SYNTHESIS AND INVESTIGATION OF 4-CARBETHOXYAMINO-3-KETOTHIOPHENE

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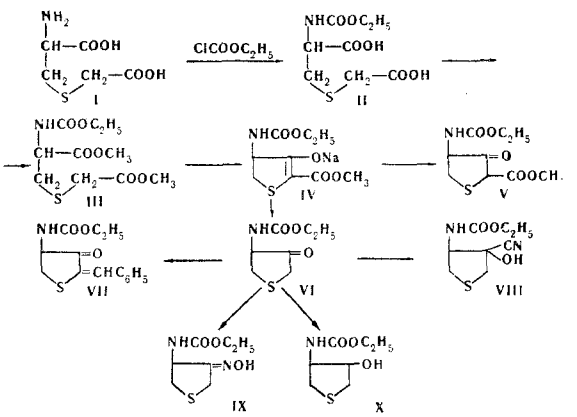
4-Carbethoxyamino-3-ketothiophane (VI) is synthesized via a number of intermediates. Derivatives with substituents at positions 2 and 3 are prepared.

The complexity of the synthesis of biotin from simple compounds lies not only in the multiplicity of stages, but also to a large extent in the steric ambiguity due to the molecule's containing three asymmetric carbon atoms. A key compound in the synthesis of biotin is cis-3, 4-diamino-2-(δ-carboxybutyl)thiophane. It appeared possible to secure cis-3, 4-substituents in the molecule by forming an imidazole ring by intramolecular cyclization of the appropriate compound; for the starting point of the latter 4-carbethoxyamino-3-ketothiophane (VI) can be used. Compound VI is synthesized in a few stages. Treatment of S-carboxymethyl-L-cysteine (I) [1] with ethyl chloroformate at -10° C in the presence of sodium acetate gives N-carbethoxy-S-carboxymethyl-L-cysteine (II). Methanol in the presence of sulfuric acid esterifies compound (II) to the dimethyl ester of N-carbethoxy-S-carboxymethyl-L-cysteine (III).



Dieckmann cyclization of III can proceed in two directions, to give a thiophane or a thiazine derivative. Cyclization of diester III in methanol in the presence of 1 mole sodium methoxide at 0° C gives a 91% yield of the sodium salt of 4-carbethoxyamino-3-keto-2-carbomethoxythiophane (IV), indicating an unambiguous reaction. Treatment of sodium salt IV with 1 N hydrochloric acid in methanol gives 4-carbethoxyamino-3-keto-2-carbomethoxythiophane (V). Heating compound IV with hydrochloric—acetic acid hydrolyzes and decarboxylates it to 4-carbethoxyamino-3-ketothiophane (VI).

It is known that 3-ketothiophanes with mobile hydrogen atoms in the position 2 methylene group can undergo the Knoevenagel [2, 3] and Michael [4] reactions. We have attempted to carry out these reactions with compound VI. Compound VI and benzaldehyde in the presence of piperidine in a current of nitrogen give 4-carbethoxyamino-3-keto-2-benzylidenethiophane (VII). This reaction could not, however, be brought about in the presence of piperidine acetate and pyridine. Furthermore, VI does not react with acrolein and methylvinylketone in the presence of pyridine, piperidine, or sodium methoxide (Michael reaction).

Treatment of compound VI with HCN in the presence of pyridine, however, gives 4-carbethoxyamino-3-cyano-3-hydrothiophane (VIII), while treatment with hydroxylamine in pyridine solution gives 4-carbethoxyamino-3-oximinothiopane (IX). $NaBH_4$ in methanol readily reduces the keto group in compound VI to a hydroxyl one, and the product is 4-carbethoxyamino-3-hydroxythiophane (X).

EXPERIMENTAL

N-Carbethoxy-S-carboxymethyl-L-cysteine (II). 10.6 ml (0.11 mole) Et chloroformate plus a solution of 11.8 g crystalline NaOAc in 100 ml water were added simultaneously to a solution of 20.0 g (0.11 mole) S-carboxymethyl-L-cysteine (I) in 64 ml 3.5 N NaOH cooled to −10° C, then the whole stirred for 1-1/2 hr at 0° C, and left for 16 hr at 18°–20° C. The reaction products were made acid to Congo Red with conc HCl, extracted with ether (3 × 50 ml), and the ether removed under vacuum. 40 ml benzene was added to the oily residue, and the solution was concentrated under vacuum. Syrupy compound, yield 20.35 g (74%).

$[\alpha]_D^{20}$ − 24.8° C (c 1.0 EtOH). Found: C 38.48; 38.62; H 5.68; 5.49; N 5.54; 5.65%, calculated for $C_8H_{13}NO_6S$: C 38.24; H 5.21; N 5.75%.

Dimethyl ester of N-carbethoxy-S-carboxymethyl-L-cysteine (III). 1 ml Conc H_2SO_4 was added to a solution of 5.0 g II in 10.0 ml dry MeOH, and the whole refluxed for 5 hr. The reaction products were poured into 10 ml water, the oily layer separated off, and the aqueous layer extracted with benzene, (5 × 3 ml). The combined extracts were washed with $NaHCO_3$ solution, then with water, and dried over Na_2SO_4. The solvent was taken off, to give 2.9 g (52.5%) of an oily substance; $[\alpha]_D^{20}$ − 34.7° C (c 1.0 EtOH). Found: C 42.75; 42.77; H 5.99; 6.11; N 5.41; 5.13; S 11.42; 11.18%, calculated for $C_{10}H_{17}NO_6S$: C 43.01; H 6.14; N 5.02; S 11.48%.

Sodium salt of 4-carbethoxyamino-3-keto-2-carbomethoxy-2, 3-dehydrothiophane (IV). A solution of Na methoxide prepared from 0.14 g (0.0063 mole) sodium and 4 ml MeOH was added to a solution of 1.75 g (0.0063 mole) III in 2 ml dry MeOH at 0° C. The whole was left for 1 hr at 18°–20° C and for 2 hr at 0° C. The precipitate was separated off and washed with ether, yield 1.53 g (91%). Found: C 40.20; 39.95; H 5.03; 5.15; N 4.75; 4.76%, calculated for $C_9H_{12}NO_5SNa$: C 40.14; H 4.49; N 5.20%.

4-Carbethoxyamino-3-keto-2-carbomethoxythiophane (V). A suspension of 8.8 g IV in MeOH was brought to pH 2 by adding 2 N HCl, then extracted with benzene. The benzene extract was washed with $NaHCO_3$ solution, then with water. The solvent was taken off, leaving an oily material, yield 7.38 g (91%). Found: C 43.21; 43.34; H 5.29; 5.25; N 5.10; 5.29%, calculated for $C_9H_{13}NO_5S$: C 43.91; H 5.29; N 5.67%.

2, 4-Dinitrophenylhydrazone: yellow needles mp 159°–160° C (ex EtOH). Found: C 42.18; 42.22; H 4.14; 4.41%, calculated for $C_{15}H_{17}N_5O_8S$: C 42.15; H 4.01%.

4-Carbethoxyamino-3-ketothiophane (VI). 7.0 g IV was dissolved in 54 ml HCl–AcOH–H_2O (1:2.5:2.5), the solution refluxed for 15–20 min, cooled, and the products extracted with $CHCl_3$. The extracts were washed with $NaHCO_3$ solution, then with water, and dried over Na_2SO_4. The solvent was taken off, an ether–petrol ether mixture (1:3) added to the residue, and the whole left for 16 hr at 0° C. The precipitate was separated off as colorless needles, soluble in EtOH, $CHCl_3$, and benzene; mp 54.5°–55° C. Yield 2.04 g (52.6%). Found: C 44.79; 44.56; H 5.77; 5.52; N 7.57; 7.71; S 16.86; 17.28%, calculated for $C_7H_{11}NO_3S$: C 44.43; H 5.86; N 7.40; S 16.94%.

2,4-Dinitrophenylhydrazone: colorless needles, soluble in EtOH and Me_2CO, mp 157°–158° C (ex EtOH). Found: C 42.52; 42.38; H 4.17; 4.11; N 18.31; 18.34%, calculated for $C_{13}H_{15}N_5O_6S$: C 42.27; H 4.09; N 18.96%.

4-Carbethoxyamino-3-keto-2-benzylidenethiophane (VII). 0.26 ml (0.0027 mole) freshly-distilled benzaldehyde and 0.05 ml piperidine were added to a solution of 0.5 g (0.0027 mole) VI in 2 ml dry MeOH, in a current of nitrogen, the whole stirred for 4 hr at 30° C, then left for 16 hr at 0° C. The precipitate was filtered off; colorless plates soluble in EtOH, mp 126°–127° C (ex EtOH–ether–petrol ether 1:6:2). Yield 0.25 g (34.2%). Found C 60.50; 60.38; H 5.40; 5.37; N 5.34; 5.08%, calculated for $C_{14}H_{15}NO_3S$: C 60.63; H 5.46; N 5.05%.

4-Carbethoxyamino-3-cyano-3-hydrothiophane (VIII). 2.0 g VI and 0.5 ml pyridine were added to 4 ml hydrocyanic acid at 0° C, the whole left at 0° C for 16–18 hr, and the hydrocyanic acid then removed under vacuum. The residue was transferred to a separating funnel, $CHCl_3$ and ice added, and the mixture shaken with 1.2 ml 2.5 N HCl. The $CHCl_3$ layer was washed with water, then $CHCl_3$ taken off, ether–petrol ether (1:3) added to the residue, and the resultant mass rubbed until a crystalline precipitate formed. The precipitate was separated off and washed with the same ether–petrol ether mixture. Yield 1.34 g (59.1%), colorless plates, soluble in EtOH, mp 84.5°–85° C. Found C 44.43; 44.50; H 5.63; 5.56; N 13.49; 13.29%, calculated for $C_8H_{12}N_2O_3S$: C 44.43; H 5.59; N 12.95%.

4-Carbethoxyamino-3-hydroximinothiophane (IX). 0.22 g (0.0033 mole) Hydroxylamine hydrochloride was added to a solution of 0.5 g (0.0025 mole) VI in 2.5 ml pyridine, and the mixture held at 30° C for 18–20 hr. 5 ml water was added, then the mixture extracted with $CHCl_3$ (3 × 4 ml). The $CHCl_3$ extracts were transferred to a separating funnel, ice added, and the mixture shaken with 3 ml 2.5 N HCl. The $CHCl_3$ layer was washed with $NaHCO_3$ solution (2 × 3 ml), and then with water (4 ml). The solvent, was taken off, the precipitate separated off and washed with petrol ether. Yield 0.25 g (64.8%), colorless prisms, soluble in EtOH and $CHCl_3$, mp 140°–140.5° C, (ex $CHCl_3$). Found: C 41.35; 41.06; H 5.99; 5.91; N 13.93; 14.28%, calculated for $C_7H_{12}N_2O_3S$: C 41.16; H 5.92; N 13.72%.

4-Carbethoxyamino-3-hydroxythiophane (X). 0.1 g $NaBH_4$ was added gradually to a solution of 0.5 g VI in 6 ml MeOH at 50°–60° C, and the whole stirred for 2 hr at the same temperature. After cooling, 15 ml water was added, the mixture made acid to Congo Red with 1 N HCl, then extracted with $CHCl_3$. The extract was dried over $MgSO_4$. The $CHCl_3$ was taken off, and the residue rubbed with ether, then recrystallized ex EtOH, yield 0.3 g (59.9%), mp 92°–93° C. Found: C 44.16; 44.18; H 6.49; 6.59; N 7.49; 7.23%, calculated for $C_7H_{13}NO_3S$: C 43.96; H 6.85; N 7.32%.

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