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N-Quaternary Compounds

Part XXXI. Sulphur Participation in the Cyclisation of a 2-Bromo-3-α-pyridylthiopropionic Acid

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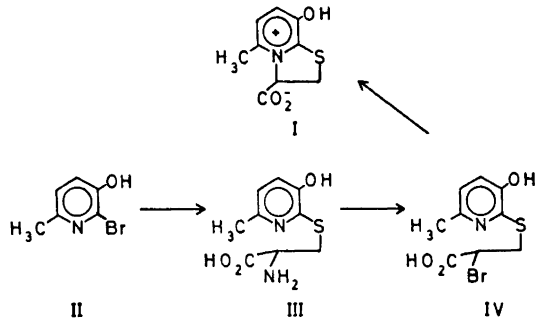
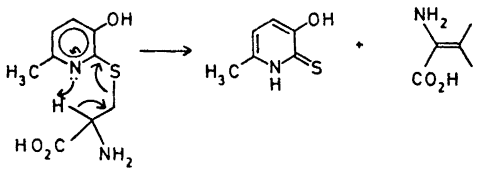
(*R*)-2-Bromo-3-(3-hydroxy-6-methyl-2-pyridylthio)propionic acid has been synthesised from (*R*)-cysteine. Cyclisation of the bromo acid gives 8-hydroxy-5-methyldihydrothiazolo[3,2-a]pyridinium-3- and -2-carboxylates with configurational inversion. The isomeric mixture is formed by sulphur participation in the reaction and the isomer ratio varies with experimental conditions.

Pyrid-2-thiones add to 2-bromo-2,3-unsaturated carbonyl compounds.[2,3] The initial Michael adduct is rapidly cyclised over the pyridyl nitrogen and the compound isolated from the reaction mixture is a dihydrothiazolo[3,2-a]pyridinium derivative.[2,3] As part of a project to establish the stereochemical course for the overall reaction this paper deals with studies of the cyclisation step. For this purpose an optically active 2-bromo-3-α-pyridylthiopropionic acid of known absolute configuration was required since the chiroptical properties of 8-hydroxy-5-methyldihydrothiazolo[3,2-a]pyridinium-3-carboxylate (I) have already been correlated to its absolute stereochemistry.[4–6] 2-Bromo-3-(3-hydroxy-6-methyl-2-pyridylthio)propionic acid (IV) is very easily cyclised and must be obtained under mild experimental conditions. A successful synthesis from L-cysteine is shown in Scheme 1. The thiol group



Scheme 1.

in cysteine can be arylated on treatment with diazotised anilines in the presence of copper(I) salts.[7,8] A similar reaction using diazotised 2-amino-3-hydroxy-6-methylpyridine gave III in very low yield. Attention was therefore turned to the reaction of the 2-bromopyridine II with cysteine. The 2-pyridyl bromine is deactivated towards nucleophilic substitution by the other nuclear substituents in II and its displacement requires vigorous conditions.[9] In its reaction with cysteine in the presence of potassium carbonate only partial



III V VI

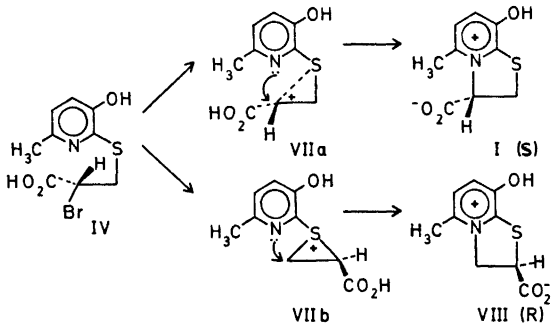
Scheme 2.

conversion to III was achieved due to decomposition reactions. Among the products on forcing the reaction, was the pyrid-2-thione V (Scheme 2). The latter must be formed from III through elimination, presumably in an intramolecular process. The amino acid III was isolated from the reaction mixture in 7 % yield, $[\alpha]_D^{25} = +129.0°$ (N HCl). Racemisation of III under the conditions for its formation was excluded by subjecting III to simulated reaction conditions in deuterium oxide. Despite the failure to incorporate deuterium at the chiral carbon the pyrid-2-thione V was formed. Any proton abstraction thus leads preferably to elimination in good agreement with the mechanism suggested in Scheme 2. As cysteine is expected to be optically stable under the reaction conditions, the product (III) is assumed optically pure.

Bromination of optically active α-amino acids by means of diazotisation in the presence of bromide ions goes with retention of the configuration. The optical purity is of the order of 90 % depending to some degree on the nature of the substituents.[10] The same stereochemical course has been claimed for the sulphur containing amino acids *S*-benzylcysteine[11] and methionine.[12] The bromo compound IV obtained by this diazotisation reaction from III has by analogy retained the (*R*)-configuration.

The bromo compound IV is highly reactive. At pH 2.5 it could be extracted from the diazonium solution into ethyl acetate but was rapidly cyclised to I at higher pH value. The cyclisation also takes place in ethyl acetate on standing. Due to its high reactivity IV is best distinguished from the hydrobromide of the cyclic product I by its spectroscopic properties. In acid solution both the amino acid III and the diazotised product have UV maxima at about 235 and 320 nm to be compared with 240 and 340 nm for the bicyclic product (I). The NMR shifts for the methylene and methine protons in trifluoroacetic acid are also different, the shifts being 6.1 and 5.3 τ for IV compared to 5.8 and 3.7 τ for I.

The optical purity of IV is uncertain. In view of previous findings [1,13] partial racemisation is expected to have taken place by nucleophilic bromide ion interchange in the bromo acid IV. On the other hand the bicyclic product (I) is optically stable.[14] The specific rotation shows the product to be of 65 % optical purity. Taking into account some racemisation of IV, the cyclisation must be highly stereospecific. The sign of the sodium D-line rotation shows the product to have the (*S*)-configuration.[4] The cyclisation therefore proceeds by configurational inversion. The same stereochemical course was observed in the cyclisation of 2-bromo-4-(3-hydroxy-6-methyl-2-pyridylthio)butyric acid.[1] The latter differs from IV in having an additional methylene group between the sulphur and the α-carbon. This higher homologue of IV requires heating for some time to effect cyclisation. It is well established that 5-membered rings are formed faster than 6-membered rings. The observed large reactivity difference in this case, however, leads to the additional invokement of sulphur participation in the cyclisation of IV (Scheme 3). Back-side displacement of the bromine results in configurational inversion (VIIa). In the next step, however, the pyridine nitrogen must add *cis* to the sulphur. A such steric course seems acceptable if the sulphur from some distance holds the positive charge and thereby the configuration. The suggested mechanism bears some resemblance to the accepted S_Ni mechanism in halogenations of alcohols which go with configurational retention.



Scheme 3.

Furthermore, in an episulphonium intermediate the nitrogen attack can occur on either the methine carbon (VIIa) or on the methylene carbon (VIIb) with the formation of the isomers I and VIII, respectively. Although I and VIII have very similar physico-chemical properties,[9] the chemical shifts in NMR of the dihydrothiazolo ring protons are different, and they can be distinguished chromatographically. In fact careful chromatography of the crude reaction product showed a small amount of VIII present. The conditions for cyclisation were then varied. The highest yield of VIII was obtained by sodium carbonate addition when the product was found to consist of I and VIII in the ratio 3:2 as estimated by NMR integration. The isomers were separated by chromatography. The specific rotation for I, $[\alpha]_D^{25} = +99°$

(0.1 N NaOH), corresponds to 65 % optical purity. The specific rotation for VIII was $[\alpha]_D^{25} = -19°$ (0.1 N NaOH). Its configuration is not known but the mechanism suggested for its formation in Scheme 3 leads to the assignment of (*R*)-configuration.

EXPERIMENTAL

(R)-*2-Amino-3-(3-hydroxy-6-methyl-2-pyridylthio)propionic acid (III).* A solution of 2-bromo-3-hydroxy-6-methylpyridine (11.3 g, 0.06 mol), (*R*)-cysteine hydrochloride (9.4 g, 0.06 mol), and potassium carbonate (24.8 g, 0.18 mol) in water (180 ml) was heated at 65°C for 3 days. The pH of the cold solution was then adjusted to 3.5, the solution extracted with 90 % phenol (3 × 30 ml), the phenolic solution washed with water (30 ml), ether (200 ml) added to the phenol solution, the separated water layer collected, the ether-phenol layer washed with water (4 × 30 ml), the combined water phases washed with a little ether and the aqueous solution concentrated to a small volume. The title compound was slowly precipitated on standing and was recrystallised from water to which had been added a little sodium bisulphite. The white crystalline material thus obtained had m.p. 221°C (decomp.); yield 1.0 g (7 %). (Found: C 47.36; H 5.11; N 11.99. Calc. for $C_9H_{12}N_2O_3S$: C 47.37; H 5.30; N 12.28). $[\alpha]_D^{25} = +129.0°$ ($c = 1$ in N HCl).

NMR in TFA: 7.20 τ (CH_3), 6.0 τ (CH_2), 5.3 τ (CH), 1.87 τ and 2.22 τ (pyridyl H^4 and H^5). UV in 0.1 N HCl: 318 nm (log ε 3.97) and 237 nm (3.59). 0.1 N NaOH: 326 nm (log ε 4.00) and 248 nm (3.90).

(R)-*2-Bromo-3-(3-hydroxy-6-methyl-2-pyridylthio)propionic acid (IV).* A solution of sodium nitrite (1.6 g, 0.02 mol) in water (10 ml) was added dropwise over 1 h with stirring to an ice-cold solution of (*R*)-2-amino-3-(3-hydroxy-6-methyl-2-pyridylthio)propionic acid (1.0 g, 0.0045 mol) in 5 N HBr (70 ml). The reaction mixture was then left at 0°C overnight before evaporation at reduced pressure.

NMR in TFA: 7.22 τ (CH_3), 6.12 τ (CH_2), 5.33 τ (CH), 1.92 τ and 2.32 τ (pyridyl H^4 and H^5). UV in 0.1 N HCl: Maxima at 320 nm and 235 nm. The absorption is variable due to the strong tendency for cyclisation to I.

(S)-*8-Hydroxy-5-methyldihydrothiazolo[3,2-a]pyridinium-3-carboxylate (I) and* (R)-*8-hydroxy-5-methyldihydrothiazolo[3,2-a]pyridinium-2-carboxylate (VIII).* An aqueous solution of the crude 2-bromopropionic acid (IV)hydrobromide on neutralisation was rapidly cyclised to I. The amount of the isomer VIII present in the product under these conditions was very small according to chromatography. Excess sodium carbonate addition led to increasing amounts of VIII reaching a maximum on saturation.

The product in either case was extracted into 90 % phenol solution from the aqueous solution at pH 3.5 as described for III, and the product isolated by freeze-drying of the final aqueous concentrate. NMR integration in TFA of the dihydrothiazolo protons for I (H^3 at 3.7 τ, $2H^2$ at 5.7 τ) and for VIII (H^2 and $2H^3$ in the region 4.2 – 5.1 τ) [9] shows the I/VIII ratio to be 3/2 after saturation of the reaction solution with sodium carbonate.

Compounds I and VIII were separated by TLC on silica gel plates using the system BuOH:AcOH:H_2O (100:22:50). Compound I has the higher R_F value. The separated bands were scraped off, extracted with methanol, the methanol solutions filtered through a short silica gel column and the filtered solutions concentrated to small volumes when the title compounds were precipitated.

Optical rotation for I $[\alpha]_D^{25} = +99°$ ($c = 0.6$ in 0.1 N NaOH); for VIII $[\alpha]_D = -19°$ ($c = 0.5$ in 0.1 N NaOH).

Physical data are otherwise as previously described.[9]

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