and neoheptyl groups compare with the simpler straight chain groups.

2. Four new alkylmercuric chlorides have been reported. These are of use as derivatives for identifying the alkyl halides.

3. A method of recrystallizing tertiary alkylmercuric halides is given.

4. Neohexyl chloride (1-chloro-3,3-dimethylbutane) has been prepared.

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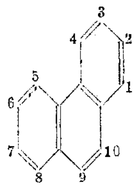
[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA]

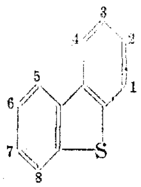
Isosteric Compounds. I. Acyl Derivatives of Dibenzothiophene

BY ALFRED BURGER, WILLIAM B. WARTMAN, JR., AND ROBERT E. LUTZ

The similarity between the physical characteristics of benzene and thiophene and their corresponding derivatives, and the agreement in the physiological behavior of certain of these compounds[1] have been subject to frequent speculation. In 1933 Erlenmeyer[2] advanced the theory that divalent sulfur contains a shell of orbit electrons similar to that of the group or "pseudoatom,"—CH=CH—, and that this similarity in electronic structure known as isosterism,[3] accounted for the formation of mixed crystals and the many like physical properties of the two series. In a few cases, isosteric compounds are interchangeable in serological reactions and cannot be differentiated by the precipitin reaction.[2a]

The present paper is the first in a series of studies on the physical and pharmacological changes effected by introducing a thiophene nucleus into condensed ring systems in place of an aromatic nucleus. The first case under investigation is dibenzothiophene (I) which may be regarded as a pseudophenanthrene. Amino alcohols derived from dibenzothiophene, characterized by the groups —$CHOHCH_2NR_2$ and $CHOHCH_2CH_2NR_2$, may be expected to resemble the corresponding alkamines of the phenanthrene series in analgesic action.[4] Their similarity to the corresponding alkamines derived from dibenzofuran[5] and carbazole[6] should be less marked, since oxygen and the imino group are not isosteric with the —CH=CH— group.





I

The preparation of acetyldibenzothiophenes as starting materials for the proposed dibenzothienyl alkamines is described in this communication. The direct introduction of the acetyl group by the Friedel–Crafts reaction was chosen as a suitable approach. The only ketone derived from dibenzothiophene known heretofore is stearoyl dibenzothiophene, prepared by the Friedel–Crafts reaction in boiling carbon disulfide.[7] No proof for the position of the stearoyl group has been offered, but the group is presumed to have entered position 3 which is known to be preferred in nitration, sulfonation, and halogenation.[8]

Friedel–Crafts reaction on dibenzothiophene with acetyl chloride at low temperature yielded a difficultly separable mixture of methyl ketones, from which one (II), melting at 111–112°, was separated by laborious fractional crystallization and was the major product. An isomeric monoketone, melting at 128–129°, was isolated in small amounts during this procedure. The structure of the major constituent of this mixture, 3-acetyldibenzothiophene (II), was proved by Beckmann rearrangement of its oxime. The resulting acetaminodibenzothiophene and the amine obtained from it by hydrolysis were

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[1] Steinkopf and Ohse, *Ann.*, **437**, 14 (1924); **448**, 205 (1926); Gilman and Pickens, THIS JOURNAL, **47**, 245 (1925); Hartmann and Wybert, *Helv. Chim. Acta*, **2**, 60 (1919); Jaffé and Levy, *Ber.*, **21**, 3458 (1888).

[2] (a) Erlenmeyer, Berger and Leo, *Helv. Chim. Acta*, **16**, 733 (1933); (b) Erlenmeyer and Leo, *ibid.*, **16**, 1381 (1933).

[3] Grimm, *Naturwissenschaften*, **17**, 535, 557 (1929).

[4] Mosettig, Shaver and Burger, THIS JOURNAL, **60**, 2464 (1938), footnote 2.

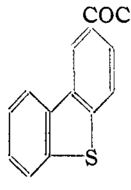
[5] Mosettig and Robinson, *ibid.*, **57**, 2186 (1935).

[6] Ruberg and Small, *ibid.*, **60**, 1591 (1938).

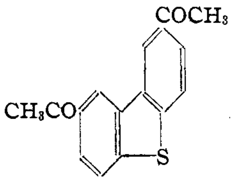
[7] Ralston and Christensen, *Ind. Eng. Chem.*, **29**, 194 (1937).

[8] (a) Courtot and Pomonis, *Compt. rend.*, **182**, 893, 931 (1926); (b) Courtot and co-workers, *ibid.*, **186**, 1624 (1928); **192**, 1667 (1931); **198**, 2003, 2260 (1934); (c) Cullinane, Davies and Davies, *J. Chem. Soc.*, 1435 (1936).

identical with 3-acetamino- and 3-aminodibenzothiophene, respectively, which had been prepared from 3-nitrodibenzothiophene.[8c]



II



III

When the Friedel–Crafts reaction was carried out in boiling carbon disulfide, the main reaction product was a diacetyldibenzothiophene. One of the acetyl groups must be attached in position 3, because the compound was formed in excellent yield by the action of acetyl chloride and aluminum chloride in boiling carbon disulfide on 3-acetyldibenzothiophene (II). The position of the second acetyl group was demonstrated when the dioxime was rearranged to 3,6-diacetaminodibenzothiophene, which on hydrolysis yielded 3,6-diaminodibenzothiophene.[8a] Our diketone must be therefore 3,6-diacetyldibenzothiophene (III).

The good yield of III obtained by drastic acetylation of dibenzothiophene and 3-acetyldibenzothiophene, respectively, suggests that the first acetyl group enters position 3 largely, and therefore II must be the chief product in the mixture of monoketones.

Experiments are under way to make more practicable the direct synthesis of dibenzothiophene ketones for preparative purposes. We are also studying the introduction of the succinoyl group. The mono- and disuccinoyl derivatives are expected to yield naphthobenzo- and dinaphthothiophenes, respectively, by the usual reactions. These compounds may exhibit carcinogenic properties similar to those of the analogous benzanthracenes and benzphenanthrene.

Experimental

Dibenzothiophene.—The dibenzothiophene used was prepared by heating diphenyl with sulfur in the presence of anhydrous aluminum chloride.[9]

Acetylation of Dibenzothiophene.—The action of acetyl chloride and anhydrous aluminum chloride on dibenzothiophene under widely varying conditions was investigated in a series of nine experiments. Carbon disulfide, nitrobenzene, tetrachloroethane, and a mixture of the latter two were employed as solvents, the reaction temperature ranging from 0 to 55°. The aluminum chloride was added to the mixture of dibenzothiophene and acetyl chloride in preference to the reverse order of addition to avoid a side reaction of the aluminum chloride with the starting material. Mixtures of methyl ketones were obtained in all cases, and only two of the experiments yielding the best results are described here.

3-Acetyldibenzothiophene.—A solution of 145 g. of aluminum chloride in 400 ml. of dry nitrobenzene was added dropwise to a well-stirred, ice-cold mixture of 95 g. of dibenzothiophene, 48 ml. of acetyl chloride, and 500 ml. of dry tetrachloroethane over a period of one hour. The mixture was stirred at 0° for two hours and allowed to stand at this temperature for twelve days. It was decomposed by pouring onto ice and hydrochloric acid. The solvent was removed by steam distillation, the brown oily residue was dissolved in benzene, the solution was filtered, and the benzene was evaporated. The crude reaction product obtained from three combined runs totalling initially 265 g. of dibenzothiophene was combined and distilled under reduced pressure, using an oil pump. The distillate was redistilled, and three fractions were collected. Treatment of the partly crystalline main fraction with methanol yielded crystals melting at 85–100°. Crystallization from benzene–petroleum ether, and purification through the semicarbazone which was hydrolyzed easily by the action of boiling dilute hydrochloric acid, failed to improve the melting point. At this stage, the yield of the purified mixture of monoketones was approximately 50%. The mixture was boiled out with two portions of 400 ml. of ether each for one half hour; the sparingly soluble portion was collected and recrystallized from methanol. Twenty grams of 3-acetyldibenzothiophene was thus obtained in colorless plates; m. p. 111–112°.

Anal. Calcd. for $C_{14}H_{10}OS$: C, 74.31; H, 4.46. Found: C, 74.10; H. 4.69.

3-Acetyldibenzothiophene semicarbazone was prepared by boiling the alcoholic solution of the ketone with a concentrated aqueous solution of the calculated amounts of semicarbazide hydrochloride and sodium acetate for ten minutes. It crystallized from ethanol as slightly yellow plates; m. p. 234–235° (dec.).

Anal. Calcd. for $C_{15}H_{13}N_3OS$: C, 63.58; H, 4.62. Found: C, 63.49; H, 5.01.

The oxime was formed by boiling 1.5 g. of 3-acetyldibenzothiophene, 1 g. of hydroxylamine hydrochloride, and 3.7 g. of barium carbonate in 75 ml. of ethanol under reflux for four hours. The barium salts were filtered, the alcoholic filtrate was concentrated and the oxime allowed to crystallize. Recrystallization from ethanol yielded colorless needles; m. p. 161–164°.

Anal. Calcd. for $C_{14}H_{11}NOS$: N, 5.81. Found: N, 5.86.

?-Acetyldibenzothiophene.—The ether extracts of the less soluble 3-isomer deposited on cooling 1 g. of a more soluble ketone as rhombic prisms. It was recrystallized from methanol; m. p. 129–130°.

Anal. Calcd. for $C_{14}H_{10}OS$: C, 74.31; H, 4.46. Found: C, 74.29; H, 5.06.

The semicarbazone formed much slower than that of the isomeric 3-acetyldibenzothiophene. It was necessary to

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[9] Private communication by A. L. Jacoby through the courtesy of Dr. Henry Gilman. See also Chapiro and Gach, *C. A.*, **27**, 2696 (1933); I. G. Farbenindustrie A.-G., *C. A.*, **28**, 1053^7 (1934).

boil the mixture for thirty minutes. It crystallized as slightly yellow plates; m. p. 302–304° (dec.).

Anal. Calcd. for $C_{15}H_{13}N_3OS$: N, 14.83. Found: N, 14.81.

Beckmann Rearrangement of 3-Acetyldibenzothiophene Oxime.—Dry hydrogen chloride was passed into a solution of 1 g. of 3-acetyldibenzothiophene oxime in 4 ml. of glacial acetic acid and 2 ml. of acetic anhydride for one hour, and the mixture was allowed to stand for twenty hours. Water was added; the crystals which had formed were filtered and recrystallized from methanol. The substance appeared as colorless needles; m. p. 181–183°.

Anal. Calcd. for $C_{14}H_{11}NOS$: C, 69.68; H, 4.60. Found: C, 69.86; H, 5.02.

A mixture melting point with 3-acetaminodibenzothiophene of the same melting point, obtained by acetylation of 3-aminodibenzothiophene with acetic anhydride in pyridine solution, showed no depression.

Hydrolysis of 3-Acetaminodibenzothiophene.—A mixture of 0.3 g. of 3-acetaminodibenzothiophene, 1.5 ml. of glacial acetic acid, and 1.5 ml. of 6 *N* hydrochloric acid was boiled under reflux for one hour. On cooling, the amine hydrochloride separated out. It was converted to the base by treatment with dilute sodium hydroxide solution, and the amine was recrystallized from alcohol. It appeared as colorless needles, m. p. 131–133°.

A mixture melting point with 3-aminodibenzothiophene of the same melting point, prepared by reduction of 3-nitrodibenzothiophene[8c] with stannous chloride and hydrochloric acid in ethanol solution showed no depression.

3,6-Diacetyldibenzothiophene.—Anhydrous aluminum chloride (3.7 g.) was added to a solution of 5 g. of dibenzothiophene and 2.1 ml. of acetyl chloride in 75 ml. of dry carbon disulfide at 10° with vigorous stirring over a period of thirty minutes. The mixture was stirred for forty-five minutes, and then boiled under reflux for five hours. It was poured onto ice and hydrochloric acid, the solvent was driven off with steam, and the brown oily residue was extracted into chloroform. The solution was evaporated, and the crystalline residue was extracted with cold benzene. The insoluble portion was recrystallized from ethanol and obtained as colorless needles; m. p. 208–209°; yield, 1.4 g.

Anal. Calcd. for $C_{16}H_{12}O_2S$: C, 71.62; H, 4.51. Found: C, 71.02; H, 4.94.

The portion soluble in benzene also contained ketones as shown by its conversion into a mixture of semicarbazones. Hydrolysis of these semicarbazones yielded a mixture of ketones, m. p. 85–100°.

3,6-Diacetyldibenzothiophene was formed in 90% yield when a solution of 1 g. of 3-acetyldibenzothiophene and 1 ml. of acetyl chloride in 20 ml. of dry carbon disulfide was treated with 1 g. of aluminum chloride, and the mixture was boiled under reflux for six hours and worked up as described above.

3,6-Diacetyldibenzothiophene Dioxime.—A mixture of 1 g. of diacetyldibenzothiophene, 1 g. of hydroxylamine hydrochloride, 3 g. of sodium acetate, and 50 ml. of ethanol was boiled under reflux for seven hours. A precipitate formed and was filtered and washed with alcohol and water. Recrystallization from ethanol yielded colorless crystals; m. p. 272–274° (dec.); yield, 1 g.

Anal. Calcd. for $C_{16}H_{14}N_2O_2S$: N, 9.38. Found: N, 8.99.

Beckmann Rearrangement of 3,6-Diacetyldibenzothiophene Dioxime.—A solution of 1 g. of the dioxime in 6 ml. of glacial acetic acid and 3 ml. of acetic anhydride was saturated with dry hydrogen chloride and allowed to stand for sixteen hours. The diacetamino compound separated out. Water was added and the product was filtered and purified by sublimation in a high vacuum and crystallization from methanol. It appeared as colorless crystals, melting at 253–255°. Courtot and Pomonis[8a] describe 3,6-diacetaminodibenzothiophene as brown crystals, m. p. 237–239° (dec.).

The diacetamino product was hydrolyzed in the same manner as the 3-acetamino compound described above. 3,6-Diaminodibenzothiophene appeared as grayish needles, m. p. 178° (dec.). This is in good agreement with the data of the French authors. However, our product could be purified by sublimation in a high vacuum and recrystallization from ethanol. It appeared then as colorless needles, m. p. 193–194° (dec.).

Summary

A Friedel–Crafts reaction with acetyl chloride on dibenzothiophene at low temperatures yields a mixture of methyl ketones from which two isomeric monoketones have been isolated. One of these ketones has been shown to be 3-acetyldibenzothiophene by degradation to 3-aminodibenzothiophene. At higher temperatures, the reaction furnishes mainly 3,6-diacetyldibenzothiophene, which could be converted to 3,6-diaminodibenzothiophene.

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