[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUQUESNE UNIVERSITY]

Mono- and Di-acetodiphenyl Sulfide and Related Compounds[1]

BY H. HARRY SZMANT AND FRANK P. PALOPOLI

Dilthey[2] compared the acetylation of diphenyl ether, diphenyl sulfide, and diphenyl selenide and concluded that the ease of monoacetylation decreases from the oxide to the selenide. In the case of the last-mentioned compound he obtained only the diacetylated product, and diphenyl sulfide gave under his experimental conditions predominantly the diacetylated product. Contrary to the experience of Dilthey, this study showed that normal Friedel–Crafts conditions yield 70 to 80 and 5 to 10% of the mono- and diacetylated products, respectively. In view of the lack of previous proof, the structure of the products was shown to be that of *p*-(phenylmercapto)-acetophenone (I) and di-(*p*-acetophenyl) sulfide (II). In a similar fashion there was also prepared the monoacylation product using chloroacetyl chloride, namely, *p*-(chloroaceto)-diphenyl sulfide.

Compounds I and II were readily oxidized to the corresponding sulfones. The preparation of the *p*-acetodiphenyl sulfoxide required repeated crystallizations of the crude oxidation product. In agreement with the observations of previous workers[3] it is believed that the many crystallizations involve the separation of the high melting racemic mixture of the optically active sulfoxide. Compound I was subjected to the Willgerodt reaction and the resulting *p*-phenylmercaptophenylacetic acid was converted to the corresponding sulfone. The compounds prepared in this study are listed in Table I.

Experimental

The Acetylation of Diphenyl Sulfide.—A solution of 75 g. of acetyl chloride in 100 cc. of carbon disulfide was added dropwise to a stirred solution of 179 g. of diphenyl sulfide and 126 g. of aluminum chloride in 250 cc. of carbon disulfide at 0°. The mixture was allowed to come to room temperature and was stirred an additional three hours. The reaction mixture was hydrolyzed and worked up in the conventional manner and the products were separated by distillation.

p-(Phenylmercapto)-acetophenone (I), 190 g., distilled at 183–184° (3 mm.) and was crystallized from alcohol.

Di-(*p*-acetophenyl) sulfide (II), 19 g., obtained at 235–240° (3 mm.) was purified by distillation (b.p. (0.8 mm.) 190–210°) and crystallization from alcohol to a constant melting point.

Proof of Structure of the Acetylation Products.—The oxidation of 1 g. of I in 10 cc. of dioxane with aqueous potassium permanganate gave an acid of m. p. 276–278°, identical with an authentic sample of phenylsulfone-4-carboxylic acid.

Compound II was oxidized by standard procedure using sodium dichromate and the resulting acid on crystallization from a benzene–ethanol mixture melted with decomposition at 370–372°. The reported[4] melting point of 4,4′-phenylsulfonedicarboxylic acid is 371°.

***p*-Acetophenyl Sulfoxide.**—To a solution of 10 g. of I in 200 cc. glacial acetic acid there was added 5 cc. of 30% hydrogen peroxide. After standing at room temperature for twenty-four hours the mixture was warmed to 80° and poured into 2 liters of ice–water. The crude product (8.4 g.) melted at 82°. Several crystallizations from isopropyl alcohol gave white large cubic crystals.

***p*-(Phenylmercapto)-phenylacetic Acid.**—A mixture of 5.7 g. of I, 2 g. of sulfur and 2.5 g. of morpholine was heated three hours at 180° in an 8″ sealed test-tube. The cool mixture was poured on ice and the oily product was extracted with ether. The ethereal solution was washed until neutral, dried, and the ether was removed by distillation. The residue was refluxed for twenty-four hours with 100 cc. of 10% sodium hydroxide and 20 cc. of dioxane

TABLE I

ACETODIPHENYL SULFIDE DERIVATIVES

Compound	M. p., °C.[a]	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	2,4-Dinitrophenylhydrazone M. p., °C.	2,4-Dinitrophenylhydrazone Carbon, % Calcd.	2,4-Dinitrophenylhydrazone Carbon, % Found	2,4-Dinitrophenylhydrazone Hydrogen, % Calcd.	2,4-Dinitrophenylhydrazone Hydrogen, % Found	Oxime M. p., °C.	Oxime Carbon, % Calcd.	Oxime Carbon, % Found	Oxime Hydrogen, % Calcd.	Oxime Hydrogen, % Found
p-(Phenylmercapto)-acetophenone	67–68[c]					161–162.5	58.83	59.06	3.95	4.01	102	69.12	69.21	5.39	5.44
Di-(*p*-acetophenyl) sulfide	90–91[d]					276–277	53.34	53.48	3.52	2.87					
p-Acetophenyl sulfoxide	100–101	68.83	68.80	4.95	4.90	210–211	56.61	56.54	3.80	3.76	127	64.85	64.79	5.05	4.98
p-Acetylphenylsulfone[e]	139	64.60	64.55	4.65	4.67	238–238.5	54.56	54.40	3.66	3.57	145	61.08	60 95	4.76	4.81
Di-(*p*-acetophenyl)-sulfone	209–211	63.56	63.62	4.67	4.72	304–305d.	50.76	51.05	3.35	3.27					
p-(Phenylmercapto)-phenylacetic acid[f]	108–110	68.83	68.90	4.95	4.94										
p-(Phenylsulfonyl)-phenylacetic acid	248–249	60.86	60.75	4.38	4.29										
p-(Chloroaceto)-diphenyl sulfide	75–76	64.00	64.39	4.22	4.42										

[a] All melting points are uncorrected. [b] Analyses by the Micro-Analytical Laboratory, University of Pittsburgh. [c] M. p. in literature,[3] 65°. [d] M. p. in literature,[3] 90–91°. [e] While this work was in progress Burton and Hu (*J. Chem. Soc.*, 601 (1948)) reported the preparation of this compound of m. p. 136–137° by a different method. [f] After completion of this work Corse and co-workers (THIS JOURNAL, **70**, 2841 (1948)) reported the preparation of this acid without stating any physical constants or analytical data.

(1) From the M.S. thesis submitted by Frank P. Palopoli to the Faculty of the Graduate School of Duquesne University.

(2) Dilthey, Neuhaus and Reis, *J. prakt. Chem.*, **124**, 81–126 (1930).

(3) Harrison, Kenyon and Phillips, *J. Chem. Soc.*, 2079 (1926).

(4) Loudon, *J. Chem. Soc.*, 221 (1936).

ane, and the mixture on dilution with 100 cc. of water was poured into 500 cc. of six *M* sulfuric acid. The product was filtered, washed with water, dried, and on crystallization from a mixture of benzene and heptane there was obtained 2.9 g. (47.5%) of the acid.

***p*-Acetophenyl sulfone, di-(*p*-acetophenyl) sulfone** and ***p*-(phenylsulfonyl)-phenylacetic acid** were prepared by the oxidation of 10 g. of I, II and *p*-(phenylmercapto)-phenylacetic acid, respectively, in 100 cc. of glacial acetic acid with excess of 30% hydrogen peroxide.

***p*-(Chloroaceto)-diphenyl Sulfide.**—This compound was prepared in the same manner as described for the preparation of I using 186 g. of diphenyl sulfide, 133 g. of aluminum chloride, and 125 g. of chloroacetyl chloride. The crude product was purified by crystallization from a mixture of benzene and petroleum ether to give a 60% yield of product melting 75–76°. The distillation of larger amounts of the product (b. p. (3 mm.) 188–190°) is accompanied by decomposition.

Summary

The Friedel–Crafts acetylation of diphenyl sulfide gives the mono- and diacetylated products. The mono-substitution product is obtained in 70–80% yields and the substitutions occur in the para positions. The *p*-(chloroaceto)-diphenyl sulfide is prepared by the Friedel–Crafts reaction, and the oxidation of the sulfides to the sulfoxides or sulfones is described. The Willgerodt reaction of *p*-(phenylmercapto)-acetophenone gives the expected substituted phenylacetic acid.

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[CONTRIBUTION FROM THE LABORATORY OF RADIOCHEMISTRY, UNIVERSITY OF CINCINNATI]

Derivatives of 2-Amino-7-iodofluorene[1]

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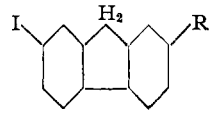
Since the discovery by Wilson, DeEds and Cox[3] of the carcinogenic activity of 2-acetylaminofluorene, there has been a good deal of experimentation with this compound. However, the synthesis and biological testing of derivatives of this carcinogen have been largely pretermitted.

Bielschowsky[4] has shown that during metabolism of 2-acetylaminofluorene the 7-position was hydroxylated and the resulting compound excreted. This pattern was previously established for carcinogenic aromatic hydrocarbons.[5] Hoch-Ligeti[6] found that 2-acetylamino-7-hydroxyfluorene was a weaker carcinogen than 2-acetylaminofluorene.

Possibly the 7-position in 2-acetylaminofluorene is of significance with respect to the carcinogenic effect of the compound. Resonance in the fluorene molecule[7] as well as the acetylamino group confers a high electron density on carbon number seven. Attack by an electrophilic compound[8] at this position might be the first in a series of reactions leading to formation of a tumor. There appears to be a correlation in some cases between high electron density in a molecule and its carcinogenic effect.[8,9]

In order to study the effect of blocking the important 7-position, it was decided to prepare 2-acetylamino-7-iodofluorene, III. In this compound the electron density at the 7-position is reduced so that the compound might not be carcinogenic in the light of the discussion mentioned previously. However, if biological testing would reveal the compound to be carcinogenic, the introduction of I^{131} in the 7-position would enable the use of tracer methods to study its action.



I, R = NO_2
II, R = NH_2
III, R = $NHCOCH_3$

2-Nitro-7-iodofluorene, I, had been prepared by Chanussot[10] by nitration of 2-iodofluorene. In the present investigation it was prepared from 2-amino-7-nitrofluorene[11] by a Sandmeyer reaction. Upon reduction with zinc dust and calcium chloride in dilute alcohol, 2-amino-7-iodofluorene, II, resulted. This showed a tendency to form a dark oil during attempted purification. Several recrystallizations, however, yielded a small pure sample. Acetylation afforded light tan needles of 2-acetylamino-7-iodofluorene, III.

Since this synthesis did not appear suitable for large scale preparations, 2-acetylaminofluorene was iodinated with a molar quantity of iodine monochloride which was dissolved in glacial acetic acid. The crystalline product was identical with the 2-acetylamino-7-iodofluorene previously obtained. However, when the synthesis was repeated on a larger scale, only a small amount of the desired product was isolated. The greater portion was a greenish-gray material of the theoretical iodine content. This decomposed when recrystallized to iodine and impure 2-acetylaminofluorene. Solution in acetone led to the formation of a lachrymatory substance. These facts indicated that the unstable material was an N-iodo compound.

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(3) Wilson, DeEds and Cox, *Cancer Research*, **1**, 596 (1941).

(4) Bielschowsky, *Biochem. J.*, **39**, 287 (1945).

(5) Chalmers and Peacock, *ibid.*, **35**, 1276 (1941).

(6) Hoch-Ligeti, *Brit. J. Cancer*, **1**, 391 (1947).

(7) Weisburger, Weisburger and Ray, in press.

(8) Pullman, *Compt. rend.*, **225**, 738 (1947).

(9) Badger, *Brit. J. Cancer*, **2**, 342 (1948).

(10) Chanussot, *Anales asoc. quim. Argentina*, **15**, 8 (1927).

(11) Cislak and Hamilton, THIS JOURNAL, **53**, 746 (1931).