carboxyglycine ethyl ester with glycine ethyl ester; N-carboxyalanine ethyl ester with alanine ethyl ester; N-carboxyleucine ethyl ester with leucine ethyl ester; N-carboxy-C-phenylglycine ethyl ester with C-phenylglycine ethyl ester.

On treating the salt of N-carboxyglycine methyl ester and glycine methyl ester with calcium hydroxide, Siegfried's calcium salt of carbaminoacetic acid was obtained.

Diazomethane reacted with the salt of N-carboxyglycine methyl ester with glycine methyl ester yielding N-carbomethoxyglycine methyl ester and free glycine methyl ester in about equimolar amounts. Similarly N-carbomethoxyglycine ethyl ester and glycine ethyl ester were obtained in about equimolar amounts from the salt of N-carboxyglycine ethyl ester with glycine ethyl ester.

By hydrolyzing N-carbomethoxyglycine methyl ester, carbomethoxyglycine was obtained.

Diazomethane reacted with ammonium benzoate and ammonium propionate giving methyl benzoate and methyl propionate, respectively.

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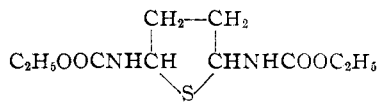
[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, CORNELL UNIVERSITY MEDICAL COLLEGE]

The Synthesis of a Tetrahydrothiophene with Substituted Amino Groups in the 2- and 5-Positions

BY GEORGE BOSWORTH BROWN AND GLEN W. KILMER

In the original discussion[1] of possible formulas for biotin, several structures came under consideration which involved the presence of nitrogen attached to one or both α-carbons of a tetrahydrothiophene. These possibilities were dismissed with the argument that "the remarkable stability of the diaminocarboxylic acid toward hydrolytic agents renders unlikely structures with both sulfur and nitrogen attached to a single carbon atom." While no compounds of the type $RSCH(NH_2)R'$ have come to our attention, cyclic compounds of the thiazolidine type with sulfur and nitrogen linked to the same carbon atom are known. For example, thiazolidine-4-carboxylic acid which has been studied by Ratner and Clarke[2] is decomposed slowly by boiling 1 N hydrochloric acid. This instability, however, is in contrast to the stability of the diaminocarboxylic acid derived from biotin (DAC).

To support or refute the argument with regard to the stability of structures involving the presence of sulfur and nitrogen attached to the same carbon atom, we decided to test the stability of a tetrahydrothiophene with nitrogen in the α-positions. 2,5-bis-(Carbethoxyamino)-tetrahydrothiophene was prepared but on hydrolysis the urethan decomposed to yield ammonia, hydrogen sulfide and succinaldehyde. This instability toward hydrolytic agents of the 2,5-diaminotetrahydrothiophene substantiated the postulation quoted above and contrasted markedly with the stability of DAC[3] and with that of 3,4-diaminotetrahydrothiophene[4,5] which has subsequently been shown to be related to biotin.[6,7,8]



The synthesis of 2,5-bis-(carbethoxyamino)-tetrahydrothiophene was accomplished by treatment of the ester of 2,5-dicarboxytetrahydrothiophene with hydrazine hydrate to give the dihydrazide. This hydrazide was smoothly converted to the azide and then to the corresponding urethan, 2,5-bis-(carbethoxyamino)-tetrahydrothiophene in 53% yield. Hydrolysis of the diurethan with boiling 1 N hydrochloric acid resulted in decomposition of the urethan with copious liberation of hydrogen sulfide, while hydrolysis with boiling 5% barium or sodium hydroxide resulted in liberation of 80% of the nitrogen as ammonia within thirty minutes. When the hydrolysis was car-

(1) V. du Vigneaud, K. Hofmann and D. B. Melville, THIS JOURNAL, **64**, 188 (1942).

(2) S. Ratner and H. T. Clarke, *ibid.*, **59**, 200 (1937).

(3) K. Hofmann, D. B. Melville and V. du Vigneaud, *J. Biol. Chem.*, **141**, 207 (1941).

(4) G. W. Kilmer, M. D. Armstrong, G. B. Brown, and V. du Vigneaud, *ibid.*, **145**, 495 (1942).

(5) K. Hofmann, G. W. Kilmer, D. B. Melville, V. du Vigneaud and H. H. Darby, *ibid.*, **145**, 503 (1942).

(6) V. du Vigneaud, *Science*, **96**, 455 (1942).

(7) V. du Vigneaud, D. B. Melville, K. Folkers, D. E. Wolf, R. Mozingo, J. C. Keresztesy and S. A. Harris, *J. Biol. Chem.*, **146**, 475 (1942).

(8) D. B. Melville, A. W. Moyer, K. Hofmann and V. du Vigneaud, *ibid.*, **146**, 487 (1942).

ried out with hydrochloric acid in dilute alcohol in the presence of *p*-nitrophenylhydrazine a compound whose properties and melting point agree with those of the bis-*p*-nitrophenylhydrazone of succinaldehyde[9] was obtained.

Experimental

cis-**2,5-Dicarboxytetrahydrothiophene.**—This was prepared from *meso*-dibromoadipic acid[10] by the method of Fredga,[11] who reported a melting point of 144–145°. The product obtained by us softened at 135° and melted at 141–143°, but it possessed the expected composition.

Anal. Calcd. for $C_6H_8O_4S$: C, 40.90; H, 4.58. Found: C, 40.79; H, 4.98.

Diethyl Ester of 2,5-Dicarboxytetrahydrothiophene.—Ten grams of the acid was dissolved in 150 ml. of absolute ethanol and the solution saturated with dry hydrogen chloride and refluxed two hours. The solution was concentrated *in vacuo*, was dissolved in 75 ml. of ether, and was washed twice with saturated sodium bicarbonate. The ether solution was dried over sodium sulfate and distilled. The product distilling at 157° at 10 mm. amounted to 11.2 g. (85%).

2,5-Dicarboxytetrahydrothiophene Dihydrazide.—Three grams of the above ester in 9 ml. of ethyl alcohol was warmed to about 70° and 1.74 g. of 100% hydrazine hydrate was added. A green color developed and faded in five minutes. The solution was allowed to crystallize at room temperature overnight. The product was recrystallized from alcohol and yielded 600 mg. (23%) of needles melting at 208–209°.

Anal. Calcd. for $C_6H_{12}O_2N_4S$: N, 27.42. Found: N, 27.24.

2,5-bis-(Carbethoxyamino)-tetrahydrothiophene.—To 200 mg. of the above hydrazide in 5 ml. of 1 *N* hydrochloric acid, cooled to 0°, was added a layer of 5 ml. of ether, and 138 mg. of sodium nitrite in 1.4 ml. of water was added dropwise during five minutes with shaking and cooling. The ether layer was separated and the water was extracted twice with 5-ml. portions of cold ether. The ether extract was dried over sodium sulfate and concentrated *in vacuo*. To the cold diazide was added 50 ml. of absolute alcohol. The solution was warmed slowly in a water-bath. At about 50°, micro-bubbles of gas were evolved and heating was continued until the alcohol boiled gently. The alcohol solution was concentrated and the residue was recrystallized from 20% alcohol yielding 120 mg. (53% yield) of crystals melting at 152–154°.

Anal. Calcd. for $C_{10}H_{18}O_4N_2S$: C, 45.78; H, 6.92; N, 10.68; S, 12.22. Found: C, 45.90; H, 6.88; N, 10.53; S, 12.14.

The authors wish to thank Professor Vincent du Vigneaud for much helpful advice and Dr. J. R. Rachele for carrying out the microanalyses.

Summary

The synthesis of 2,5-bis-(carbethoxyamino)-tetrahydrothiophene has been accomplished. It has been shown that it is readily hydrolyzed to yield ammonia, hydrogen sulfide and succinaldehyde.

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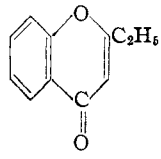
(9) C. Harries and H. Krütz feld, *Ber.*, **39**, 3670 (1906).
(10) B. Holmberg and E. Müller, *ibid.*, **58**, 1601 (1925).
(11) A. Fredga, *J. prakt. Chem.*, **150**, 124 (1938).

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

Oxidation Potentials of Methoxyacetophenones

BY ROBERT H. BAKER AND JACK G. SCHAFER

It has been observed[1] that 2-ethylchromone, I, is not reduced by the Meerwein–Ponndorf method.



I

It seems logical to account for this behavior on the basis of the fact that the compound is a vinylog of an ester. Although esters suffer alkoxyl exchange with aluminum alkoxides, they are not reduced even under forcing conditions.[2] Open chain vinylogs of esters have also been found to resist such reduction,[1] but it appeared that if the vinyl group is contained in an aromatic nucleus the compound should have properties intermediate between those of esters and ketones.

It has been possible to combine *o*-, *m*- and *p*-methoxyacetophenones with fluorenol in the presence of aluminum *t*-butoxide according to the equation, acetophenone + fluorenol ⟷ methylphenylcarbinol + fluorenone. Since the normal potential of fluorenone is known,[3] the determination of the concentrations at equilibrium in such reactions allows the assignment of normal potentials to these ketones. The normal potential of acetophenone is 151 mv.[3] and that of *m*-methoxyacetophenone, which is not an ester vinylog, is

(1) This will be reported in a forthcoming publication.
(2) Baker, THIS JOURNAL, **60**, 2673 (1938).
(3) Baker and Adkins, *ibid.*, **62**, 3305 (1940).