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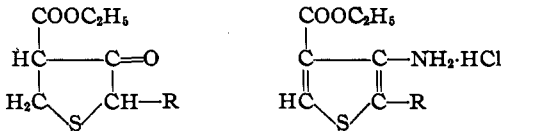
The Synthesis of 3-Aminothiophenes by Aromatization of β-Keto Ester Oximes[1]

BY LEE C. CHENEY AND J. ROBERT PIENING

The search for a practical synthesis of biotin and kindred compounds has led to the preparation of various 4-carboalkoxy-3-keto-2-(ω-R-alkyl)-tetrahydrothiophenes by Dieckmann cyclization of diester sulfides.[2] The β-keto ester oximes were readily obtained in nearly quantitative yields. The latter exhibited no tendency to form isoxazolones.

In a particular experiment, the catalytic hydrogenation of ethyl 3-keto-2-γ-phenoxypropyl-4-tetrahydrothiophenecarboxylate oxime was attempted after reduction experiments involving nascent hydrogen had failed to yield the desired ethyl 3-amino-2-γ-phenoxypropyl-4-tetrahydrothiophenecarboxylate or the corresponding free amino acid. A mixture consisting of the liquid oxime of I dissolved in absolute alcohol containing three equivalents of hydrogen chloride and a relatively large amount of palladium-barium sulfate catalyst was shaken overnight under three atmospheres of hydrogen. No change was observed in the gage reading. Starting material, however, was not recovered. Instead, the product isolated was an amine hydrochloride, m. p. 163.5–164.5°. Treatment of the salt with ammonium hydroxide afforded the free base, m. p. 56–57°. Analytical data indicated that the molecular formula of the compound was $C_{15}H_{19}O_3NS$. The facts suggested that the oxime had lost one molecule of water with an accompanying redistribution of hydrogen atoms. An aromatization had apparently taken place with the formation of ethyl 3-amino-2-γ-phenoxypropyl-4-thiophenecarboxylate hydrochloride (II).



I R = —$(CH_2)_3$—OC_6H_5 II R = —$(CH_2)_3$—OC_6H_5
III R = —$(CH_2)_3$—$OCH_2C_6H_5$
IV R = —$(CH_2)_3$—$OCH_2C_6H_5$
VI R = —$(CH_2)_4$—$COOC_2H_5$
VIII R = —$(CH_2)_4$—$COOC_2H_5$

Oximes of I, III, and VI $\xrightarrow{HCl}$ II, IV, and VIII, respectively

The amine hydrochloride was readily diazotized, and the diazonium salt gave an orange-pink dye when coupled with 2-naphthol, thus establishing that the product was a primary aromatic amine. Since the original tetrahydrothiophene β-keto ester from which the oxime was derived had been prepared by an unequivocal ring closure,[2] the assigned thiophene structure was thus confirmed.

The paucity of aminothiophenes in the literature added interest to this unexpected reaction. In 1926, Steinkopf and Müller[3] reported that only five aminothiophenes had been described, and two of these were extremely unstable. From 1926 to January, 1944, with the exception of reduced forms, only three additional aminothiophenes have appeared in *Chemical Abstracts*.[4,5,6]

A further study of the reaction disclosed that the palladium catalyst, which is known to promote disproportionation and dehydrogenation,[7] had played no essential role in the transformation. As the following table shows, hydrogen chloride effectively brings about the aromatization of the oxime of I to the corresponding amino compound (II) under a variety of conditions.

TABLE I

CONVERSION OF THE β-KETO ESTER (I) OXIME INTO THE 3-AMINOTHIOPHENE HYDROCHLORIDE (II)

Expt.	Ml. solvent/0.1 mole	HCl, mole	Temp., °C.	Hr.	Yield, %
1[a]	200 abs. alc.	0.30	25	12	35
2[b]	200 ether	.11	0 → 25	24	71
3[b]	200 ether	.11	0 → 25	48	81
4[b]	100 ether	.11	0 → 25	48	58
5	300 acetic acid 37 acetic anhydride	Satd. soln.	100	1	15
6	200 acetic acid	Satd. soln.	25	16	8

[a] Shaken with palladium-barium sulfate catalyst under hydrogen. [b] The hydrogen chloride was introduced in absolute alcohol (22.8 ml. of 4.83 molar solution).

Later, another series of experiments was conducted on the aromatization of the closely related oxime of III. Under conditions which were found most favorable (81% yield) for the conversion of the oxime of I, significantly inferior yields (53–57%) of IV were realized. This result was ascribed to partial cleavage of the benzyl ether by the alcoholic hydrogen chloride. Elimination of the alcohol by saturating an anhydrous ether solution of the oxime with dry hydrogen chloride at room temperature and then stirring the mixture for twenty hours afforded 78–79% yields of IV. This convenient procedure has consistently given yields of 78–85% for the conversion of other oximes. Consequently, it is regarded as the best method thus far developed for carrying out the reaction.

A useful application of this aromatization was the structural elucidation of the compound ob-

(1) Presented before the Division of Organic Chemistry, 108th Meeting of the American Chemical Society, New York, N. Y., September 12, 1944.

(2) The synthesis of these β-keto esters will be presented in forthcoming papers.

(3) Steinkopf and Müller, *Ann.*, **448**, 214 (1926).

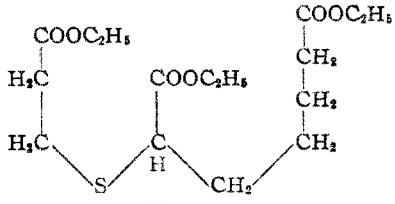
(4) Finzi, *Gazz. chim. ital.*, **60**, 159 (1930) [*C. A.*, **24**, 3783 (1930)].

(5) Steinkopf and Höpner, *Ann.*, **501**, 183 (1933).

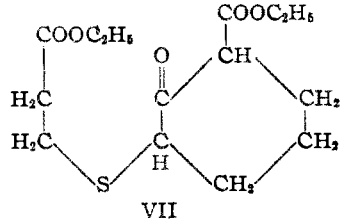
(6) Dann, *Ber.*, **76**, 427 (1943).

(7) Linstead, Michaelis and Thomas, *J. Chem. Soc.*, 1139 (1940).

tained by Dieckmann cyclization of 2-carbethoxyethyl 1,5-dicarbethoxyamyl sulfide (V). This derivative could possess either structure VI or VII, depending upon whether a five- or a six-membered ring had been formed in the ring closure. The product was converted almost quantitatively into the oxime of either VI or VII or a mixture of the two compounds. The latter was then dissolved in anhydrous ether and treated with dry hydrogen chloride at room temperature to obtain a definite reaction. Assuming a six-membered ring had been formed, with the proviso that its oxime could react under the mild conditions imposed, one would expect a Beckmann rearrangement to take place, resulting in the formation of a seven-membered lactam. In contrast, one would expect the oxime of the five-membered ring to undergo aromatization. Actually, an 85% yield of a mixture of VIII and its mono acid was isolated. The cyclization product, therefore, was thus proved to be almost entirely, if not exclusively, the tetrahydrothiophene derivative (VI) utilized in the synthesis of 2,3,4,5-tetradehydrobiotin.[8]



V



VII

Although a search of the literature has failed to detect closely related aromatizations involving heterocyclic systems, several analogous carbocyclic transformations have been found, particularly in the excellent reviews of Blatt[9] and Horning.[10]

Speculation concerning the mechanism of the described reaction raises questions for further experimentation to answer. Because no precipitate is formed during the introduction of the hydrogen chloride into the ethereal solution, the reaction does not proceed through a typical oxime salt. But regardless of the exact mechanism involved, the transformation results only in dehydration and a redistribution of hydrogen atoms under the influence of surprisingly mild conditions. From a practical viewpoint, therefore, this aromatization provides a useful method for the synthesis of various 3-aminothiophenes difficult to prepare by aromatic substitutions. Moreover, the reaction should be generally applicable to the synthesis of analogous furan and pyrrole derivatives. The relative accessibility of the alicyclic precursors, with their predetermined side-chains and functional groups for the aromatic systems, will largely determine the utility of this reaction for future synthetic work.

(8) Cheney and Piening, THIS JOURNAL, 67, 731 (1945).

(9) Blatt, *Chem. Rev.*, 12, 218 (1933).

(10) Horning, *ibid.*, 33, 101, 130 (1943).

Experimental[11]

Ethyl 3-Keto-2-γ-phenoxypropyl-4-tetrahydrothiophenecarboxylate Oxime (I).—A mixture of 61.6 g. (0.20 mole) of the β-keto ester,[2] 61.6 g. of hydroxylamine hydrochloride, 92.5 g. of anhydrous barium carbonate and 600 ml. of absolute alcohol was protected by a calcium chloride tube and refluxed on the steam-bath for sixteen hours. Following filtration, the inorganic salt was washed with 500 ml. of boiling absolute alcohol in several portions, and solvent was distilled under reduced pressure from the combined filtrate and washings. The oily residue was taken up in 1500 ml. of ether, and the solution was washed with 600 ml. of cold water in four portions and dried over sodium sulfate. Filtration and removal of solvent left an orange oil which was desiccated *in vacuo* over phosphorus pentoxide. After twenty-four hours the oil had set to a semi-solid crystalline mass; yield, 62.0 g. (96%). The nitrogen analysis reported below was obtained for this mixture of isomers. A sample was treated with a small portion of cold alcohol and the crystals which failed to dissolve were recrystallized from 80% alcohol in the form of colorless needles, m. p. 101°.

Anal. Calcd. for $C_{16}H_{21}O_4NS$: C, 59.42; H, 6.54; N, 4.33. Found: C, 59.26; H, 6.33; N, 4.56.

Ethyl 3-Amino-2-γ-phenoxypropyl-4-thiophenecarboxylate Hydrochloride (II).—A solution of 111.1 g. (0.36 mole) of the dry crude oxime in 720 ml. of anhydrous ether was protected from moisture by a calcium chloride tube and cooled in an ice-bath. To the stirred solution was added 83 ml. (10% excess) of 4.83 molar absolute alcoholic hydrogen chloride. The yellow solution gradually turned red-brown in color while the ice melted without replacement. Crystals separated during the night. After forty-eight hours had elapsed, the pink amine hydrochloride was collected in a Büchner funnel, washed thoroughly with dry ether and dried *in vacuo;* m. p. 161–163°; yield, 99.5 g. (81%). Recrystallization of a sample from acetone following treatment with Darco produced ivory crystals, m. p. 163.5–164.5°.

Anal. Calcd. for $C_{16}H_{19}O_3NS \cdot HCl$: N, 4.10. Found: N, 4.19.

A small sample of the weakly basic amine was diazotized in concentrated sulfuric acid, and the diazonium salt was coupled with 2-naphthol in basic solution to yield an orange-pink dye.

Ethyl 3-Amino-2-γ-phenoxypropyl-4-thiophenecarboxylate.—To 17.1 g. (0.05 mole) of the aforementioned amine hydrochloride was added a solution prepared by diluting 50 ml. of concentrated ammonium hydroxide with 50 ml. of water. Lumps were broken up and the suspension was stirred occasionally for two hours. Following filtration and thorough washing with water, the light-brown amorphous product was desiccated *in vacuo* over phosphorus pentoxide; m. p. 55.5–56.5°; yield, 15.3 g. (quantitative). Crystallization from methanol subsequent to treatment with Darco yielded cream-colored needles, m. p. 56–57°.

Anal. Calcd. for $C_{16}H_{19}O_3NS$: C, 62.93; H, 6.27; N, 4.59; S, 10.50. Found: C, 62.98; H, 6.23; N, 4.65; S, 9.88.

Ethyl 2-γ-Benzyloxypropyl-3-keto-4-tetrahydrothiophenecarboxylate Oxime (III).—A mixture of 189 g. (0.59 mole) of ethyl 2-γ-benzyloxypropyl-3-keto-4-tetra-

(11) All melting points are corrected.

hydrothiophenecarboxylate,[3] 189 g. of hydroxylamine hydrochloride, 296 g. of anhydrous barium carbonate and 1500 ml. of absolute alcohol was refluxed on the steam-bath for twenty-two hours while a drying tube excluded moisture. The oily oxime was isolated by the same procedure as described for oxime I; yield, 175 g. (88%).

Anal. Calcd. for $C_{17}H_{23}O_4NS$: N, 4.16. Found: N, 4.38.

Ethyl 3-Amino-2-γ-benzyloxypropyl-4-thiophenecarboxylate Hydrochloride (IV).—A solution of 67.5 g. (0.20 mole) of the aforementioned oxime in 500 ml. of anhydrous ether was protected by a calcium chloride tube and saturated with dry hydrogen chloride over a period of thirty-five minutes. A brown color soon developed. After the mixture had stirred for twenty hours at room temperature the tan crystals were filtered from the dark-brown solution and washed thoroughly with dry ether; yield, 55.4 g. (78%); m. p. 121–125°. Recrystallization of a sample from methyl isobutyl ketone–ether did not improve the melting point.

Anal. Calcd. for $C_{17}H_{21}O_3NS \cdot HCl$: N, 3.93. Found: N, 4.10.

In cases where the amine hydrochloride failed to crystallize from solution, the ether and the excess hydrogen chloride were removed in a current of air. Dry ether was then stirred into the dark-brown, oily residue while cooling the mixture to induce crystallization.

Acknowledgment.—The authors wish to thank Mr. A. W. Spang and Mrs. Margaret Ledyard for the microanalyses.

Summary

Ethyl 3-keto-2-γ-phenoxypropyl-4-tetrahydrothiophenecarboxylate oxime undergoes aromatization with loss of water to yield ethyl 3-amino-2-γ-phenoxypropyl-4-thiophenecarboxylate hydrochloride when treated with hydrogen chloride in anhydrous ether. In like manner ethyl 2-γ-benzyloxypropyl - 3 - keto - 4 - tetrahydrothiophenecarboxylate oxime is converted into ethyl 3 - amino -2 - γ - benzyloxypropyl - 4 - thiophenecarboxylate hydrochloride.

Because of the favorable yields obtained, this aromatization provides a new method for the synthesis of hitherto inaccessible derivatives of 3-aminothiophene.

This transformation has furnished a structural proof and a key intermediate required for the synthesis of 2,3,4,5-tetradehydrobiotin.

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The Total Synthesis of 2,3,4,5-Tetradehydrobiotin[1]

BY LEE C. CHENEY AND J. ROBERT PIENING

The observation that the oximes of certain tetrahydrothiophene β-keto esters could be transformed with surprising ease into the corresponding 3-aminothiophenes[2] suggested the possibility of obtaining biotin through its aromatic analog. Such an approach to the synthesis of biotin offered certain advantages. It would not only eliminate steps involving troublesome stereoisomers, but, since the amino groups in the 3,4-diaminothiophenevaleric acid would necessarily be in a position facilitating ring closure with phosgene, it would also provide a sure means of forming the ureylene bridge. Whether or not the sulfur-containing bicyclic system could be reduced to biotin was considered an open question. The fact that the physiological activity of "aromatic biotin" would be of pharmacological interest added significance to the venture. A preliminary communication[3] has outlined the steps by which the synthesis of 2,3,4,5-tetradehydrobiotin (XVIII) was accomplished.

Either α-bromo- or α-chloropimelic acid was required as an intermediate for the preparation of the key β-keto ester (IX). A search of the literature revealed that no mono α-halopimelic acids had been described. Although α-bromosuberic acid has been prepared by the Hell–Volhard–Zelinsky method, considerable dibromo acid is formed in the reaction.[4] The direct monohalogenation of adipic acid has led to mixtures which are separated only with difficulty.[5] Consequently, v. Braun and Meyer[6] have devised a six-step process for the synthesis of pure α-bromoadipic acid.

The route to α-chloropimelic acid (VI) involved the shown sequence of reactions. Since the completion of this work, Karrer, Keller and Usteri[7] have reported the preparation of α-bromopimelic acid by the bromination of the identical malonic acid (IV) followed by decarboxylation.

β-Mercaptopropionic acid condensed readily with VI in alkaline solution to produce VII. The purification of VII was not attempted, since esterification afforded pure VIII in yields of 73–77% based on VI.

The Dieckmann cyclization of VIII, which could lead to the formation of either a cyclohexanone or a tetrahydrothiophene derivative, proceeded smoothly at room temperature in the presence of two moles of sodium ethoxide suspended in benzene to produce the β-keto ester (IX) in yields of 84–89%. It gave an intense red coloration with ferric chloride in alcoholic solution

(1) Presented in part before the Division of Organic Chemistry, 108th meeting of the American Chemical Society, New York, N. Y., September 12, 1944.

(2) Cheney and Piening, THIS JOURNAL, 67, 729 (1945).

(3) Cheney and Piening, *ibid.*, 66, 1040 (1944).

(4) Gantter and Hell, *Ber.*, 15, 142 (1882); Hell and Rempel, *ibid.*, 18, 812 (1885).

(5) Gal and Gay-Lussac, *Ann.*, 155, 250 (1870); Ince, *J. Chem. Soc.*, 67, 159 (1895); Ingold, *ibid.*, 119, 961 (1921).

(6) v. Braun and Meyer, *Ber.*, 74, 19 (1941).

(7) Karrer, Keller and Usteri, *Helv. Chim. Acta*, 27, 237 (1944).