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REACTION OF OXIRANECARBONITRILE WITH L-CYSTEINE METHYL ESTER

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Summary: The title reaction yields (3R,5R) and (3R,5S) isomers of methyl 5-cyanotetrahydro-1,4-2H-thiazine-3-carboxylate, together with methyl 2-acetylthiazole-4-carboxylate as a minor by-product. The stereochemistry of the tetrahydrothiazine derivatives is discussed.

4-Acetyl-5-cyanotetrahydro-1,4-2H-thiazine-3-carboxylic acid (1) has recently been found as an unprecedented metabolite of acrylonitrile in rat.[1] The formation of 1 can be explained to be a resultant of a series of consecutive biotransformations, starting with metabolic oxidation of acrylonitrile to oxiranecarbonitrile (2)[2,3] which then undergoes enzyme-catalyzed conjugation with glutathione. We have attempted to prepare 1 according to Coghill *et al.*,[4-6] but the synthesis gave only a polymeric, non-melting (up to 300° C) material. In view of the postulated biosynthetic route it appeared interesting to study the reaction of 2 with L-cysteine methyl ester (3) with the aim to obtain preparative quantities of 1 and determine its stereochemistry.

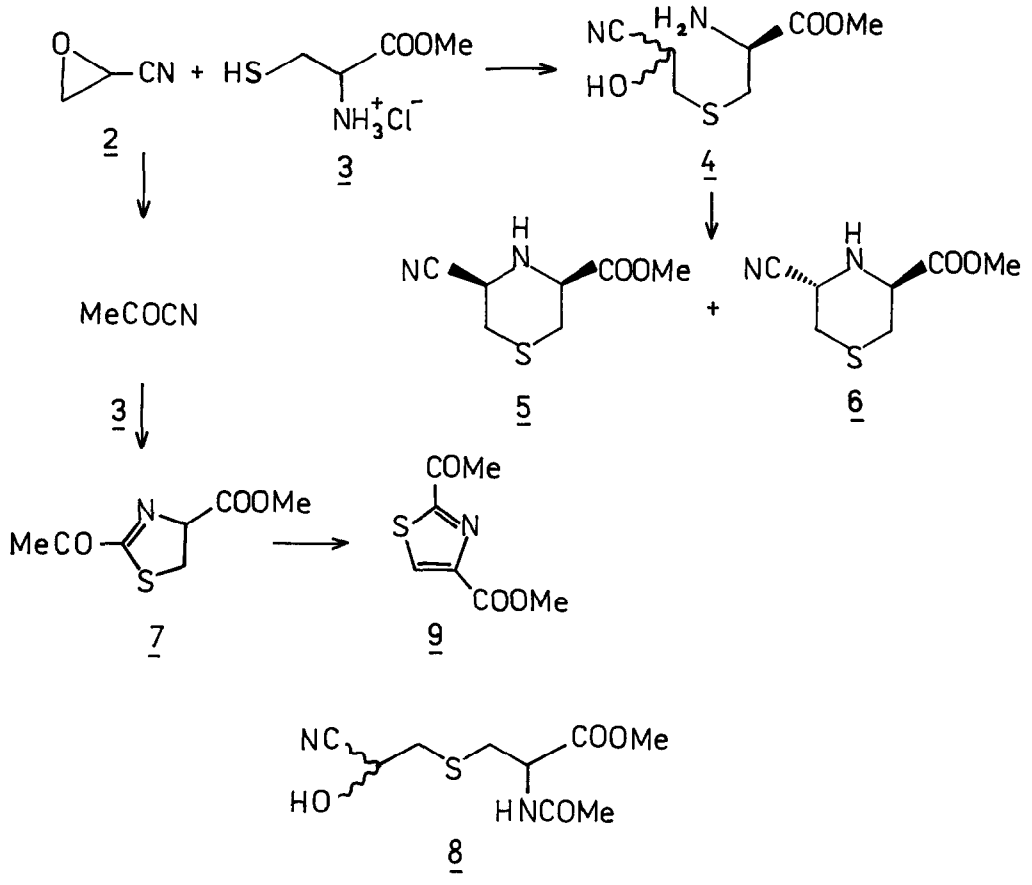
The reaction of 2[7] with the hydrochloride of 3 in a very diluted aqueous solution, to which potassium cyanide was successively added, afforded an oily product in 63% yield. The product, a mixture of three components by TLC (ethyl acetate-chloroform, 3:1), was separated by column chromatography (benzene-chloroform) to give two diastereoisomeric methyl 5-cyanotetrahydro-1,4-2H-thiazine-3-carboxylates, 5 (*cis*, m.p. 86 - 86.5°C, R_F 0.73) and 6 (*trans*, oil, R_F 0.67) accompanied by minor amounts of methyl 2-acetylthiazole-4-carboxylate, 9 (m.p. 99 - 101°C, R_F 0.80).[8] The structure of the methyl esters 5 and 6 was established through their ^{1}H-NMR and mass spectra.[9]

The formation of 5 and 6 can be accounted for by opening of the oxirane ring in 2 by the sulfur nucleophile of 3, giving rise to an intermediate S-(2-cyano-2-hydroxyethyl)-L-cysteine (4), which undergoes intramolecular Strecker reaction to give thiazines 5 and 6 (Scheme 1). By contrast, the reaction of 2 with an N-acetyl derivative of 3 stopped after the nucleophilic displacement step to yield exclusively N-acetyl-S-(2-cyano-2-hydroxyethyl)-L-cysteine (8), the structure of which was established by means of ^{1}H- and ^{13}C-NMR and mass spectral data.[10] No cyclized products were detected in the reaction mixture in this case, contrary to the findings of Guengerich *et al.*[3] It should be noted that acetylation of 5 and 6 with acetic

anhydride cleanly afforded the corresponding acetamides 10 (*cis*, m.p. 140 - 141°C, R_F 0.43 in chloroform-acetone, 3:1) and 11 (*trans*, m.p. 115 - 116°C, R_F 0.69).[11]

The formation of the minor product 9 from 2 and 3 can be visualized as being initiated by isomerisation of 2 to pyruvonitrile which reacts with 3 to give a thiazoline 7. Oxidation of the latter with air eventually leads to thiazole 9. Accordingly, 9 was detected by TLC as a product of the reaction of 3 with pyruvonitrile.

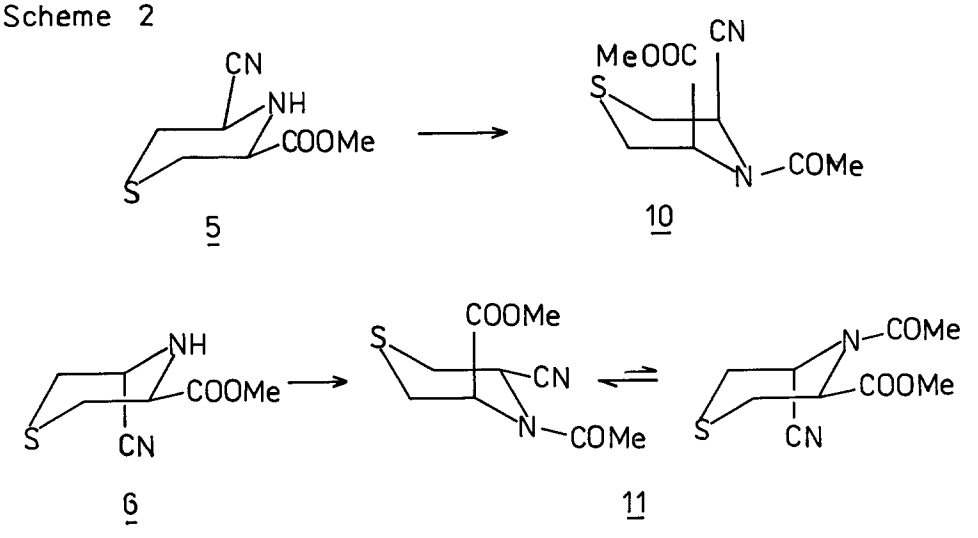
Scheme 1



The relative configuration of the cyano and ester groups in 5, 6, 10 and 11 and the conformation of the tetrahydrothiazine ring were examined through variable-temperature ^{1}H-NMR spectra.[12] The vicinal coupling constants of H-3 (δ 3.69, J = 9.4, 3.1 Hz) and H-5 (δ 4.05, J = 9.7, 2.7 Hz) in 5 indicate that the *cis*-isomer exists in a diequatorial conformation. In 6

the signal of H-5 is shifted downfield (δ 4.50, J = 3.4, 3.4 Hz) and the coupling pattern shows that the cyano group assumes an axial position. This simple situation is reversed in N-acetyl derivatives 10 and 11. The ^{1}H-NMR spectrum of the former isomer shows that the molecule exists in a reversed-chair conformation with both the ester and nitrile group being axial. This conformer is stable in the range of -60 to +20°C, at least. On the contrary, the *trans*-isomer 11 exists as a 2:1 mixture of two conformers, where the dominating component bears an axial ester group. Hence the presence of the amide moiety in 10 and 11 destabilizes conformers with equatorial groups in adjacent positions C-3 and C-5. Provided the configuration at the cysteine chirality center has not been changed in the cyclization step, it is possible to assign absolute configuration to all four thiazine derivatives 5, 6, 10 and 11, i.e. (3R,5S) for 5 and 10 and (3R,5R) for 6 and 11 (Scheme 2).

Scheme 2



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8. The physical constants and spectral data (^{1}H-NMR, IR, MS) of 9 agreed with those in: T.T. Sakai, J.M. Riordan, T.E. Booth and J.D. Glickson, J. Med. Chem., 1981, 279.
9. 5: ^{1}H-NMR ($CDCl_3$, 23°C): δ 4.05 (m, J = 9.7, 2.7 Hz, 1H), 3.79 (s, 3H), 3.69 (m, J = 9.4, 3.1 Hz, 1H), 2.88 (m, J = 12.0, 9.7 Hz, 1H). 2.75 (m, J = 13.3, 2.7, 1.0 Hz, 1H), 2.81 (m, J = 12.0, 3.1, 1.0 Hz, 1H), 2.77 (m, J = 12.0, 3.1, 1.0 Hz, 1H), 2.75 (bs, 1H); MS(m/z): 186 ($M^{+\cdot}$), 159 $(M - HCN)^{+\cdot}$, 127 $(M - COOCH_3)^+$.
6: ^{1}H-NMR ($CDCl_3$, 23°C): δ 4.50 (t, J = 3.4 Hz, 1H), 3.94 (m, J = 10.1, 2.6 Hz, 1H), 2.99 (dd, J = 13.5, 3.4 Hz, 1H), 2.92 (m, J = 13.3, 2.6 Hz, 1H), 2.78 (m, J = 13.3, 10.1 Hz, 1H), 2.66 (ddd, J = 13.5, 3.4, 1.5 Hz, 1H), 3.80 (s, 3H), 2.42 (bs, 1H); MS(m/z): 186 ($M^{+\cdot}$), 159 $(M - HCN)^{+\cdot}$, 127 $(M - COOCH_3)^+$.
10. 8: ^{1}H-NMR ($CDCl_3$, 22°C): δ 7.02 (m, 1H), 5.70 (bs, 1H), 3.19 (m, J = 14.3, 5.2 Hz, 1H), 3.06 (m, J = 14.3, 4.0 Hz, 1H), 4.65 (m, 1H), 2.97 (m, J = 15 Hz, 2H), 2.10 (s, 3H); ^{13}C-NMR ($CDCl_3$ + CD_3OD): δ 119.17 (d, ^3J = 5.4 Hz), 61.37 + 61.26 (dm, ^1J = 154 Hz, ^2J = 3.5 Hz), 52.40 (qs), 52.10 (dm, ^1J = 143 Hz), 36.76 (tm, ^1J = 142 Hz, ^3J = 8.5, 3.8 Hz), 34.49 + 34.57 (tm, ^1J = 143 Hz), 22.14 (qs); MS(m/z): 219 $(M - HCN)^{+\cdot}$, 201, 176, 144, 43.
11. 10: ^{1}H-NMR (CD_3COCD_3, -30°C): δ 6.09 (t, J = 3.5 Hz, 1H), 5.33 (t, J = 3.5 Hz, 1H), 3.78 (s, 3H), 3.32, 3.17 (m), 3.11 (d, J = 3.5 Hz), 3.03 (d, J = 3.5 Hz), 2.20 (s, 3H); MS(m/z): 228 ($M^{+\cdot}$), 186 $(M - CH_2CO)^{+\cdot}$, 185 $(M - CH_3CO)^+$, 127.
11: ^{1}H-NMR (CD_3COCD_3, -30°C): major conformer, δ 5.83 (dd, J = 6.0, 3.5 Hz), 5.34 (t, J = 3.5 Hz), 3.54, 3.42, 3.17 (d, J = 3.5 Hz), 3.22 (m), 2.10 (s, 3H), 3.87 (s, 3H); minor conformer, δ 5.78 (t, J = 3.5 Hz), 4.80 (dd, J = 6.0, 3.5 Hz), 3.22 (m), 3.50, 3.42 (d, J = 3.5 Hz), 3.73 (s, 3H), 2.30 (s, 3H); IR ($CHCl_3$): 10 or 11: 1680 vs (N-C=O), 1750 vs (ester) cm^{-1}.
12. The variable-temperature measurements were kindly carried out by Dr. P. Trška, Institute of Chemical Technology, Prague. The autors are grateful for his help.

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