SYNTHESIS OF SOME ω-(2,5-DICHLORO-3-THIENYL)ALKANOIC ACIDS AND THEIR INTRAMOLECULAR RING CLOSURE

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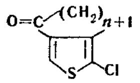
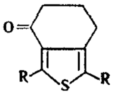
The synthesis of 1-chloro-4,5,6,7-tetrahydrobenzo[c]-4-thiophenone and 1-chloro-5,6,7,8-tetrahydro-4H-cyclohepta[c]-4-thiophenone was accomplished by the cyclization of the acid chlorides of γ-(2,5-dichloro-3-thienyl)butyric acid and δ-(2,5-dichloro-3-thienyl)valeric acid, respectively, to 1,3-dichloro-4,5,6,7-tetrahydrobenzo[c]-4-thiophenone and 1,3-dichloro-5,6,7,8-tetrahydro-4H-cyclohepta[c]-4-thiophenone and by partial dehalogenation of the latter by heating with copper metal in propionic acid.

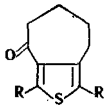
Ketones of the I type seemed of interest as starting compounds for the synthesis of systems that are close to desthiobiotin [1]. Condensed systems of the II and III type, which are similar to them with respect to the carbon skeleton, were previously synthesized [2,3] by the usual methods – cyclization of the appropriate acids or acid chlorides of the thiophene series. Intramolecular acylation also was the basis for the synthetic route that we planned. However, we encountered difficulties in an attempt to obtain the (2,5-dichloro-3-thienyl)alkanoic acids (IV) necessary for this. The fact is that we could not reduce keto acids V (see [4,5] for their preparation) to acids IV under the conditions of the Wolff–Kishner and Clemmensen reactions, probably because of the lability of the halogen atom due to the presence of a keto group in the 3 or 5 position of the thiophene ring (see [6]). Profound resinification was observed in all of our experiments. This compelled us to use a roundabout route.



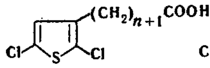
Ia,b



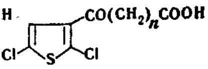
II



III



IVa,b



Va,b

I, IV, Va $n=2$; b $n=3$; II, III $R=CH_3, C_2H_5$

The activating effect of an electron-acceptor substituent (a nitro group, for example) on the lability of the halogen bonded to the adjacent carbon atom in the aromatic ring is well-known. It has repeatedly been used for the elimination of chlorine or bromine by the action of copper metal in an organic acid [7-9]. In addition, it is known that the keto group also has an activating effect on the lability of an adjacent halogen. This enabled us [4,5] to accomplish the synthesis of β-(5-chloro-3-thenoyl)propionic acid (VIa) and γ-(5-chloro-3-thenoyl)butyric acid (VIb) from keto acids Va and Vb, respectively, by heating them with copper metal in propionic acid. The subsequent route used for the synthesis is shown in the scheme on page 1271. No difficulties were encountered in the Kishner reduction of keto acids VI [4]. Since the cyclization of VII to the β position of the thiophene ring cannot be accomplished when the α position is free, it was necessary to introduce a substituent into this position that could be removed during subsequent transformations. This was realized by the action of sulfuryl chloride (see [10]). The acids obtained (VIII) were converted to acid chlorides (IX), which were then cyclized in the presence of aluminum chloride in chloroform. The same method that was used in the dehalogenation of V was used to remove the chlorine from the 3 position in ketones X. Ketones Ia and Ib were obtained.

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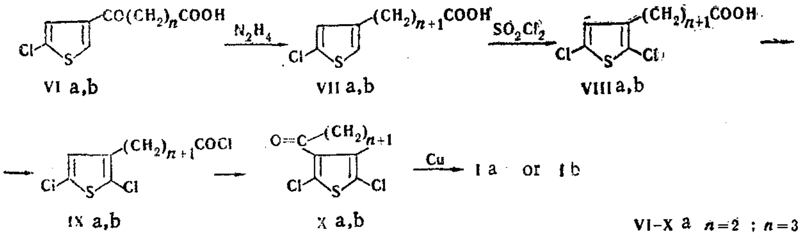

EXPERIMENTAL

δ-(2,5-Dichloro-3-thienyl)valeric Acid (VIIIb). Sulfuryl chloride (7.4 ml) was added to a solution of 10 g (0.043 mole) of VIIb (see [4]) in 50 ml of carbon tetrachloride. The solution was decanted from the resin that formed and was vacuum-evaporated. The residue was distilled to give 9.4 g of a substance with bp 175-177° (about 2 mm), the recrystallization of which from 40 ml of hexane gave 8.5 g (73%) of VIIIb with mp 44-45.5°. Found: C 43.1, 42.9; H 4.1, 3.9; Cl 28.1, 28.3; S 12.7, 12.8%. $C_9H_{10}Cl_2O_2S$. Calculated: C 42.7; H 4.0; Cl 28.0; S 12.7%.

γ-(2,5-Dichloro-3-thienyl)butyric Acid (VIIIa). This compound was similarly obtained in 74% yield and had mp 42.5-45° (from hexane) and bp 162-165° (about 2 mm). Found: C 40.5, 40.5; H 3.3, 3.5; Cl 29.7, 29.7; S 13.4, 13.4%. $C_8H_8Cl_2O_2S$. Calculated: C 40.2; H 3.4; Cl 29.7; S 13.4%.

δ-(2,5-Dichloro-3-thienyl)valeryl Chloride (IXb). A mixture of 13.6 g (0.054 mole) of VIIIb, 11 ml of thionyl chloride, and 35 ml of benzene was refluxed for 3 h, the solution was vacuum-evaporated, and the residue was distilled to give 12.9 g (88%) of IXb with bp 146-148° (about 2 mm). Found: C 40.3; H 3.4; Cl 39.1; S 11.8%. $C_9H_9Cl_3OS$. Calculated: C 39.8; H 3.3; Cl 39.2; S 11.8%.

γ-(2,5-Dichloro-3-thienyl)butyryl Chloride (IXa). This compound was similarly obtained from VIIIa in 82% yield and had bp 125-127° (about 2 mm). Found: C 37.6, 37.4; H 2.8, 2.9; Cl 41.3, 41.2; S 12.5, 12.4%. $C_8H_7Cl_3OS$. Calculated: C 37.3; H 2.7; Cl 41.3; S 12.5%.

1,3-Dichloro-5,6,7,8-tetrahydro-4H-cyclopenta[c]-4-thiophenone (Xb). A solution of 9.5 g (0.035 mole) of IXb in 250 ml of chloroform was added dropwise at 18-20° to a stirred suspension of 14 g (about 0.1 mole) of anhydrous aluminum chloride in 250 ml of dry, purified chloroform, and the mixture was stirred for 1 h. It was then poured into cold water and acidified with hydrochloric acid. The organic layer was washed with dilute hydrochloric acid, water, and sodium carbonate solution, and dried with magnesium sulfate. Distillation yielded 5.4 g (65%) of Xb with bp 133-134° (about 2 mm) and n_D^{20} 1.5998. Found: C 46.2, 46.0; H 3.4, 3.2; Cl 30.0, 30.1; S 13.6, 13.6%. $C_9H_8Cl_2OS$. Calculated: C 46.0; H 3.4; Cl 30.2; S 13.6%.

1,3-Dichloro-4,5,6,7-tetrahydrobenzo[c]-4-thiophenone (Xa). This compound was similarly obtained in 71% yield and had mp 42-43° (from hexane) and bp 127-129° (about 2 mm). Found: C 43.6, 43.4; H 2.7, 2.9; Cl 32.0, 32.0; S 14.4, 14.4%. $C_8H_6Cl_2OS$. Calculated: C 43.5; H 2.7; Cl 32.1; S 14.5%.

1-Chloro-5,6,7,8-tetrahydro-4H-cyclopenta[c]-4-thiophenone (Ib). A mixture of 5.15 g (0.022 mole) of Xb, 5.2 ml of formic acid, 5.2 g (0.082 g-atom) of copper powder, and 52 ml of propionic acid was refluxed for 6 h. The copper was separated from the hot solution by filtration and washed with hot propionic acid. The filtrate was vacuum-evaporated on a water bath, and the residue was boiled with 40 ml of water and acidified with hydrochloric acid. The oil was extracted with ether, and the extract was washed with salt and sodium carbonate solutions and dried with magnesium sulfate. Distillation yielded a fraction with bp 115-120° (about 2 mm), which was recrystallized from 20 ml of hexane to give 2.23 g (51%) of IIIb. A second crystallization from hexane gave a product with mp 50-52°. Found: C 54.0, 54.0; H 4.4, 4.2; Cl 17.5, 17.7; S 15.8, 15.9%; M 201 (mass spectrum). C_9H_9ClOS. Calculated: C 53.9; H 4.5; Cl 17.7; S 16.0%; M 201. The oxime had mp 114.5-116° (from dilute alcohol). Found: N 6.6, 6.7%. $C_9H_{10}ClNOS$. Calculated: N 6.5%.

1-Chloro-4,5,6,7-tetrahydrobenzo[c]-4-thiophenone (Ia). This compound was similarly obtained in 73% yield and had mp 82-83.5° (from hexane) and bp 132-135° (6 mm). Found: C 51.2, 51.5; H 3.6, 3.6; Cl 18.8, 18.7; S 17.0, 16.9%; M 186 (mass spectrum). C_8H_7ClOS. Calculated: C 51.5; H 3.8; Cl 19.0; S 17.2%; M 186. The oxime had mp 155-156° (from dilute alcohol). Found: N 7.4, 7.3%. C_8H_8ClNOS. Calculated: N 6.9%.

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