SYNTHESIS OF 2-OXOHEXAHYDROTHIENO[3,4-d]IMIDAZOLE DERIVATIVES

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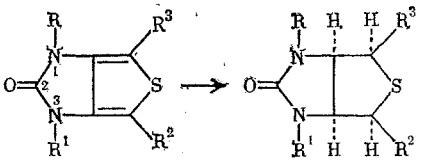
The synthesis of 2-oxo-2,3-dihydro-1H-thieno[3,4-d]imidazole derivatives with substituents at N^1, N^3, C^4, and C^6 (I)-(III) was described in a previous paper [1]. In the present paper we studied the reduction of (I)-(III) with triethylsilane in CF_3COOH as described in [2-4]. The reduction of the 3- and 4-methyl-2-oxo-2,3-dihydro-6-(δ-carbomethoxybutyl)-1H-thieno[3,4-d]imidazoles (I) and (II), and subsequent alkaline hydrolysis of the intermediate methyl ethers (IV) and (V), gave in yields of 82 and 72% the 3- and 4-methyl-2-oxo-6-(δ-carboxybutyl)hexahydrothieno[3,4-d]imidazoles (VI) and (VII), which on the basis of the following data were assigned a complete cis configuration.



(I)-(III); (XIV) (IV)-(X)

R=R²=H, R¹=Me (I), (IV), (VI); R=R¹=H, R²=Me (II), (V), (VII); R=R¹=Me, R²=H (III), (IX); R=R¹=R²=H (VIII), (X), (XIV); R³=$(CH_2)_4COOMe$ (I)—(V), (X), (XIV); $(CH_2)_4COOH$ (VI)—(IX).

Compounds (VI) and (VII) are stable when heated with dilute H_2SO_4 solution, similar to biotin (VIII) with a cis-coupling of the rings [5]. The complete cis configuration of (VI) is also indicated by the fact that the methylation of (VI) with a mixture of CH_2O and HCOOH gives the N,N'-dimethyl derivative (IX), which is identical with the methylation product of the authentic d*l*-biotin (VIII). Compound (VII) in its melting point, IR spectrum, and TLC data coincides with the previously described high-melting stereoisomer of 2-oxo-4-methyl-6-(δ-carboxybutyl)hexahydrothieno[3,4-d]imidazole, which has a complete cis configuration [6].

The IR spectra of (VI)-(VIII) have certain characteristics that can be used to identify them. Compounds (VI) and (VIII) give three bands in the region of the stretching vibrations of carbonyl groups (1635-1710 cm^{-1}), while (VII) gives two absorption bands. Two bands in the region of higher frequencies (1695-1745 cm^{-1}) are observed for the corresponding methyl ethers (V) and (X).

The high stereoselectivity of the cis-reduction of (I) and (II) can be explained if it is assumed that the approach of the $HSiEt_3$ to the intermediate protonated forms (XI) and (XII), and also the approach of the proton to the dihydrothiophene derivative (XIII), is from the less shielded side. The number and position of the substituents both exert a substantial influence on the ease of reducing the 2-oxo-2,3-dihydro-1H-thieno[3,4-d]imidazole system. As can be seen from the above given data, (I) and (II), which contain electron-donor groups at N^3, C^4, and C^6, which facilitate the formation of cations (XI) and (XII), are reduced very smoothly. The reduction of compound (XIV), which lacks alkyl substituents at N^1, N^3, and C^4, proceeds with great difficulty and, after hydrolysis of the intermediate methyl ether (X), leads only to traces of biotin (VIII). However, unsatisfactory results are also obtained in the reduction of compound (III) with CH_3 groups on both of the nitrogen atoms N^1 and N^3, which probably hinder the approach of $HSiEt_3$ to the intermediate cation (XII).

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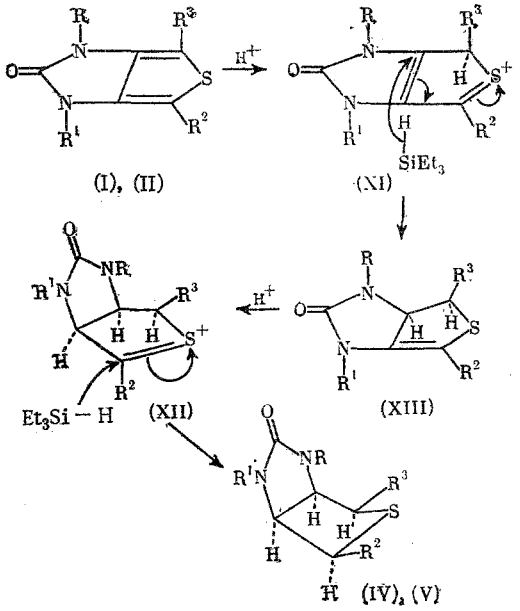

EXPERIMENTAL

The IR spectra were taken as KBr pellets on a UR-20 spectrometer, while the PMR spectra were taken in CF_3COOH solution on a Tesla B5497 instrument, using HMDS as the internal standard. The TLC was run on Silufol plates in the system: 3:2 ethyl acetate (EA)—alcohol (the spots were detected with aqueous $K_3Fe(CN)_6$ solution, and then with iodine vapors).

2-Oxo-3-methyl-6-(δ-carboxybutyl)hexahydrothieno[3,4-d]imidazole (VI). A mixture of 0.3 g of 2-oxo-2,3-dihydro-3-methyl-6-(δ-carbomethoxybutyl)-1H-thieno[3,4-d]imidazole (I) [1] and 0.8 ml of $HSiEt_3$ in 3 ml of CF_3COOH was heated for 30 h at 50° (here and subsequently the bath temperature), evaporated in vacuo, and the residue was mixed with 1 ml of conc. HCl and 5 ml of alcohol, kept for 12 h at 20°, and evaporated. The residue was treated with a solution of 0.5 g of KOH in 5 ml of alcohol, left standing for 12 h at 20°C, and evaporated again. The residue was dissolved in 2 ml of water and acidified with dilute HCl solution (1:1) to pH ∿1. The precipitate was filtered, washed in succession with water and acetone, and dried in the air. We obtained 0.28 g of crude (VI), which was purified by heating with 3 ml of 10% H_2SO_4 solution for 1 h at 140°. After cooling to 20°, the precipitate was filtered, washed with water, dissolved in a solution of 0.16 g of Na_2CO_3 in 50 ml of water; 0.3 g of AB-172 P resin was added, and the mixture was refluxed for 5 min. The filtrate was cooled to 20° and acidified with dilute HCl solution (1:1) to pH ∿1. The precipitate was filtered, washed in succession with water and acetone, and dried in the air. We obtained 0.24 g (82%) of (VI), mp 205-206°, R_f 0.53. Infrared spectrum (ν, cm^{-1}): 1188, 1198, 1235, 1269, 1290, 1312, 1326, 1338, 1412, 1468, 1522, 1635, 1680, 1700, 2865, 2935, 3290. PMR spectrum (δ, ppm): 1.24 m ($CH_2CH_2CH_2$), 2.06 d (CH_2CO), 2.52 s (CH_3N), 2.64 s (CH_2S), 2.90 m (CHS), 4.00 m, 4.18 m (NCHCHN) [2].

1,8-Dimethyl-2-oxo-6-(δ-carboxybutyl)hexahydrothieno[3,4-d]imidazole (IX). A mixture of 0.5 g of imidazole (VI) and 1 g of formalin in 5 g of HCOOH was heated for 40 h at 100°, evaporated in vacuo, and the residue was treated with a 1:1 EA—MeOH mixture. The precipitate was filtered, washed with EA, and dried in the air. We obtained 0.2 g (38%) of (IX), mp 140-142° (from MeOH), R_f 0.71. Infrared spectrum (ν, cm^{-1}): 765, 1191, 1230, 1265, 1296, 1315, 1414, 1464, 1508, 1678, 1718, 2930, 3120. PMR spectrum (δ, ppm): 1.23 m ($CH_2CH_2CH_2$), 2.06 d (CH_2CO), 2.50 s (CH_3N), 2.60 s (CH_3N, CH_2S), 3.02 m (CHS), 3.88 m and 4.12 m (NCHCHN). Found: C 52.58; H 7.36; N 10.34; S 11.62%. $C_{12}H_{20}N_2O_3S$. Calculated: C 52.90; H 7.31; N 10.30; S 11.76%. The (IX), obtained by the methylation of dl-biotin (VIII), under the above described conditions, had the same properties.

2-Oxo-4-methyl-6-(δ-carboxybutyl)hexahydrothieno[3,4-d]imidazole (VII). The reduction of 0.3 g of 2-oxo-2,3-dihydro-4-methyl-6-(δ-carboxybutyl)-1H-thieno[3,4-d]imidazole (II) [1] with $HSiEt_3$, as described above, gave 0.28 g of crude (VII). After purification we isolated 0.21 g (72%) of (VII) with mp 264-265°, R_f 0.63. Infrared spectrum (ν, cm^{-1}):

1198, 1256, 1320, 1330, 1467, 1495, 1660, 1710, 2870, 2932, 3056, 3270. PMR spectrum (δ, ppm): 0.96 t (CH_3CH), 1.30 m ($CH_2CH_2CH_2$), 2.06 d (CH_2CO), 3.02 m (2CHS), 3.78 m and 4.18 s (NCHCHN). Found: C 51.30; H 7.08; N 10.67; S 12.55%. $C_{11}H_{18}N_2O_3S$. Calculated: C 51.16; H 6.95; N 10.85; S 12.40%. The obtained (VII) did not depress the mixed melting point with an authentic specimen (mp 260-261°) [6] and had the same IR spectrum and R_f.

Infrared spectrum of dl-biotin (VIII) (ν, cm^{-1}): 1164, 1201, 1215, 1236, 1268, 1290, 1325, 1412, 1432, 1468, 1488, 1655, 1690, 1710, 2875, 2940, 3074, 3245.

Infrared spectrum of d-biotin (ν, cm^{-1}): 1020, 1079, 1102, 1120, 1142, 1158, 1206, 1240, 1272, 1295, 1320, 1342, 1432, 1465, 1484, 1645, 1694, 1710, 1955, 2480, 2840, 2856, 2860, 2900, 2921, 2935, 2960, 3310, 3365.

2-Oxo-4-methyl-6-(δ-carbomethoxybutyl)hexahydrothieno[3,4-d]imidazole (V). With stirring and cooling in ice, to 14 ml of MeOH was gradually added 3.5 ml of $SOCl_2$, and then 0.7 g of (VII), and the mixture was kept for 72 h at 20° and then evaporated in vacuo. The residue was treated with excess aqueous Na_2CO_3 solution and then extracted with EA. The extract was dried over $MgSO_4$, the solvent was removed, and the precipitate was washed with ether and dried in the air. We obtained 0.44 g (60%) of (V), mp 205-206° (from H_2O), R_f 0.65. Infrared spectrum (ν, cm^{-1}): 1144, 1212, 1465, 1695, 1738, 2942, 3400. PMR spectrum (δ, ppm): 0.97 t (CH_3CH), 1.31 m ($CH_2CH_2CH_2$), 2.06 t (CH_2CO), 3.03 m (2CHS), 3.37 s (CH_3O), 3.79 m and 4.18 m (NCHCHN). Found: C 53.01; H 7.47; N 10.53; S 11.73%. $C_{12}H_{20}N_2O_3S$. Calculated: C 52.90; H 7.31; N 10.30; S 11.76%.

The methyl ether of dl-biotin [6, 7] was obtained in a similar manner in 66% yield, mp 130-132° (from H_2O). Infrared spectrum (ν, cm^{-1}): 1175, 1208, 1468, 1710, 1745, 2950, 3278.

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CONCLUSIONS

We synthesized the cis-3- and 4-methyl-2-oxo-6-(δ-carboxybutyl)hexahydro[3,4-d]-imidazoles by the reduction of the 3- and 4-methyl-2-oxo-2,3-dihydro-6-(carboxybutyl)-1H-thieno[3,4-d]imidazoles with $HSiEt_3$ in CF_3COOH and subsequent alkaline hydrolysis of the intermediate methyl ethers.

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