FORMATION OF AN ACYCLIC DISULFIDE FROM AN 4-ACYLAMINO-3-OXO-THIOPHAN

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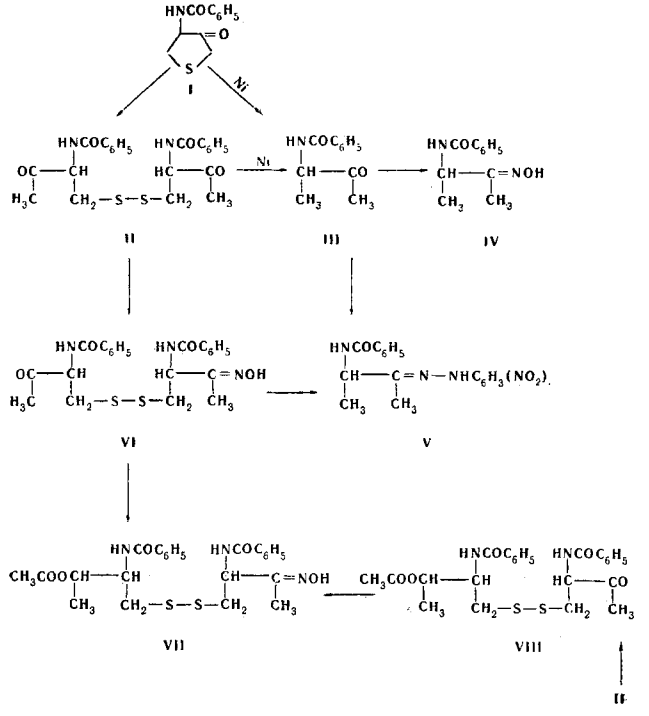
It has been established that 4-benzoylamino-3-oxothiophan is cleaved at a S—C bond by methanol in the presence of sodium methoxide with the formation of an acyclic disulfide.

We have shown that the reaction of 4-benzoylamino-3-oxothiophan (I) with methanol in the presence of sodium methoxide forms a substance with mp 211-212° C with a doubled molecular weight in relation to I. We ascribed to the substance obtained the structure of di(2-benzoylamino-3-oxobutyl) disulfide (II). Its formation can apparently be explained by the reductive cleavage of I to the corresponding mercaptan at the S—C bond of the —CO—CH_2—S— grouping of the heterocyclic ring with subsequent oxidation by atmospheric oxygen to the disulfide. This reaction does not take place in a current of nitrogen. In the presence of ethanol, the yield of compound II is considerably smaller. The reductive power of alcohols has been reported in a number of papers [1,2]. It must also be mentioned that the cleavage of a substituted oxothiophan [4-hydroxy-2-(δ-isopropoxycarbonyl) butyl-3-oxothiophan] under the action of aluminum isopropoxide led to the corresponding disulfide [3] (the oxo group was reduced to an alcohol group).



On desulfuration with Raney nickel, both I and II form 2-benzoylamino-3-butanone (III), which gives an oxime (IV) and a 2,4-dinitrophenylhydrazone (V).

In the IR spectrum of II there is an absorption band at 450 cm^{-1} relating to the stretching vibrations of the —S—S— bond (the vibrations of the —S—S— group of cystine are represented by a frequency of 454 cm^{-1}) [4].

The oximation of II leads to the monooxime (VI). The presence of one free keto group in this compound was established by the preparation from it, after desulfuration with Raney nickel and reaction with 2,4-dinitrophenylhydrazone, of the hydrazone V and also by the absence of a reaction for an alcohol group with acetyl chloride in the presence of pyridine. The reduction of VI with $NaBH_4$ and subsequent acetylation gave 3-acetoxy-2-benzoylaminobutyl 2-benzoylamino-3-hydroxyiminobutyl disulfide (VII), which was also obtained by the $NaBH_4$ reduction of II to VIII with subsequent acetylation and oximation. It follows from these reactions that only one keto group in compound II was reduced.

EXPERIMENTAL

Di(2-benzoylamino-3-oxobutyl) disulfide (II). A solution of sodium methoxide (from 0.02 g of Na and 2 ml of methanol) was added to 6 g of 4-benzoylamino-3-oxothiophan (I) in 25 ml of methanol and the mixture was stirred at 35°-40°C for 3 hr and was then neutralized with 1 N hydrochloric acid. The precipitate that deposited was filtered off and was washed with water and acetone. Yield 5.86 g (84%). Colorless prisms, mp 211°-212°C. Found, %: C 60.10, 59.90; H 5.45, 5.16; N 6.29, 6.46; S 14.66, 14.55; mol. wt. 444.5, 431.2 (Rast). Calculated for $C_{22}H_{24}N_2O_4S_2$, %: C 59.43; H 5.44; N 6.30; S 14.43; mol wt. 444.56.

2-Benzoylamino-3-butanone (III). a) To a solution of 4.4 g of I in 40 ml of methanol was added 23 g of Raney nickel, and the mixture was boiled for 9 hr. The catalyst was separated off and the filtrate was concentrated in vacuum to give a sirupy residue. Yield 3.6 g (94.8%). Found, %: C 68.78, 69.19; H 7.07, 7.12; N 7.08, 7.20. Calculated for $C_{11}H_{13}NO_2$, %: C 69.15; H 6.87; N 7.32.

b) By the same method, 10 g of II yielded 7.8 g (78%) of compound III. Found, %: C 68.36, 68.59; H 6.96, 7.00; N 7.41, 7.33.

Oxime of 2-benzoylamino-3-butanone (IV). A mixture of 0.5 g of compound III, obtained by method (a), 3 ml of pyridine, and 0.2 g of hydroxylamine hydrochloride was kept at 30°C for 22 hr. The pyridine was evaporated off in vacuum, 10 ml of chloroform was added and the solution was washed with 0.2 N hydrochloric acid and with water and was dried with magnesium sulfate. The solvent was distilled off and 1 ml of ethanol was added to the residue. The precipitate was separated off and washed with ether. Yield 0.37 g (69.2%). Colorless needles, mp 172°-173°C (from ethanol). Found, %: C 63.89, 63.87; H 6.70, 6.68; N 13.93, 14.28. Calculated for $C_{11}H_{14}N_2O_2$, %: C 64.06; H 6.84; N 13.58. From the compound III prepared by method (b) an oxime was obtained which gave no depression of the melting point on admixture with substance IV. Found, %: N 13.44, 13.74; mol. wt. 200.0, 205.1. Calculated for $C_{11}H_{14}N_2O_2$, %; N 13.58; mol. wt. 206.254.

2,4-Dinitrophenylhydrazone of 2-benzoylamino-3-butanone (V). A solution consisting of 0.3 g of 2,4-dintrophenylhydrazine, 0.3 g of sulfuric acid, and 6 ml of anhydrous ethanol was added to a solution of 0.3 g of III obtained from I in 6 ml of anhydrous ethanol. After 4 hr, the precipitate that had deposited was separated off. Yield 0.35 g (64.3%). Yellow needles, mp 200°–201°C (from acetone). Found, %: C 55.14, 54.89, H 4.46, 4.52, N 18.76, 19.03. Calculated for $C_{17}H_{17}N_5O_6$, %: C 54.98; H 4.61; N 18.86. The 2,4-dinitrophenylhydrazone of compound III obtained by method (b) gave no depression of the melting point in admixture with substance V.

Monooxime of di(2-benzoylamino-3-oxobutyl) disulfide (VI). A mixture of 0.7 g of II, 6 ml of pyridine, and 0.14 g of hydroxylamine hydrochloride was kept at 30°C for 22 hr. The pyridine was evaporated off, 10 ml of water was added, and the mixture was extracted with chloroform. The chloroform extract was acidified with 2.5 N hydrochloric acid to Congo Red, washed with water, and dried with magnesium sulfate. The solvent was driven off. Yield 0.2 g (41.5%). Colorless plates, mp 179°–180°C (from ethanol). Found, %: C 57.94, 58.02; H 5.29, 5.34; N 8.96, 8.70; mol wt. 465.2, 449.5. Calculated for $C_{22}H_{25}N_3O_4S_2$, %: C 57.49; H 5.48; N 9.15; mol. wt. 459.60.

Desulfuration of compound VI. Eight grams of Raney nickel was added to a solution of 1 g of VI in 15 ml of methanol and the mixture was boiled for 8 hr. The catalyst was separated off and the solvent was distilled off. The residue was extracted with ether. The ether was driven off, and from the oily residue (0.5 g) a 2,4-dinitrophenylhydrazone was obtained. Yield 0.3 g, mp 200°–201°C (from acetone). The substance gave no depression of the melting point in admixture with compound V.

3-Acetoxy-2-benzoylaminobutyl-2-benzoylamino-3-hydroxyiminobutyl disulfide (VII). One gram of $NaBH_4$ was slowly added to a solution of 2.5 g of VI in 25 ml of methanol and the mixture was stirred at 30°C for 2 hr 30 min, after which 50 ml of water was added and the mixture was acidified with 2 N hydrochloric acid and extracted with chloroform. The chloroform extract was washed with water and dried with magnesium sulfate. The chloroform was driven off and to the residue were added 2.5 ml of pyridine and, at 0°C, 0.7 ml of acetyl chloride, and the mixture was left at 0-3°C for 16 hr. Then 5 ml of water was added and the mixture was extracted with chloroform; the chloroform was driven off and the residue was recrystallized from ethanol. Yield 1.1 g (42.5%). Colorless plates, mp 100°–101°C (decomp.). Found, %: C 57.77, 57.46; H 5.99, 5.86; N 7.52, 7.76; S 12.40, 12.26. Calculated for $C_{24}H_{31}N_3O_5S_2$. %: C 57.24; H 5.80; N 8.34; S 12.73.

2-Benzoylamino-3-acetoxybutyl-2-benzoylamino-3-oxobutyl disulfide (VIII). Over 2 hr, 0.5 g of $NaBH_4$ was added to a suspension of 1 g of II in 30 ml of ethanol and the mixture was stirred for 2 hr. The ethanol was driven off, the residue was treated with 30 ml of water, and the precipitate that deposited was separated off and recrystallized from ethanol (mp 238°–240°C); to it were added 3 ml of pyridine and, at 0°C, 2 ml of acetyl chloride and the mixture was left at 0°C for 18 hr. The solvent was driven off in vacuum and the residue was extracted with chloroform; the chloroform extracts were washed with 2.5 N hydrochloric acid and water and were dried with magnesium sulfate. The chloroform was driven off. The residue was recrystallized from ethanol. Yield 0.6 g (54.5%), mp 225°–226°C. Found, %: C 57.33, 57.10; H 5.61, 5.67; N 5.89, 5.59. Calculated for $C_{22}H_{20}N_2O_4S_2$, %: C 57.30; H 5.55; N 5.55.

Compound VII was obtained from VIII in the same way as VI from II. The substance obtained gave no depression of the melting point in admixture with substance VII synthesized from VI.

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