Analyses. Subs., 0.1541: CO_2, 0.1837; H_2O, 0.0390. Subs., 0.1594, 0.1506: 16.2 cc. of N_2 (23°, 749.5 mm.); 14.8 cc. of N_2 (27°, 763 mm.). Calc. for $C_{11}H_{11}O_3N_3Br_2$: C, 33.58; H, 2.79; N, 10.68. Found: C, 32.5; H, 2.8; N, 11.2, 10.8.

Summary

The yellow methyl and ethyl esters of benzoylacrylic acid are transformed in the sunlight into the corresponding stereo-isomeric colorless esters. The reverse transformation of the colorless into the yellow esters takes place if the former are exposed to the sunlight in solutions containing a trace of iodine or bromine.

The hydrolysis of these esters with both alkaline and acid reagents has been studied.

Attempts have been made to prepare an isomeric benzoylacrylic acid corresponding in configuration to the colorless esters.

The colorless esters react with 1 molecule of semicarbazide to form addition products and with 2 molecules of this reagent to form semicarbazones of the addition products. The yellow esters form the same product as the colorless esters with 1 molecule of semicarbazide but with 2 molecules of this reagent they form pyrazolone derivatives.

Benzoylacrylic acid reacts with semicarbazide to form isomeric semicarbazones.

New York, N. Y.

[Contribution from the Chemical Laboratories of Columbia University]

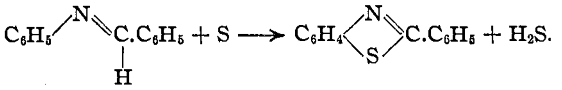
RESEARCHES ON SELENIUM ORGANIC COMPOUNDS. II. SYNTHESIS OF DIARYL THIOPHENES AND DIARYL SELENOPHENES[1]

By Marston Taylor Bogert and Pilar Perez Herrera

Received October 16, 1922

Introductory

In view of the ease with which benzal aniline condenses to the thiazole (I) on fusion with sulfur, it was hoped that a similar fusion of acetophenone anil with sulfur would give the *p*-thiazine (II), or possibly the thionaphthene (III). When the actual experiments were carried out, however, neither thiazine nor thionaphthene was obtained, but a fair yield of 2,4-diphenyl-thiophene (IV).

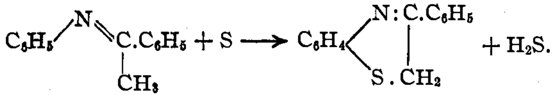


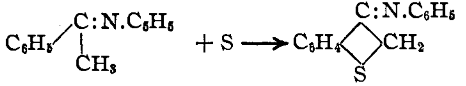
$$C_6H_5\overset{N}{\diagup\diagdown}\underset{\displaystyle H}{\underset{|}{C}}.C_6H_5 + S \longrightarrow C_6H_4{<}\overset{N}{\underset{S}{}}{>}C.C_6H_5 + H_2S.$$

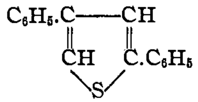
(I)

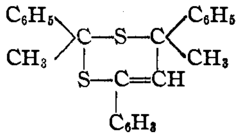
---

[1] The acetophenone used in these experiments was supplied by Mr. Burton T. Bush, President, Antoine Chiris Co., and the selenium by Mr. E. W. Rouse, of the Baltimore Copper Smelting and Rolling Co., to both of whom we are most grateful.


(II)


(III)

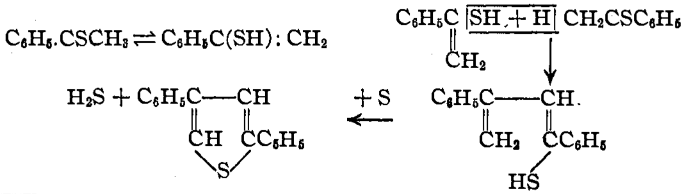

(IV)


(V)

This 2,4-diphenyl-thiophene has been described by various authors,[2,3,4,5,6] all of whom appear to have encountered difficulties in obtaining it pure and in good yield.

Among the methods they employed are those using as initial materials cinnamic acid, phenylethylene, trithio-acetophenone, or acetophenone in presence of hydrogen sulfide and ammonia (or yellow ammonium sulfide). In all cases, both 2,4- and 2,5-diphenyl-thiophene were formed in the reaction, generally accompanied by ethyl benzene or phenylethylene, and occasionally by other products (phenylacetamide, phenylacetic acid, etc.) as well. Baumann and Fromm[7] found that when anhydro-acetophenone disulfide (V) was heated it broke up into hydrogen sulfide, phenylethylene and 2,4-diphenyl-thiophene, without formation of any of the isomeric 2,5-diphenyl-thiophene. The natural deduction from this is that this disulfide was the immediate progenitor of the 2,4-diphenyl-thiophene in the experiments conducted by them.

In our own experiments, however, we found neither ethyl benzene, nor phenylethylene, nor 2,5-diphenyl-thiophene, although we searched for them in our crude products. It is suggested that what probably happens is a decomposition of the anil by hydrogen sulfide (formed first by side reactions of the sulfur, and later as a product of the main reaction), with liberation of the aromatic amine (which distils) and production of a thioacetophenone, which in turn condenses as follows.



---

[2] Baumann and Fromm, *Ber.*, **28**, 891 (1895).

[3] Baumann and Fromm, *ibid.*, **30**, 111 (1897).

[4] Manchot and Krische, *Ann.*, **337**, 183 (1894).

[5] Fromm and Holler, *Ber.*, **40**, 2979 (1907).

[6] Willgerodt and Merk, *J. prakt. Chem.*, [2] **80**, 193 (1909).

[7] Ref. 2, p. 905.

By fusing acetophenone anil with sulfur at 220–240°, 28% yields of pure 2,4-diphenyl-thiophene (m. p. 122.5° corr.) are obtained. Instead of the anil, the tolils may be used with equal success. By starting with substituted acetophenones, the corresponding diaryl thiophenes are produced.

The results having proved so satisfactory in the sulfur field, the investigation was extended to the corresponding selenium compounds, with equally good yields, and 2,4-diaryl selenophenes synthesized by wholly analogous methods. But few selenophenes of any kind are described in the literature, and it is hoped, therefore, to expand the work in this direction also.

Experimental

Aniline Zinc Chloride, $(C_6H_5.NH_2)_2.ZnCl_2$, and the analogously constituted *o*- and *p*-toluidine derivatives, were prepared according to the directions of Lachowicz and Bandrowski.[8] The toluidine zinc chlorides form fine colorless needles, and the yields are good (90%).

Acetophenone Anil, $C_6H_5C(:NC_6H_5)CH_3$, was obtained by the method of Reddelien[9] using a Bogert vacuum fractionating receiver.[10]

Acetophenone *p*-Tolil has also been prepared previously by Reddelien.[11] We followed his specifications and obtained a yield of 33.7%.

Acetophenone *o*-Tolil.—A mixture of 380 g. of acetophenone, 475 g. of *o*-toluidine and 19 g. of *o*-toluidine zinc chloride was heated for an hour at 170–180°, and then allowed to cool. The tolil was extracted with chloroform, and the filtered chloroform extracts distilled at atmospheric pressure up to 220°, when the apparatus was partially evacuated and the distillation continued at 57mm. pressure. The tolil came over at 210–220° at 57 mm. as a light yellow oil, gradually turning brown in the air; yield, 323 g., or 48.8%.

***p*-Methyl-acetophenone Anil,** $CH_3.C_6H_4.C(:N.C_6H_5).CH_3$.—One hundred g. of *p*-methyl-acetophenone (methyl *p*-tolyl ketone) and 125 g. of freshly distilled aniline were intimately mixed and the mixture heated to 160°. Five g. of aniline zinc chloride was then added and the heating maintained for an hour at 180°. The anil was extracted from the cooled melt by chloroform and the filtered extracts distilled at ordinary pressure up to 200°. The residue was then fractionated at 53 mm., the main fraction being collected at 220–240°, as a light yellow oil, which soon turned brown in the air; yield, 46 g., or 29.5%.

2,4-Diphenyl-thiophene.—A mixture of 60 g. (0.3 mole) of acetophenone anil and 20 g. (0.3 mole) of powdered roll sulfur was placed in a distilling flask connected with an air condenser and heated at a temperature of 220–240° for 13 hours. Hydrogen sulfide was evolved and aniline distilled. The residual melt was then fractionated at 36mm. pressure, the major portion distilling at 260–265° as a yellow oil, which solidified in the receiver to a yellow crystalline mass. Recrystallized from absolute alcohol, in presence of a little Norite, until the melting point remained constant, it was obtained in lustrous colorless scales, m. p. 122.5° (corr.); yield, 10 g., or 28%.

---

[8] Lachowicz and Bandrowski, *Monatsh.*, **9,** 513 (1888).

[9] Reddelien, *Ber.*, **43,** 2478 (1910).

[10] Bogert, *J. Ind. Eng. Chem.*, **7,** 785 (1915).

[11] Reddelien, *Ann.*, **388,** 185 (1912); *Ber.*, **46,** 2716 (1913).

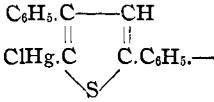
It is easily soluble in chloroform, ether or acetone; and it dissolves also in hot petroleum ether, alcohol, glacial acetic acid or benzene, but is practically insoluble in water, hydrochloric acid or alkali. With conc. sulfuric acid it gives a yellow color, and a red one with conc. nitric acid. Conc. sulfuric acid and isatin (indophenine test)[12] precipitate a bluish-green solid. Subjected to the Laubenheimer[13] reaction, a green solid separates, which is soluble in ether, alcohol, glacial acetic acid or benzene, with a cherry-red color. In the Liebermann[14] reaction, the sulfuric acid is colored first green, then dark red. No addition product is formed with methyl iodide.

Neither phenylethylene, nor ethyl benzene, nor 2,5-diphenyl-thiophene was encountered in the course of the preparation.

Analyses. Calc. for $C_{16}H_{12}S$: C, 81.3; H, 5.08; S, 13.54. Found: C, 81.19, 81.03; H, 4.89, 4.88; S, 13.67, 13.80.

When acetophenone *o*- or *p*-tolil was substituted for the anil in the above process, 2,4-diphenyl thiophene was likewise obtained, identical in all respects with that produced from the anil, the by-products being the respective toluidines instead of the aniline; yield from the *o*-tolil, 23.6%; from the *p*-tolil, 32.4%.

5-Chloromercuri-2,4-diphenyl-thiophene,



.—Steinkopf and Bauermeister[15] have observed that when 2-phenyl-thiophene is treated with mercuric chloride, hydrogen chloride is evolved and one of the hydrogens is replaced by the –HgCl residue. This procedure was therefore applied to the 2,4-diphenyl-thiophene with wholly successful results.

To a solution of 1 g. of the 2,4-diphenyl-thiophene in 200 cc. of 95% alcohol, there were added 10 g. of a 33% solution of sodium acetate and 50 g. of a cold saturated solution of mercuric chloride. After thoroughly mixing the solution it was allowed to stand in the cold, and at the end of 2.5 days 1.5 g. of the chloromercuri derivative had precipitated. After it had stood for 4 days longer, an additional 0.5 g. had separated. It was recrystallized to constant melting point from alcohol, in which it is difficultly soluble, and was thus obtained in colorless, silky needles, m. p. 223° (corr.); yield, 1.5 g., or 75%.

Analysis. Calc. for $C_{16}H_{11}SHgCl$: Hg, 42.57. Found: 43.93.

In view of the greater reactivity of the α position, it is believed that the chloromercuri group enters in Position 5, and an attempt will be made to prove this in the further progress of the work.

Nitration of 2,4-Diphenyl-thiophene.—A mixture of 5 g. of the diphenyl-thiophene and 50 cc. of acetic anhydride was placed in a round-bottom flask provided with a 3-hole stopper. This stopper carried a connection to the air pump, a glass tube with capillary tip, and a dropping funnel containing 1.5 cc. of fuming nitric acid (sp. gr. 1.5) and a like amount of acetic anhydride. The flask was kept at a temperature of 0–5°, and the nitrating mixture added slowly drop by drop, while a gentle current of air was drawn through the capillary. After all the nitrating mixture had been added, the flask was left at the same temperature (0–5°) for 5 or 10 minutes, and the contents then poured into ice water and thoroughly agitated.

---

[12] Baeyer, *Ber.*, **12,** 1311 (1879). Meyer, *ibid.*, **16,** 1478 (1883); etc.

[13] Laubenheimer, *ibid.*, **8,** 224 (1875). Sleicher, *ibid.*, **19,** 673 (1886); etc.

[14] Liebermann, *ibid.*, **20,** 3231 (1887). Schwalbe, *ibid.*, **37,** 324 (1904); etc.

[15] Steinkopf and Bauermeister, *Ann.*, **403,** 66 (1914).

A reddish oil separated which soon solidified to a reddish-brown crystalline mass, insoluble in water, alkali, petroleum ether, methyl or ethyl alcohol, soluble in hot glacial acetic acid, and easily soluble in ether, chloroform, acetone, ethyl acetate, benzene or toluene. No satisfactory crystallizing medium was found. Filtered out, dried and aowdered, it formed a yellowish-brown solid, which began to decompose at 80–85°, pnd melted to a brownish liquid at 110–115°. It was not volatile with steam. No analysis was attempted, as the product was apparently impure.

2,4-Diphenyl-selenophene.—An equimolar mixture of acetophenone anil (60 g.) and metallic selenium (48.6 g.) was placed in a distilling flask connected with an air condenser, and heated for 16 hours at 280–295°. The reaction began at 280° and aniline distilled, about 30 cc. being collected. The residual melt was distilled under a pressure of 31 mm. and the main fraction collected at 270–280°. This was a reddish oil which solidified in the receiver and was crystallized to constant melting point from absolute alcohol in presence of a little Norite. The purified product formed lustrous colorless scales, m. p. 112.3° (corr.); yield, 13 g., or 30%.

It is insoluble in water, aqueous sodium hydroxide solution or hydrochloric acid, soluble in hot alcohol or glacial acetic acid, and easily soluble in chloroform, ether, acetone or benzene. With conc. nitric acid it turns dark red and appears to undergo oxidation. In conc. sulfuric acid it dissolves to give an orange solution. With isatin and sulfuric acid it gives a brown color, and on dilution a brown solid is precipitated. In the Laubenheimer reaction it gives a green color, and on adding water a green flocculent solid separates which dissolves in alcohol, ether, or glacial acetic acid with an orange color, in benzene with a deeper orange, and in conc. sulfuric acid with a violet-red color. The Liebermann test gives first a green, and then a brownish-black color.

Analyses. Calc. for $C_{16}H_{12}Se$: C, 67.77; H, 4.27. Found: C, 67.74; H, 4.30.

The same 2,4-diphenyl-selenophene was produced when acetophenone *o*- or *p*-tolil was substituted for the anil, with the formation of the corresponding toluidines as by-products. The yield of the selenophene in the case of the *o*-tolil was 23%, and with the *p*-tolil 29.3%.

5-Chloromercuri-2,4-diphenyl-selenophene was prepared in a manner entirely similar to that already described for the corresponding diphenyl-thiophene derivative. The crude product was purified by crystallization to constant melting point from 95% alcohol, and then appeared in fine colorless needles, m. p. 224° (corr.); yield, 89%.

It is insoluble in water, difficultly soluble in alcohol or ether, easily soluble in hot chloroform, glacial acetic acid or benzene. Qualitative analysis disclosed the presence of both selenium and mercury. A mixture of equal parts of this chloromercuri derivative with the corresponding thiophene compound (m. p. 223°) melted at 219° (corr.).

2,4-Di-*p*-tolyl-selenophene.—The method of preparation followed closely that given above for the diphenyl homolog. Equimolar amounts of *p*-methyl-acetophenone anil and metallic selenium were fused together for 11 hours at 260–270°, the reaction commencing at 260° with evolution of aniline. The residual melt was distilled at 38 mm. pressure, and the major fraction collected at 260–280° as a reddish oil, which rapidly solidified. Recrystallized to constant melting point from absolute alcohol, in presence of a little Norite, it appeared in beautiful colorless lustrous leaflets, m. p. 136.3° (corr.); yield from 46 g. of anil, 7 g., or 20.5%.

Its solubilities are approximately the same as those given for the diphenyl homolog. Nitric acid seems to oxidize it. In conc. sulfuric acid it dissolves with a red color. With isatin and conc. sulfuric acid it gives a bright red coloration. In the Laubenheimer test a green solid is precipitated which dissolves in ether with an orange-yellow color, in alcohol, glacial acetic acid or benzene with an orange color, and in conc. sulfuric acid to give a brown solution. Dilution of the latter (sulfuric) solution, reprecipitates the green solid. In the Liebermann reaction a dark green color is imparted to the sulfuric acid.

Analyses. Calc. for $C_{18}H_{16}Se$: C, 69.45; H, 5.14. Found: C, 69.40; H, 5.39.

Acetophenone Dimethyl Acetal, $C_6H_5.C(OCH_3)_2.CH_3$.—In the course of the investigation, we had occasion also to prepare this compound.

Methyl orthoformate (22 g.), acetophenone (16.2 g.), anhydrous methyl alcohol (18.9 g.) and conc. hydrochloric acid (5 drops) were mixed in a flask equipped with a calcium chloride guard tube, and heated carefully for several hours at 40°, with constant shaking. After the mixture had stood for 16 hours, a few drops of alcoholic sodium methylate were added carefully to alkaline reaction, and the methyl alcohol distilled. On fractionating the residue at 20mm. pressure, the acetal passed over at 90°, as a colorless liquid of agreeable floral odor; yield, 20 g., or 89.3%.

This acetal is mentioned by Claisen[16] as formed from acetophenone and the hydrochloride of formiminomethyl ether in methyl alcohol solution, but he gives no details concerning the method of preparation or the properties of his product.

Summary

1. 2,4-Diaryl thiophenes and diaryl selenophenes may be produced in fair yields from ketone anils, of acetophenone anil type, by fusion with sulfur or selenium.

2. The properties of these thiophenes and selenophenes are recorded.

3. The following new compounds are described: acetophenone *o*-tolil, *p*-methyl-acetophenone anil, chloromercuri (HgCl) derivatives of 2,4-diphenylthiophene and of the corresponding selenophene, 2,4-diphenylselenophene, and 2,4-di-*p*-tolyl-selenophene.

4. The following compounds, already mentioned in the literature, have been prepared by new methods: 2,4-diphenyl-thiophene, acetophenone dimethyl acetal.

NEW YORK, N. Y.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF ELI LILLY AND COMPANY]

SOME NEW HYPNOTICS OF THE BARBITURIC ACID SERIES

BY H. A. SHONLE AND A. MOMENT

Received October 16, 1922

We know that the introduction of homologous groups in an identical way and position into the same or similar compounds tends to produce compounds having a similar therapeutic action, and that the hypnotic activity of the aliphatic hydrocarbons increases with increasing molecular weight until a chain of 6 or 8 carbon atoms is reached, after which the action decreases. Though the toxicity of isomeric alcohols decreases in the following order—primary, secondary and tertiary, the hypnotic activity increases.

Certain chemical substances which have specific affinity for particular groups of cells may be made to carry other groups therapeutically active

---

[16] Claisen, *Ber.*, **31**, 1012 (1898).