When increasing amounts of β-3-thienyl-DL-alanine were added to the medium in which *E. coli* grew well, it completely inhibited the growth and was about 30% more effective than β-2-thienylalanine. This is illustrated by the data of Fig. 3. The toxicity on the growth of *E. coli* was also prevented by phenylalanine.

Discussion

The results of previous work[3,6,7,13] show that the replacement of the benzene ring in phenylalanine by the thiophene, furan or pyrrole ring results in the formation of antagonists of phenylalanine. Of these three antagonists the thiophene analog was probably the most active. The results described in this paper indicate that when the alanine side chain is in the 3-position the antagonist is more potent than if it is in the 2-position. These results suggest that if the best antagonist of a compound which contains a phenyl ring is to be designed it would be most likely obtained by replacing the phenyl group by a thiophene ring with the side chain in the 3-position.

Acknowledgment.—The author wishes to acknowledge the very excellent assistance of Mr. Robert P. Martin in the chemical phase of this work, and of Mrs. Charmion McMillan and Mrs. Virginia Janda for the microbiological tests. The analyses were made by Mrs. Philippa Szerwo of this department. The author also wishes to thank Mr. G. A. Harrington of the Socony-Vacuum Oil Company for a generous gift of 3-methylthiophene.

Summary

β-3-Thienyl-DL-alanine was synthesized by alkaline hydrolysis of diethyl (2-bromo-3-thenyl)-acetamidomalonate, yielding N-acetyl-β-(2-bromo-3-thienyl)-alanine. The N-acetyl derivative was converted to the β-(2-bromo-3-thienyl)-alanine hydrobromide by acid hydrolysis. The bromine was removed by hydrogenation in the presence of palladium on charcoal catalyst, yielding pure β-3-thienylalanine.

This new isostere of phenylalanine was tested for its inhibitory properties on the growth of *Saccharomyces cerevisiae*, strain 139, and on an unidentified strain of *Escherichia coli*. For yeast, the β-3-thienylalanine was about twice as active as β-2-thienylalanine. It was about 30% more effective against *E. coli*. In each instance the toxicity was reversed by phenylalanine.

BOULDER, COLORADO RECEIVED AUGUST 17, 1948

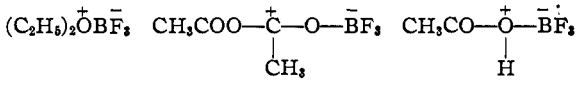
[CONTRIBUTION NO. 701 FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PITTSBURGH]

Further Studies in the Acylation of Thiophene and Furan in the Presence of Boron Fluoride Complexes[1]

BY ROBERT LEVINE, JOHN V. HEID[2] AND MARTIN W. FARRAR

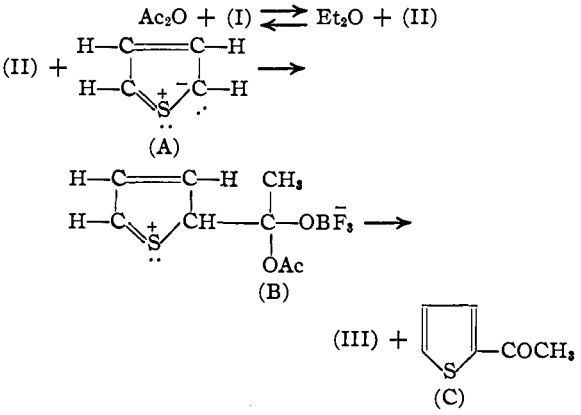
In an earlier paper[3] from this Laboratory it was reported that high yields of 2-thienyl and 2-furyl ketones are obtained when thiophene and furan are acylated with anhydrides in the presence of catalytic amounts of boron fluoride etherate as the condensing agent.

In the present work, we were interested in investigating the course of these acylations. In this discussion, the boron fluoride complexes will be referred to as follows



(I)	(II)	(III)
Etherate	Complex with acetic anhydride	Complex with acetic acid

The following scheme indicates a possible reaction mechanism whereby catalytic amounts of (I) could result in high yields of the heterocyclic ketones. The acylation of thiophene with acetic anhydride is taken as an example.



The first step in the reaction probably involves the interaction between acetic anhydride and (I) to give (II). This reactive intermediate then condenses with thiophene (A), to give the complex of (II) and thiophene (B), which then decomposes to produce (III) and 2-thienyl methyl ketone (C). We postulate that the acylating agent is (II) and the actual condensing agent (the catalyst) is (III). As this complex of acetic acid and boron fluoride (III) is formed it functions as (I) did in the first step of the reaction and is con-

(1) Presented before the Organic Division of the American Chemical Society, St. Louis Meeting, September, 1948.

(2) Present address: Mellon Institute, Pittsburgh, Pa.

(3) Heid and Levine, *J. Org. Chem.*, **13**, 409 (1948).

tinually being recycled. Hence catalytic amounts of (I) could result in high yields of ketone.[4]

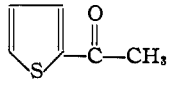
Some support of the mechanism proposed above would be available if the acylations of thiophene and furan could be effected using a complex of boron fluoride and a carboxylic acid as the condensing agent. Therefore, thiophene and furan were acylated with acetic, propionic and *n*-butyric anhydrides in the presence of catalytic amounts of (III). High yields of the 2-acyl derivatives of thiophene and furan were obtained. These yields compare favorably with those obtained in the same acylations using (I) as the condensing agent,[3] and hence it is felt that the above mechanism represents the actual course of the reaction.[5]

We then prepared 2-thienyl methyl (51%), ethyl (55%), *n*-propyl (69%), and phenyl (38%) ketones by acylating thiophene with the appropriate acid chlorides in the presence of (I) as the condensing agent.

The direct acylation of thiophene with acetic acid in the presence of two boron fluoride complexes was then studied. Two types of experiments were performed. In the first experiment one equivalent of boron fluoride etherate was allowed to react with equivalents of thiophene and glacial acetic acid. It was anticipated that the following reactions would occur.

(a) $BF_3.Et_2O + CH_3COOH \rightleftharpoons Et_2O + BF_3.CH_3COOH$

(b)  $+ BF_3.CH_3COOH \longrightarrow$

$BF_3.H_2O +$ 

Apparently, under the conditions employed, the equilibrium of reaction (a) lies largely to the left, since only 7% of 2-thienyl methyl ketone was obtained. In the second experiment, in which the preformed complex of boron fluoride and acetic acid was allowed to react with thiophene (reaction b), a 25% yield of the ketone was obtained. Earlier, Hartough and Kosak[6] reported the direct acylation of thiophene and furan with carboxylic acids in the presence of phosphorus pentoxide in fair to good yield.

Finally, 2,5-dimethylfuran was acylated with acetic, propionic and *n*-butyric anhydrides in the presence of catalytic amounts of boron fluoride etherate to give the corresponding 3-acyl-2,5-dimethylfurans in good yields. One of these, 3-acetyl-2,5-dimethylfuran, was prepared in high yield by Hurd and Wilkinson,[7] by the interaction of 2,5-dimethylfuran and acetic anhydride in the presence of a catalytic amount of stannic chloride as the condensing agent.

(4) It should be pointed out that in the acylations involving propionic and *n*-butyric anhydrides, the actual condensing agent is probably the complex of boron fluoride and the corresponding carboxylic acid.

(5) Although no study was made of the use of the complexes of boron fluoride and propionic and *n*-butyric acids as condensing agents, yields comparable to those obtained with (III) would probably have been obtained had such experiments been performed.

(6) Hartough and Kosak, THIS JOURNAL, 69, 3098 (1947).

Experimental

Acylation of Thiophene and Furan with Anhydrides in the Presence of the Complex of Boron Fuoride and Acetic Acid. General Procedure.—The apparatus used in these experiments consisted of a 500-ml. three-necked round-bottomed flask equipped with a mercury-sealed stirrer, a reflux condenser (protected from atmospheric moisture by a drying tube filled with Drierite), and a thermometer so that the temperature of the reaction mixture could be recorded. One mole of furan (68 g.), or thiophene (84 g.), and 1.15 moles of the appropriate anhydride were placed in the flask. To the rapidly stirred solution of furan and anhydride, cooled to 0° in an ice-bath, or of thiophene and anhydride at room temperature, 18.5 g. of the complex of boron fluoride and acetic acid was added all at once. The temperature of the reaction mixture rapidly rose to 100–115° and then dropped to room temperature over a period of about fifteen minutes. Stirring was continued for one-half hour longer and then about 200 ml. of water was added to hydrolyze the reaction mixture. The contents of the reaction flask were made basic with sodium carbonate solution, extracted with ether, and the ethereal phase dried over Drierite. The solvent was distilled at atmospheric pressure and the residue distilled in vacuum. From 75–92% yield of the ketones were obtained. The m. p. of the semicarbazones agreed with those reported previously.[8]

Acylation of Thiophene with Acid Chlorides in the Presence of Boron Fluoride Etherate. General Procedure.—The apparatus used was the same as that described above except that a hydrogen chloride trap was attached to the top of the condenser. The thiophene (1.5 moles) and acid chloride (0.5 mole) were placed in the flask, and 14 g. of boron fluoride etherate was added all at once. The reaction mixture was then refluxed until the evolution of hydrogen chloride was practically complete (one to two hours). The reaction mixture was then worked up as described above.

The Acylation of 2,5-Dimethylfuran with Anhydrides in the Presence of Boron Fluoride Etherate. General Procedure.—The reactions were carried out exactly as described above for the acylation of furan with anhydrides in the presence of the complex of boron fluoride and acetic acid, except that boron fluoride etherate (14 g.) was used as the condensing agent and that the 2,5-dimethylfuran and the anhydrides were at room temperature when the catalyst was added.

In this way the following 3-acyl-2,5-dimethylfurans were prepared: 3-acetyl (65%), b. p. 95° (23 mm.), oxime, m. p. 75–76°[7]; 3-propionyl (63%), b. p. 105–108° (23 mm.). *Anal.* Calcd. for $C_9H_{12}O_2$: C, 71.05; H, 7.89. Found: C, 71.07; H, 7.74; 2,4-dinitrophenylhydrazone, m. p. 171–172°; 3-*n*-butyryl (60%), b. p. 115–117° (23 mm.). *Anal.* Calcd. for $C_{10}H_{14}O_2$: C, 72.29; H, 8.43. Found: C, 72.54; H, 8.77; 2,4-dinitrophenylhydrazone, m. p. 146–147°.

The Direct Acylation of Thiophene with the Complex of Boron Fluoride and Acetic Acid.—Thiophene (64 g., 0.76 mole) and 200 ml. of carbon disulfide were placed in the apparatus described above, and heated to 45°. Forty-nine grams (0.38 mole) of the complex of boron fluoride and acetic acid was then added over a two-hour period. The reaction mixture was then refluxed for one hour longer and worked up as described above for the other acylations. Upon distillation, there was obtained 12.2 g. (25.4%) of 2-acetylthiophene, b. p. 79–80° (7 mm.).

Acknowledgment.—The authors are very grateful to Dr. P. E. Cholet of the General Chemical Division of the Allied Chemical and Dye Corpora-

(7) Hurd and Wilkinson, *ibid.*, 70, 740 (1948).

tion for supplying the complex of boron fluoride and acetic acid, and to E. I du Pont de Nemours and Company for contributing the furan used in this investigation.

Summary

Thiophene and furan have been acylated with several aliphatic acid anhydrides in the presence of the complex of boron fluoride and acetic acid to give high yields of the corresponding 2-acyl derivatives.

Thiophene has been acylated with four acid chlorides in the presence of boron fluoride etherate in fair yields.

The direct acylation of thiophene with the complex of boron fluoride and acetic acid has given only a low yield of 2-thienyl methyl ketone.

PITTSBURGH, PA. RECEIVED OCTOBER 11, 1948

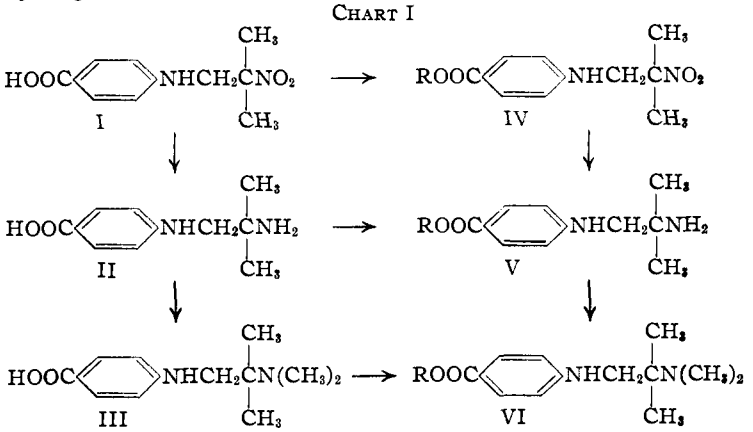
[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF DEPAUW UNIVERSITY]

Esters of Nitrogen-substituted *p*-Aminobenzoic Acid

BY J. M. FULMER AND HOWARD BURKETT

In 1942 it was suggested by Dr. H. G. Johnson[1] that from *p*-(2-nitro-2-methylpropylamino)-benzoic acid[2] (I) (see Chart I) alkyl *p*-(2-dialkylamino-2-methylpropylamino)-benzoates (VI, R = alkyl) be prepared and tested for local anesthetic activity. He synthesized *p*-(2-amino-2-methylpropylamino)-benzoic acid[2] (II) by the catalytic hydrogenation of I.

CHART I



The authors have made a number of esters (IV, V, VI) in which R is methyl, ethyl, *n*-propyl and γ-diethylaminopropyl, according to the equations shown. Methyl *p*-(2-amino-2-methylpropylamino)-benzoate (V, R = CH_3) was prepared in good yield both from the hydrogenation of the corresponding nitro-ester (IV, R = CH_3) and by the esterification of the acid (II). Using methyl sulfate, attempts to methylate the primary amine group in the acid (II) or the ester (V, R = CH_3) to give III or VI (R = CH_3), respectively, failed. However, no reactions were tried at elevated pressures. Use of the methylation procedure described by Clarke, *et al.*,[3] gave good yields in both cases.

All of the esters were prepared by direct esterification, except the γ-diethylaminopropyl esters, which were synthesized by the reaction of γ-diethylaminopropyl chloride on the sodium salt of the appropriate acid. The ethyl and *n*-propyl esters of VI were obtained only in poor yields by esterification. It was found in the case of the ethyl ester that better yields were obtained by the methylation of V (R = C_2H_5).

The pharmacological properties of these compounds are being studied by Graam, Ott and Schultz, who plan to publish their report in the *Journal of Pharmacology and Experimental Therapeutics*.

Acknowledgment.—The authors thank Dr. Jerome Martin for his suggestions and Commercial Solvents Corporation for the financial aid which made this investigation possible. The authors also thank Commercial Solvents Corporation for running all high-pressure hydrogenations and analyses.

Experimental

Procedure A. Ethyl *p*-(2-Nitro-2-methylpropylamino)-benzoate.—To a mixture of 25 g. of *p*-(2-nitro-2-methylpropylamino)-benzoic acid[2] and 150 ml. of ethanol was added 2 ml. of concd. sulfuric acid, with shaking. After refluxing for twelve hours, the reaction mixture was cooled and filtered. Two recrystallizations from ethanol yielded 15.7 g. (56%) of ester, m. p. 137–138°.

The methyl and *n*-propyl esters, as noted in Table I, were prepared in a similar manner. They were recrystallized from methanol and *n*-propanol, respectively.

Procedure B. γ-Diethylaminopropyl *p*-(2-Nitro-2-methylpropylamino)-benzoate.—To a suspension of 29.0 g. (0.12 mole) of finely powdered *p*-(2-nitro-2-methylpropylamino)-benzoic acid in 150 ml. of ethanol was added 72.5 ml. (0.12 mole) of a 1.660 *N* solution of sodium hydroxide in ethanol. After a few minutes, 19.8 g. (0.132 mole) of γ-diethylaminopropyl chloride, along with 50 ml. of ethanol, was added. After refluxing for four and one-half hours, the solution was filtered hot, collecting 7.0 g. of sodium chloride (theory was 7.0 g.). The filtrate was cooled overnight in the refrigerator. Filtration, followed by washing with ethanol and drying, gave 33.2 g. of the ester, m. p. 110–110.5°. Evaporation

(1) Private communication.
(2) H. G. Johnson, THIS JOURNAL, 68, 14 (1946).
(3) Clarke, Gillespie and Weisshaus, *ibid.*, 55, 4571 (1933).