AN INVESTIGATION OF THE SYNTHESIS OF 3-AMINO-4-ETHOXYCARBONYLAMINOTETRAHYDROTHIOPHENE

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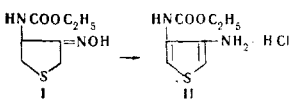
Methods of synthesis of 3-amino-4-ethoxycarbonylaminotetrahydrothiophene (VIII), and of other diamines, from 4-ethoxycarbonylaminotetrahydro-3-hydroxyiminothiophene (I), 2-benzylidene-4-ethoxycarbonylaminotetrahydro-3-hydroxyiminothiophene (III) and 4-ethoxycarbonylaminotetrahydro-3-hydroxythiophene (V) were investigated. Chlorination of V followed by the Gabriel synthesis gave VIII.

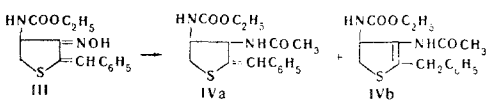
The possibility of converting the keto group of 4-ethoxycarbonylaminotetrahydro-3-oxothiophene, which we have synthesized earlier [1], into the amino group via the oxime (I) has been examined. The hydroxyimino group in the tetrahydrothiophenes is known to be rather difficult to reduce to the amino group [2–4]. We have not succeeded in reducing either I or III with zinc in acetic or hydrochloric acid, or by catalytic hydrogenation over a palladium catalyst (on $BaSO_4$ or carbon). It is possible to obtain the amino derivative II from I only with concomitant dehydrogenation of the tetrahydrothiophene. The reaction was carried out by passing hydrogen chloride into the solution in anhydrous ether. The structure of 3-amino-4-ethoxycarbonylaminothiophene (II) was confirmed by its UV absorption spectrum, which has λ_{max} at 266 nm (ε 0.69 · 10^4; compound I does not absorb in the near UV), and by its IR spectrum, which shows a band at 1615 cm^{-1} which is characteristic of conjugated double bonds (formation of the thiophene ring)



Similar reactions have been observed previously, for example with 4-ethoxycarbonyltetrahydro-3-hydroxyiminothiophene [2].

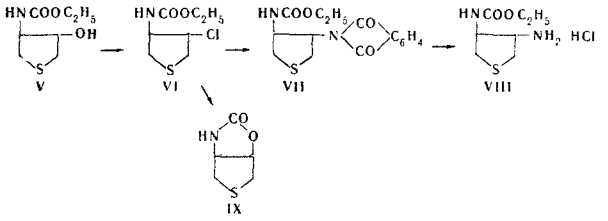
Compound III was obtained by the oximation of 2-benzylidene-4-ethoxycarbonylaminotetrahydro-3-oxothiophene in pyridine solution.

The acylamino derivative IV was obtained by the reduction of III with zinc in acetic acid, in the presence of acetic anhydride. Addition of hydrogen apparently took place in the 1,2- and 1,4-positions, which is characteristic of conjugated systems [5]. The amino derivative IV, as in the case of similar compounds [5], appears to be a mixture of isomers (3-acetamido-2-benzylidene-4-ethoxycarbonylaminotetrahydrothiophene (IVa) and 3-acetamido-2-benzyl-4-ethoxycarbonylamino-4,5-dihydrothiophene (IVb)).



Attempted selective hydrolysis of IV (a and b) to the free amino compounds was, however, unsuccessful.

The hydrochloride VIII was prepared from V. The hydroxy group of V was first replaced by chlorine by the action of thionyl chloride in the presence of pyridine in chloroform solution, followed by the Gabriel reaction with the resulting 3-chloro-4-ethoxycarbonylamino tetrahydrothiophene (VI) to give 4-ethoxycarbonylaminotetrahydro-3-phthalimidothiophene (VII). This was hydrolyzed to the diamine VIII.



Attempts to replace the chlorine atom in VI directly by the amino group by treatment with 30% methanolic ammonia at 150°–175° C in presence of copper sulfate gave the cyclic lactone IX. The chlorine was apparently replaced by a hydroxy group, with subsequent lactonization. Reaction in liquid ammonia at 100°–120° C led to the recovery of unchanged starting material VI.

EXPERIMENTAL

3-Amino-4-ethoxycarbonylaminothiophene hydrochloride (II). A solution of I [1] (0.5) in anhydrous ether (10 ml) and anhydrous ethanol (10 ml) was saturated with hydrogen chloride for 30 min at 0° C, and kept for 16 hr at 18°–20° C. The precipitate which separated was filtered off and washed with ether. Yield 0.27 g (48.8%) of colorless plates, mp 166°–167° C (from ethanol). Found, %: C 38.04, 38.00; H 4.65, 4.87; N 12.24, 12.66; Cl 16.13, 16.05. Calculated for $C_7H_{10}N_2O_2S \cdot HCl$, %: C 37.75; H 4.98; N 12.58; Cl 15.91.

2-Benzylidene-4-ethoxycarbonylaminotetrahydro-3-hydroxyiminothiophene (III). Hydroxylamine hydrochloride (0.3 g) was added to a solution of 2-benzylidene-4-ethoxycarbonylaminotetrahydro-3-oxothiophene [1] (1.0 g) in pyridine (6 ml), and the mixture heated for 18–20 hr at 35°–40° C. Water (12 ml) was added and the mixture extracted with chloroform (3 × 8 ml). The chloroform extracts were transferred to a separating funnel, ice was added, and they were shaken with 2.5 N HCl (about 8 ml). The chloroform layer was washed with sodium bicarbonate solution (2 × 6 ml) and water (10 ml). The precipitate was separated off and washed with ether. Yield 0.4 g (29%). colorless prisms, soluble in chloroform and ethanol, mp 153°–154° C (from ethanol). Found, %: C 41.35, 41.06; H 5.99, 5.91; N 13.93, 14.28. Calculated for $C_{14}H_{16}N_2O_3S$, %: C 41.16; H 5.92; N 13.72.

3-Acetamido-2-benzylidene-4-ethoxycarbonylaminotetrahydrothiophene (IVa) and 3-acetamido-2-benzyl-4-ethoxycarbonylamino-4,5-dihydrothiophene (IVb). A solution of III (0.4 g) in a mixture

of acetic acid (7 ml) and acetic anhydride (8 ml) was stirred, and zinc dust (1.5 g) was added at 18°–20° C. After 18 hr, a further 1.5 g of zinc dust was added at 35°–40° C, and the mixture kept at this temperature for 5 hr. The reaction mixture was cooled to 0° C, and filtered from zinc and zinc acetate. The filtrate was evaporated in vacuo, the residue triturated with ether, and the IVa and IVb that separated out were filtered off. Yield 0.25 g (58%) of colorless prisms, mp 184°–185° C (from ethanol). Found, %: C 59.78, 59.89; H 6.44, 6.30; N 8.73, 8.54. Calculated for $C_{16}H_{20}N_2O_3S$, %: C 59.98; H 6.30; N 8.74.

3-Chloro-4-ethoxycarbonylaminotetrahydrothiophene (VI). To a solution of V [1] (1.0 g) in chloroform (3 ml) and pyridine (0.5 ml) at 0° C was added slowly a mixture of chloroform (3 ml) and thionyl chloride (1.5 ml), and the mixture stirred for 2 hr at 18°–20° C. The solvent was removed in vacuo, the residue was extracted with chloroform, and the chloroform extracts were washed with water and dried over sodium sulfate. The chloroform was removed and the residue was recrystallized from petroleum ether (1:4). Yield 0.65 g (59.5%), colorless prisms, mp 90°–92° C. Found, %: C 40.03, 40.20; H 5.48, 5.64; Cl 16.78, 16.85; N 6.60, 6.45. Calculated for $C_7H_{12}ClNO_2S$, %: C 40.09; H 5.77; Cl 16.91; N 6.68.

4-Ethoxycarbonylaminotetrahydro-3-hydroxythiophene-γ-lactone (IX). A mixture of VI (1 g), methanol (20 ml) saturated with ammonia to 30% concentration, and copper sulfate (0.01 g) was heated at 150°–175° C for 10 hr. The mixture was cooled and filtered, the solvent was removed in vacuo, and the residue was recrystallized from benzene to give 0.46 g (67%) of colorless plates, mp 127°–128° C. Found, %: C 41.36; H 5.15; N 9.29, 9.37; S 22.20, 22.07. Calculated for $C_5H_7NO_2S$, %: C 41.36; H 4.86; N 9.65; S 22.10.

4-Ethoxycarbonylaminotetrahydro-3-phthalimidothiophene (VIII). A solution of VI (1.3 g) in dimethylformamide (6 ml) was added slowly with stirring to a suspension of potassium phthalimide (1.4 g) in dimethylformamide (7 ml) at 20° C. The mixture was stirred for 4 hr at 50°–60° C, 6 hr at 90°–100° C, and 1 hr at 150° C. After cooling, the precipitate was filtered off, the dimethylformamide was distilled off and the residue was extracted with chloroform. The chloroform extracts were washed with 2 N KOH and water. The chloroform was removed and the residue was recrystallized from ethanol, giving 0.8 g (65.4%) of colorless needles, mp 199.5°–200.5° C. Found, %: C 56.45, 56.10; H 4.86, 5.09; N 8.45, 8.01. Calculated for $C_{15}H_{16}N_2O_4S$, %: C 56.23; H 5.05; N 8.73.

3-Amino-4-ethoxycarbonylaminotetrahydrothiophene hydrochloride (VIII). A solution of VII (0.4 g) and hydrazine hydrate (0.01 g) in methanol (10 ml) was boiled for 2 hr. The methanol was removed, 5 N HCl (8 ml) was added to the residue, and the mixture was boiled for 2 hr. The precipitate was filtered off, and the filtrate was extracted with chloroform to remove unchanged VII, neutralized with KOH, and again extracted with chloroform. The chloroform was removed and hydrochloric acid (0.5 ml) was added to the oily residue. Excess acid was removed in vacuo, and the residue was recrystallized from a mixture of dioxane and ether (1:2). Yield 0.23 g (79.5%), colorless prisms mp 167°–168° C. Found, %: C 37.01, 36.80; H 6.92, 6.84; Cl 15.62, 16.20; N 12.05, 12.33. Calculated for $C_7H_{14}N_2O_2S \cdot HCl$, %: C 37.13; H 6.67; Cl 15.64; N 12.35.

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