title compound was eluted with 0.6 N aq. NH_3 . Evaporation of the NH_3 -eluates left the betaine; yield 78%, m.p. 220–222°C (decomp.).

7-Chlorodihydrothiazolo[3,2-a]pyridinium-8-olate HBr-salt 9. A solution of 7-bromodihydrothiazolo[3,2-a]pyridinium-8-olate as HBr-salt (2.0 g, 0.006 mol) in DMF (175 ml) at 90°C was saturated with sodium chloride and kept

at this temperature for 4 h. The reaction mixture was then allowed to reach room temperature and the precipitated salt removed before the filtrate was evaporated to dryness. The residue was triturated with ether and recrystallised from a small volume of water; yield 0.9 g (56 %), m.p. > 270°C (decomp.). Anal. C₂₁H₃₄ClNOS.HBr: C, H. ¹H NMR (60 MHz, TFA): δ 3.9 (CH₂-S), 5.2 (CH₂-N), 7.6 and 8.2 (Pyr., J 6.5 Hz).

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Isoabienol, the Principal Diterpene Alcohol in *Pinus sylvestris* Needles

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The abienols, labdane diterpenoids with conjugated double bonds in the side chain, are widely distributed in the firs. To our knowledge there is only one isolation of isoabienol reported, namely from the oleoresin of *Abies sibirica* Ldb. (Siberian fir).¹ However, it has later been shown, that this natural product was actually impure *trans*-abienol.²

The present paper reports the finding of isoabienol as the principal diterpene alcohol in needles of *Pinus sylvestris* L. (Scots pine). In an earlier paper the major diterpene alcohol from technical foliage of Scots pine has erroneously been characterized as abienol.³

The isolated compound had m.p. 68–68.5°C, $[\alpha]_D^{20}$ –6.4 (CHCl₃), λ_{max} (EtOH) 227 nm (log ϵ 4.26) ν_{max} (KBr) 3320, 2920, 1600, 1463, 1390, 890 cm⁻¹.

Hydrogenation yielded a product identical with tetrahydroabienol (a quasiracemic compound⁴) obtained from the hydrogenation of *cis*-abienol from the oleoresin of Norway spruce, (¹³C NMR, MS, GLC), suggesting a normal labdane skeleton.

The mass spectrum of compound 1 [IP 70 eV; *m/e* (rel. int.): 290 (2, M), 275 (3, M–CH₃), 272 (5, M–H₂O), 257 (13, M–H₂O–CH₃), 191 (100, M–H₂O–side chain) indicated the presence of a bis-unsaturated side chain and the λ_{max} value led us to suggest conjugation.

The ¹H NMR spectrum showed signals from five vinylic protons. Three of the protons formed an AMX-system at 270 MHz (CDCl₃): δ 6.38 (H-14, dd, *J* 10.6 and 17.6 Hz), 5.34 (H-15, dd, *J* 17.6 and 0.7 Hz), 5.09 (H-15, dd, *J* 10.6 and 0.7 Hz). The two vinylic protons at C-16 gave a rather broad singlet at δ 5.05. Three separate methyl singlets were shown, one from the C-18 and C-19 methyls at δ 0.80, one from the C-17 methyl at δ 1.16 and one from the C-20 methyl at δ 0.88. The allylic protons at C-12 gave a symmetrical multiplet centered at δ 2.32.

The low field part of the noise decoupled ¹³C NMR spectrum (CDCl₃) showed four signals due to the olefinic carbons in the side chain. Two of the signals appeared as triplets in the off-resonance decoupled spectrum confirming the presence of two terminal vinylic methylene groups. In analogy to the spectrum of myrcene,⁵ the triplet at δ 113.5 was assigned to C-16 and the other one at δ 115.6 to C-15. In the off-resonance decoupled spectrum the C-14 signal