settled to the bottom was washed several times with dry ether and all residual ether removed in vacuum. The liquid did not crystallize even at −78°. The same result was obtained when no solvent was used. No precipitate formed upon addition of 2% barium chloride solution.

To an aqueous solution of the above liquid was added a few drops of chloroplatinic acid. A yellow solid immediately precipitated. This was removed by filtration and washed with alcohol; m.p. 145°. *Anal.* Calcd. for $C_{14}H_{28}Cl_6PtS_2$: Pt, 29.3. Found: Pt, 28.4. This shows that the compound is bis-(methyldiallylsulfonium)-chloroplatinate.

General Procedure for Preparing Mercuric Halide Complexes.—One-hundredth mole of mercuric iodide was placed in a flask with 20 ml. of acetone. To this was added 0.01 mole of allyl bromide and 0.01 mole of diallyl sulfide. The mixture was shaken and when all the mercuric iodide had dissolved, the acetone was evaporated in vacuum. Dry ether was then added and the solid product recrystallized from methyl isobutyl ketone; m.p. 64.5°. *Anal.* Calcd. for $C_9H_{15}I_3HgS$: C, 14.67; H, 2.05. Found: C, 14.85; H, 2.23.

The compound formed from 1,2-di-(allylthio)-ethane, allyl iodide and mercuric iodide was purified by adding dry ether to its acetone solution. The liquid members were isolated by evaporating the acetone in vacuum, adding and decanting ether, and evaporating all residual ether in vacuum.

The properties and analyses of seven of these compounds are recorded in Table I. In addition, isopropyldiallylsulfonium iodide mercuric iodide, *n*-butyldiallylsulfonium iodide mercuric iodide, and methallyldiallylsulfonium chloride mercuric chloride were prepared, but decomposed before they could be isolated from solution.

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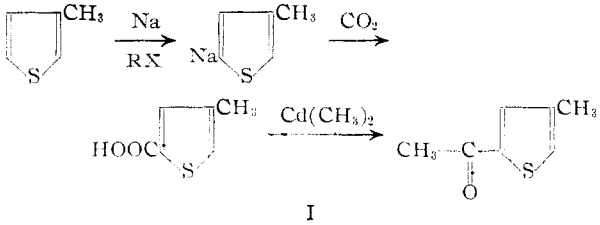
Alkylation During Transmetalation of 3-Methylthiophene

BY JOSEPH A. BLANCHETTE AND ELLIS V. BROWN

RECEIVED OCTOBER 31, 1951

In the course of our investigation of the Willgerodt reaction in the heterocyclic series,[1] it became necessary to prepare 4-methyl-2-acetylthiophene by a method which would circumvent the isomeric mixture of 3-methyl- and 4-methyl-2-acetylthiophenes obtained by the direct acetylation of 3-methylthiophene. One of the possible routes available for the synthesis of 4-methyl-2-acetylthiophene is shown by equation I.



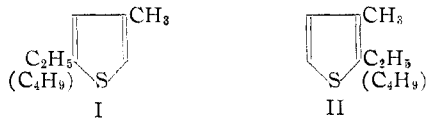
I

Schick and Hartough[2] reported that 3-methylthiophene metalated exclusively in the 5-position in the presence of alkyl or aryl halides such as ethyl chloride, bromobenzene or *n*-butyl bromide. On carbonation and acidification, they obtained a 42% yield of 4-methyl-2-thiophenecarboxylic acid with no trace of 3-methyl-2-thiophenecarboxylic acid being detected. The results obtained by us when this procedure of transmetalation was attempted with ethyl bromide and *n*-butyl bromide are shown in Table I.

TABLE I

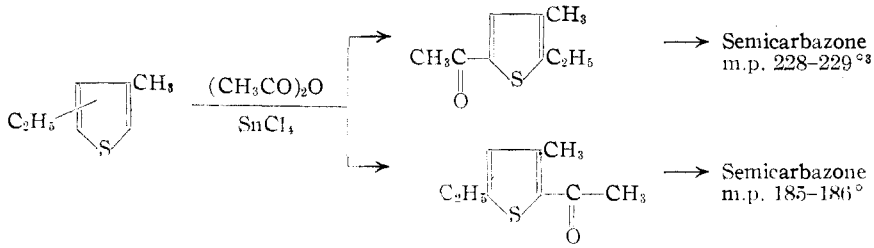
Alkyl or aryl halide	3-Methylthiophene recovered, %	4-Methyl-2-thiophenecarboxylic acid, %	Organic residue, %	B.p., °C.
Ethyl bromide	60	10	40	164–166, 46–48 (13 mm.)
n-Butyl bromide	46	21	60	198–202

It can be seen that the highest yield of 4-methyl-2-thiophenecarboxylic acid obtained was 21% with *n*-butyl bromide which does not approach the 42% reported by Schick and Hartough using ethyl chloride. With both *n*-butyl bromide and ethyl bromide, high boiling liquid organic residues remained after the unreacted 3-methylthiophene had been recovered by fractional distillation. It seemed probable that these organic liquids were alkylated 3-methylthiophenes with the formulas I or II formed by Wurtz–Fittig coupling of 3-methylthienylsodium and the alkyl halides.



I II

Since metalation takes place exclusively in the 5-position of 3-methylthiophene, as shown by the isolation of 4-methyl-2-thiophenecarboxylic acid after carbonation, I was the most probable and the scheme in equation II summarizes the experimental data which support this structure.



The two possible structures, I and II, are 2-ethyl-4-methylthiophene and 2-ethyl-3-methylthiophene. Acetylation would yield, either the known 2-ethyl-3-methyl-5-acetylthiophene, which can be converted to a known semicarbazone ($C_{10}H_{15}N_3OS$) with a melting point of 228–229°, or 2-ethyl-4-methyl-5-acetylthiophene. Acetylation of the compound obtained in this study gave a ketone whose semicarbazone had a melting point of 185–186° and analyzed for $C_{10}H_{15}N_3OS$. These results show that the original compound is a methylethylthiophene and seem to eliminate 2-ethyl-3-methylthiophene as a possibility. The structure is, therefore, most likely to be 2-ethyl-4-methylthiophene and, by analogy, the compound obtained with *n*-butyl bromide is 2-*n*-butyl-4-methylthiophene. A Willgerodt reaction on 2-ethyl-4-methyl-5-acetylthiophene gave the expected 2-ethyl-4-meth-

(1) J. A. Blanchette and E. V. Brown, THIS JOURNAL, **73**, 2779 (1951).

(2) J. W. Schick and H. D. Hartough, *ibid.*, **70**, 1645 (1948).

(3) W. Steinkopf, A. Merckoll and H. Strauch, *Ann.*, **545**, 45 (1940).

yl-5-thienylacetamide and the corresponding acid was obtained by hydrolysis.

Experimental

Attempted Transmetalation of 3-Methylthiophene.—A mixture of 23 g. (1 gram atom) of sodium sand, 250 ml. of anhydrous ether and 98 g. (1 mole) of 3-methylthiophene was refluxed and 68.5 g. (0.5 mole) of *n*-butyl bromide in 100 ml. of anhydrous ether was added dropwise with mechanical stirring. After the addition was completed the mixture was refluxed for an additional 2 hours and was carbonated with pieces of Dry Ice. Water was cautiously added, the alkaline aqueous layer was separated and acidified with concentrated hydrochloric acid whereupon 15 g. (21%) of 4-methyl-2-thiophenecarboxylic acid, m.p. 119–120°, was obtained.

There was also obtained from the ethereal layer 46% of 3-methylthiophene and 60% of a liquid, b.p. 198–202°. Using ethyl bromide as the alkyl halide there was obtained 10% of 4-methyl-2-thiophenecarboxylic acid, 60% of 3-methylthiophene and 40% of a liquid, b.p. 164–166°, 46–48° (13 mm.). For some unaccountable reason, when bromobenzene was used only a high recovery of 3-methylthiophene was observed.

2-Ethyl-4-methyl-5-acetylthiophene.—The organic liquid, b.p. 46–48° (13 mm.) obtained from the attempted transmetalation of 3-methylthiophene with ethyl bromide, was acetylated with acetic anhydride and stannic chloride by the method of Johnson and May.[4] From 16 g. (0.13 mole) there was obtained 15 g. (70%) of a colorless liquid, b.p. 125–126° (15 mm.). A semicarbazone was prepared in the usual manner and crystallized from alcohol, m.p. 185–186°.

Anal. Calcd. for $C_{10}H_{15}N_3OS$: C, 53.33; H, 6.66; N, 18.67. Found: C, 53.55; H, 6.60; N, 18.78.

The molecular formula, $C_{10}H_{15}N_3OS$, was calculated for the semicarbazone of a methylethylacetylthiophene. The semicarbazone of 5-ethyl-4-methyl-2-acetylthiophene is a known compound and has a m.p. of 228–229°. The ketone obtained is believed to be 2-ethyl-4-methyl-5-acetylthiophene.

2-Ethyl-4-methyl-5-thenylacetamide.—2-Ethyl-4-methyl-5-acetylthiophene was converted to 2-ethyl-4-methyl-5-thienylacetamide, m.p. 98–99°, in a yield of 35% by the Willgerodt reaction.[1]

Anal. Calcd. for $C_9H_{13}NOS$: N, 7.65. Found: N, 7.77.

Hydrolysis of this amide gave an oil which readily formed a solid *p*-bromophenacyl ester, m.p. 95–97°.

Anal. Calcd. for $C_{17}H_{17}BrO_3S$: C, 53.54; H, 4.46. Found: C, 53.82; H, 4.31.

(4) J. R. Johnson and C. E. May, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 8.

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Optical Rotation of Peptides. V. Alanine Tetra-, Penta- and Hexapeptides[1]

BY ERWIN BRAND, BERNARD F. ERLANGER AND HOWARD SACHS

Previous papers in this series dealt with the synthesis and specific rotation of alanine dipeptides[2] and tripeptides.[3] In this paper the syntheses and specific rotations (in 0.5 *N* HCl) of four isomeric alanine tetrapeptides,[4] pentaalanine (5L) and hexaalanine (6L) are presented. More detailed data on their specific rotations and on the *residue rotations*[5] of alanine residues will be reported subsequently.

(1) Presented in part before the Division of Biological Chemistry at the 119th Meeting of the A. C. S., Boston, Mass., April, 1951.

(2) B. F. Erlanger and E. Brand, THIS JOURNAL, **73**, 3508 (1951).

(3) E. Brand, B. F. Erlanger, H. Sachs and J. Polatnick, *ibid.*, **73**, 3510 (1951).

(4) For abbreviations see Table I, footnote *a*.

(5) E. Brand and B. F. Erlanger, THIS JOURNAL, **72**, 3314 (1950).

Experimental

The synthesis and properties of most of the starting materials have been previously described: L- and D-alanine[2]; L- and D-alanine benzyl esters (ref. 2, Cmpds. 5, 6); carbobenzoxy-D-alanine hydrazide (ref. 2, Cmpd. 3); carbobenzoxydialanine hydrazide (Z.Ala-Ala.$NHNH_2$(2L), ref. 2, Cmpd. 17); and three isomeric carbobenzoxytrialanine hydrazides (ref. 3, Cmpds. 14–16).

The benzyl ester hydroiodides of di- and trialanine were used as intermediates in the synthesis of some of the higher peptides. These benzyl esters were prepared from their corresponding carbobenzoxy derivatives by reduction with phosphonium iodide, which removes the N-carbobenzoxy group more rapidly than the benzyl ester group.[6]

(1) **H.Ala-Ala.OBz.HI** (2L) ($C_{13}H_{18}O_3N_2$.HI, mol. wt. 378.2).—0.15 mole of Z.Ala-Ala.OBz (2L) (ref. 2, Cmpd. 13) is dissolved in 65 cc. of glacial acetic acid and warmed to 35–40°. PH_4I (0.45 mole) is added and hydrogen passed through the solution for about two hours, when CO_2 evolution stops. The solution is evaporated *in vacuo*. Water is added and then distilled off *in vacuo*, in order to remove acetic acid; this treatment is repeated several times. The solution is finally distilled down to an oil, which is taken up in about 15 cc. of water and extracted with several portions of ether (caution—lachrymator!). The amount of H.Ala-Ala.OBz.HI (2L) present in this aqueous solution is determined by Van Slyke amino nitrogen determination. From this solution the free dipeptide benzyl ester is prepared in the usual fashion[2,3] for use in further synthesis.

Since neither the hydroiodide, the hydrochloride, nor the free dialanine benzyl ester is obtained in crystalline form, Compound 1 is identified by converting it into derivatives. Reaction of the free dialanine benzyl ester in ethyl acetate with an ethereal solution of carbobenzoxy-L-alanine azide yields a compound with the same melting point, mixed melting point (201°) and analysis as Z.Ala-Ala-Ala.OBz (3L), previously prepared by a different procedure (ref. 3, Cmpd. 9). Compound 1 is further identified by converting it into Z.Ala-$(Ala)_3$-Ala.OBz (5L) (*cf.* below, Cmpd. 7).

(2) **H.Ala-Ala-Ala.OBz.HI** (3L) ($C_{16}H_{23}O_4N_3$.HI, mol. wt. 449.3).—This compound is prepared from Z.Ala-Ala-Ala.OBz(3L)(ref. 3, Cmpd. 9) as described above for Compound 1. Since neither the hydroiodide nor the free trialanine benzyl ester is obtained in crystalline form, Compound 2 is identified by converting it into derivatives (*cf.* below, Cmpds. 6, 7 and 8).

Carbobenzoxytetraalanine Benzyl Esters (Compounds 3–6).—Compounds 3–5 are prepared by coupling the azide of a carbobenzoxytrialanine hydrazide[3] with free alanine benzyl ester essentially as described in detail for the synthesis of carbobenzoxydipeptide and -tripeptide esters.[2,3]

(3) **Z.Ala-$(Ala)_2$-Ala.OBz** (4L).—For the preparation of this compound, 0.1 mole of Z.Ala-Ala-Ala.$NHNH_2$ (3L) (ref. 3, Cmpd. 14) is dissolved in 150 cc. of glacial acetic acid, 12.5 cc. of 5 *N* HCl and 100 cc. of water. The solution is cooled to −5°, sodium nitrite (0.11 mole) added, and allowed to stand in an ice–salt-bath for three minutes, after which an additional 300 cc. of ice-cold water and 250 cc. of ice-cold ethyl acetate are added. The azide is extracted and washed with water, 3% aqueous $NaHCO_3$ and water (all ice-cold), dried over sodium sulfate and added in one portion to a cold, dry, ethereal solution of L-alanine benzyl ester[2] (previously prepared from 0.15 mole of its hydrochloride). After standing at room temperature for about 20 hours, the carbobenzoxytetraalanine ester is isolated and recrystallized from dioxane.

(4) **Z.Ala-$(Ala)_2$-Ala.OBz** (LDLL). (5) **Z.Ala-$(Ala)_2$-Ala.OBz** (LLDL).—For the preparation of these compounds, the carbobenzoxytrialanine azides are prepared from their respective carbobenzoxytrialanine hydrazides (ref. 3, Cmpds. 15, 16) by following exactly the procedure described for the preparation of carbobenzoxydialanine azides,[3] except that the carbobenzoxytrialanine azides are extracted with ethyl acetate instead of with ether–ethyl acetate. The azide solutions are then added in one portion to a 50% molar excess of free alanine benzyl ester in ether. After 20 hours the carbobenzoxytetraalanine benzyl esters are collected and recrystallized from 95% ethanol.

(6) **Z.Ala-$(Ala)_2$-Ala.OBz** (DLLL).—This compound is prepared by coupling 0.1 mole of carbobenzoxy-D-alanine azide[2] with 0.15 mole of H.Ala-Ala-Ala.OBz (3L) in ethyl

(6) C. R. Harington and T. H. Mead, *Biochem. J.*, **30**, 1599 (1936).